METHODS OF TREATING CANCER AND/OR CHEMOTHERAPY RELATED CONDITIONS USING NON-NATURALLY OCCURRING MELANOCORTIN ANALOGS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application 63/618587 filed January 8, 2024, which is incorporated herein by reference in its entirety.

SEQUENCE LISTING INCORPORATED BY REFERENCE

[0002] This application contains an ST.26 compliant Sequence Listing, which is submitted concurrently in .xml format via Patent Center and is hereby incorporated by reference in its entirety. The .xml copy, created on February 16, 2024, is named 146316_8019_WO00_SL.xml and is 1,552,278 bytes in size.

BACKGROUND

[0003] The use of anti-cancer agents, including chemotherapeutic agents, to treat patients is often restricted because the patient suffers from certain conditions such as anorexia, emesis, weight loss, fat and muscle wasting, and fatigue. These conditions may be caused by the subject's cancer or may be side effects of the anti-cancer agents. Restrictions on anti-cancer agent use may include limited duration and dose of cancer treatment due to subject's suffering from one or more of these conditions. Accordingly, these conditions limit treatment tolerance of a subject to an anti-cancer agent thereby reducing the overall treatment efficacy, reducing quality of life in cancer patients, and increasing risk that treatments are not as effective as they otherwise could be.

[0004] Despite recent advances in cancer treatment, there is a demand for novel approaches to make anti-cancer agents and associated cancer therapeutic methods more tolerable for patients, including reduced adverse side effects compared to conventional methods, yet retaining or increasing robust therapeutic activity.

[0005] Body weight of rats will be recorded before any doses of TCMCB07 and/or cisplatin are administered, between TCMCB07 and/or cisplatin doses, and after all doses of TCMCB07 and/or cisplatin are administered.

SUMMARY

[0001] In some embodiments, the present technology comprises a method of treating, preventing, or reducing one or more side effects associated with an anti-cancer agent in a subject, comprising administering a non-naturally occurring melanocortin analog to the subject prior to, during, and/or after administration of the anti-cancer agent, wherein the one or more side effects are selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

[0002] In some embodiments, the present technology comprises a method of maintaining or increasing weight in a subject prior to, during, and/or after administration of an anti-cancer agent, comprising administering a non-naturally occurring melanocortin analog to the subject, wherein the weight of the subject is maintained or increased by preventing or reducing anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and/or loss of appetite in the subject.

[0003] In some embodiments, the present technology comprises a method of maintaining or increasing weight in a subject prior to, during, and/or after administration of an anti-cancer agent, comprising administering a non-naturally occurring melanocortin analog to the subject, wherein the weight of the subject is maintained or increased by preventing or reducing one or more side effects associated with the anti-cancer agent selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

[0004] In some embodiments, the present technology comprises a use of a non-naturally occurring melanocortin analog to treat, prevent, or reduce one or more side effects associated with an anti-cancer agent in a subject, the one or more side effects are selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite, wherein the non-naturally occurring melanocortin analog is administered to the subject prior to, during, and/or after administration of the anti-cancer agent.

[0005] In some embodiments, the present technology comprises a use of a non-naturally occurring melanocortin analog to maintain or increase weight in a subject prior to, during, and/or after administration of an anti-cancer agent, wherein the weight of the subject is maintained or increased by preventing or reducing anorexia, weight loss,

muscle mass loss, fat mass loss, wasting, reduced appetite, and/or loss of appetite in the subject.

[0006] In some embodiments, the present technology comprises a use of a non-naturally occurring melanocortin analog to maintain or increase weight in a subject prior to, during, and/or after administration of an anti-cancer agent, comprising administering a non-naturally occurring melanocortin analog to the subject, wherein the weight of the subject is maintained or increased by preventing or reducing one or more side effects associated with the anti-cancer agent selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

[0007] In some embodiments, the subject experiences an increase in weight by at least about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%,10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 225%, 250%, 275%, 300%, 350%, 400%, 450%, or 500% compared to baseline or a control.

[0008] In some embodiments, the present technology comprises a method of maintaining or increasing muscle mass, fat mass, or cardiac mass in a subject prior to, during, and/or after administration of an anti-cancer agent, comprising administering a non-naturally occurring melanocortin analog to the subject.

[0009] In some embodiments, the present technology comprises a use of a non-naturally occurring melanocortin analog to maintain or increase muscle mass, fat mass, or cardiac mass in a subject prior to, during, and/or after administration of an anti-cancer agent.

[0010] In some embodiments, the subject experiences an increase in muscle mass, fat mass, or cardiac mass by at least about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%,10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% compared to a baseline or a control.

[0011] In some embodiments, the present technology comprises a method of maintaining or increasing bone density in a subject prior to, during, and/or after

administration of an anti-cancer agent, comprising administering a non-naturally occurring melanocortin analog to the subject.

[0012] In some embodiments, the present technology comprises a use of a non-naturally occurring melanocortin analog to maintain or increase bone density in a subject prior to, during, and/or after administration of an anti-cancer agent.

[0013] In some embodiments, the subject experiences an increase in bone density by at least about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%,10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% compared to a baseline or a control.

[0014] In some embodiments, the present technology comprises a method of increasing or maintaining a Functional Assessment of Anorexia/ Cachexia Therapy (FAACT) score in a subject prior to, during, and/or after administration of an anti-cancer agent, comprising administering a non-naturally occurring melanocortin analog to the subject.

[0015] In some embodiments, the present technology comprises a use of a non-naturally occurring melanocortin analog to maintain or increase a Functional Assessment of Anorexia/ Cachexia Therapy (FAACT) score in a subject prior to, during, and/or after administration of an anti-cancer agent.

[0016] In some embodiments, the subject experiences an increase in the FAACT score compared to baseline or control by at least 1, 2, 3, 4, or 5 points.

[0017] In some embodiments, the present technology comprises a method of stimulating appetite or reducing loss of appetite induced by an anti-cancer agent in a subject, comprising administering a non-naturally occurring melanocortin analog to the subject prior to, during, and/or after administration of the anti-cancer agent.

[0018] In some embodiments, the present technology comprises a use of a non-naturally occurring melanocortin analog to stimulate appetite or reduce loss of appetite induced by an anti-cancer agent in a subject.

[0019] In some embodiments, the subject experiences an increase in appetite as measured by an increased food intake by about 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1200, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000, 2500, 3000, or more calories compared to baseline a control.

[0020] In some embodiments, the present technology comprises a method of preventing, reducing, or restoring weight loss induced by an anti-cancer agent in a subject, comprising administering a non-naturally occurring melanocortin analog to the subject prior to, during, and/or after administration of the anti-cancer agent.

[0021] In some embodiments, the present technology comprises a method of treating, preventing, or reducing one or more side effects associated with an anti-cancer agent in a subject who failed to respond to an antiemetic treatment, comprising administering a non-naturally occurring melanocortin analog to the subject prior to, during, and/or after administration of the anti-cancer agent, wherein the one or more side effects are selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

[0022] In some embodiments, the present technology comprises a method of treating, preventing, or reducing one or more side effects associated with an anti-cancer agent in a subject who failed to respond to nutritional intervention, comprising administering a non-naturally occurring melanocortin analog to the subject prior to, during, and/or after administration of the anti-cancer agent, wherein the one or more side effects are selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

[0023] In some embodiments, the present technology comprises a method of preventing or reducing an anti-cancer agent induced side effect in a subject having cancer, comprising administering the anti-cancer agent and a non-naturally occurring melanocortin analog to the subject.

[0024] In some embodiments, the present technology comprises a method of treating, preventing, or reducing iatrogenic injury caused by an anti-cancer agent in a subject having cancer, comprising administering the anti-cancer agent and a non-naturally occurring melanocortin analog to the subject.

[0025] In some embodiments, the present technology comprises a method of preventing reduction of, maintaining, or improving Eastern Cooperative Oncology Group (ECOG) and/or Karnofsky performance status (KPS) score of a subject having cancer relative to a baseline or a control, comprising administering an anti-cancer agent and a non-naturally occurring melanocortin analog to the subject.

[0026] In some embodiments, the present technology comprises a use of a non-naturally occurring melanocortin analog for preventing, reducing, or restoring weight loss induced by an anti-cancer agent in a subject.

[0027] In some embodiments, the present technology comprises a use of a non-naturally occurring melanocortin analog for treating, preventing, or reducing one or more side effects associated with an anti-cancer agent in a subject who failed to respond to an antiemetic treatment, the one or more side effects are selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

[0028] In some embodiments, the present technology comprises a use of a non-naturally occurring melanocortin analog for treating, preventing, or reducing one or more side effects associated with an anti-cancer agent in a subject who failed to respond to nutritional intervention, the one or more side effects are selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

[0029] In some embodiments, the present technology comprises a use of a non-naturally occurring melanocortin analog for preventing or reducing an anti-cancer agent induced side effect in a subject having cancer.

[0030] In some embodiments, the present technology comprises a use of a non-naturally occurring melanocortin analog for treating, preventing, or reducing iatrogenic injury caused by an anti-cancer agent in a subject having cancer.

[0031] In some embodiments, the present technology comprises a use of a non-naturally occurring melanocortin analog prior to, during, and/or after administration of an anti-cancer agent for preventing reduction of, maintaining, or improving ECOG and/or KPS score of a subject having cancer relative to a baseline or a control.

[0032] In some embodiments, the subject experiences a reduction in ECOG performance score by about 1, 2, or 3 compared to baseline or control.

[0033] In some embodiments, the subject experiences an increase in KPS score by about 100, 90, 80, 70, 60, 50, 40, or 30 compared to baseline or control.

[0034] In some embodiments, the present technology comprises a method of preventing reduction of, maintaining, or improving overall survival (OS) or progression

free survival (PFS) in a subject having cancer relative to a baseline or a control, comprising administering an anti-cancer agent and a non-naturally occurring melanocortin analog to the subject.

[0035] In some embodiments, the present technology comprises a use of a non-naturally occurring melanocortin analog prior to, during, and/or after administration of an anti-cancer agent for preventing reduction of, maintaining, or improving OS or PFS in a subject having cancer relative to a baseline or a control.

[0036] In some embodiments, the subject experiences an increase in OS or an increase in PFS compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%.

[0037] In some embodiments, the present technology comprises a method of reducing time to cancer treatment failure in a subject having cancer relative to a baseline or a control, comprising administering an anti-cancer agent and a non-naturally occurring melanocortin analog to the subject.

[0038] In some embodiments, the present technology comprises a method of increasing or maintaining body mass index (BMI) in a subject relative to a baseline or a control, comprising administering an anti-cancer agent and a non-naturally occurring melanocortin analog to the subject.

[0039] In some embodiments, the present technology comprises a use of a non-naturally occurring analog for reducing time to cancer treatment failure in a subject having cancer relative to a baseline or a control, prior to, during, and/or after administration of an anti-cancer agent.

[0040] In some embodiments, the present technology comprises a use of a non-naturally occurring melanocortin analog for increasing or maintaining BMI in a subject relative to a baseline or a control, prior to, during, and/or after administration of an anti-cancer agent.

[0041] In some embodiments, the subject experiences an increase in BMI compared to baseline or control by at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35 points.

[0042] In some embodiments, the subject experiences in an increase in BMI durability compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%.

[0043] In some embodiments, the present technology comprises a method of reducing a proinflammatory transcript or protein level in a subject having cancer relative to a baseline or a control, comprising administering an anti-cancer agent and a non-naturally occurring melanocortin analog to the subject.

[0044] In some embodiments, the present technology comprises a use of a non-naturally occurring melanocortin analog for reducing a proinflammatory transcript or protein level in a subject having cancer relative to a baseline or a control, prior to, during, and/or after administration of an anti-cancer agent.

[0045] In some embodiments, the subject experiences a reduction in an inflammatory transcript level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%.

[0046] In some embodiments, the subject experiences a reduction in an inflammatory protein level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%.

[0047] In some embodiments, the proinflammatory transcript is a transcript selected from the group consisting of an IL1 transcript, an IL6 transcript, an IL1R1 transcript, a TNFα transcript, a Selectin P transcript, a cytokine transcript, and a chemokine transcript.

[0048] In some embodiments, the proinflammatory protein is a protein selected from the group consisting of an IL1 protein, an IL6 protein, an IL1R1 protein, a TNFα protein, a Selectin P protein, a cytokine protein, and a chemokine protein.

[0049] In some embodiments, the method or the use maintains or increases lean body mass, fat body mass, and/or weight of the subject relative to a baseline or a control.

[0050] In some embodiments, the method or the use maintains or increases lean body mass, fat body mass, and/or body weight of the subject relative to a baseline or a control.

[0051] In some embodiments, the failure to respond to an antiemetic treatment further comprises clinically and/or therapeutically insufficient weight gain, muscle mass gain, fat mass gain, increased appetite, and/or increased food intake in the subject.

[0052] In some embodiments, the nutritional intervention further comprises nutritional supplementation.

[0053] In some embodiments, the iatrogenic injury is selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

[0054] In some embodiments, the improvement, maintenance, or prevented reduction of ECOG and/or KPS score occurs by inhibiting or reducing anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and/or loss of appetite in the subject.

[0055] In some embodiments, the subject has a cancer.

[0056] In some embodiments, the anti-cancer agent comprises a chemotherapy.

[0057] In some embodiments, the method or the use reduces chemotherapy induced mass loss and/or wasting in the subject and increases lean body mass and body weight of the subject relative to a baseline or a control.

[0058] In some embodiments, the method or the use maintains or increases weight of the subject prior to, during, or after administration of the chemotherapy, and wherein the method reduces mass loss and/or wasting in the subject relative to a baseline or a control.

[0059] In some embodiments, the anorexia is associated with weight loss.

[0060] In some embodiments, the subject has not previously received an anti-cancer agent.

[0061] In some embodiments, the subject has previously received an anti-cancer agent.

[0062] In some embodiments, the subject is receiving an anti-cancer agent.

[0063] In some embodiments, the administration of the non-naturally occurring melanocortin analog enhances tolerability of the anti-cancer agent.

[0064] In some embodiments, the enhanced tolerability results in a greater dosage, an increased frequency of administration, and/or an increased duration of administration of the anti-cancer agent, relative to a baseline or control, wherein the baseline or control is the subject prior to the administration of the non-naturally occurring melanocortin analog and/or a subject who is receiving or has received the anti-cancer agent without the non-naturally occurring melanocortin analog.

[0065] In some embodiments, the anti-cancer agent comprises a chemotherapy comprising at least two chemotherapeutic agents, and wherein the enhanced tolerability results in a second chemotherapeutic agent being administered to the subject during or after administration of a first chemotherapeutic agent.

[0066] In some embodiments, the administration of the non-naturally occurring melanocortin analog prevents or reduces a downward titration in dosing regimen of the anti-cancer agent relative to a baseline or a control.

[0067] In some embodiments, the downward titration comprises a decreased dosage, a decreased frequency of administration, and/or a decreased duration of administration, compared to a baseline or control, wherein the baseline or control is the subject prior to the administration of the non-naturally occurring melanocortin analog and/or a subject who is receiving or has received the anti-cancer agent without the non-naturally occurring melanocortin analog.

[0068] In some embodiments, the subject experiences loss of appetite, reduced appetite, decreased food consumption, and/or weight loss prior to the administration of the non-naturally occurring melanocortin analog.

[0069] In some embodiments, the loss of appetite, reduced appetite, decreased food consumption, and/or weight loss is caused by cancer.

[0070] In some embodiments, the loss of appetite, reduced appetite, decreased food consumption, and/or weight loss is caused by the anti-cancer agent.

[0071] In some embodiments, the subject is receiving or has received an antiemetic.

[0072] In some embodiments, the antiemetic is marijuana, megestrol, somatropin, or dronabinol.

[0073] In some embodiments, the non-naturally occurring melanocortin analog and the anti-cancer agent are administered concurrently.

[0074] In some embodiments, the non-naturally occurring melanocortin analog is administered before and/or after the anti-cancer agent.

[0075] In some embodiments, administration of the non-naturally occurring melanocortin analog treats, prevents or reduces the one or more side effects associated with an anti-cancer agent in a subject.

[0076] In some embodiments, administration of the non-naturally occurring melanocortin analog maintains or increases weight in the subject relative to a baseline or a control by preventing or reducing anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and/or loss of appetite in the subject.

[0077] In some embodiments, administration of the non-naturally occurring melanocortin analog maintains or increases weight in the subject relative to a baseline or a control by preventing or reducing one or more side effects selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

[0078] In some embodiments, administration of the non-naturally occurring melanocortin analog stimulates appetite or reduces loss of appetite induced by an anti-cancer agent in the subject relative to a baseline or a control.

[0079] In some embodiments, administration of the non-naturally occurring melanocortin analog prevents, reduces, or restores weight loss induced by an anti-cancer agent in the subject relative to a baseline or a control.

[0080] In some embodiments, administration of the non-naturally occurring melanocortin analog treats, prevents, or reduces the one or more side effects in the subject who failed to respond clinically and/or therapeutically to an antiemetic treatment, relative to a baseline or a control.

[0081] In some embodiments, administration of the non-naturally occurring melanocortin analog treats, prevents, or reduces the one or more side effects in the subject who failed to respond clinically and/or therapeutically to nutritional intervention, relative to a baseline or a control.

[0082] In some embodiments, administration of the non-naturally occurring melanocortin analog prevents or reduces the anti-cancer agent induced side effect in the subject, relative to a baseline or a control.

[0083] In some embodiments, administration of the non-naturally occurring melanocortin analog treats, prevents, or reduces the iatrogenic injury caused by an anti-cancer agent in the subject, relative to a baseline or a control.

[0084] In some embodiments, administration of the non-naturally occurring melanocortin analog prevents reduction of, maintains, or improves ECOG and/or KPS score of the subject, relative to a baseline or a control.

[0085] In some embodiments, the subject's mass and/or weight is not more than 5% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent.

[0086] In some embodiments, the subject's mass and/or weight is not more than 10% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent.

[0087] In some embodiments, the subject has an ECOG score of 1 or higher prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent.

[0088] In some embodiments, the subject has an ECOG score of 2 or higher prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent.

[0089] In some embodiments, the method lowers the ECOG scale of the subject, relative to a baseline or a control.

[0090] In some embodiments, the subject has a KPS score not more than 70 prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent.

[0091] In some embodiments, the subject has a KPS score not more than 50 prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent.

[0092] In some embodiments, the method or the use increases the subject's cumulative mass relative to a baseline or control.

[0093] In some embodiments, the method or the use reduces the subject's rate of loss of cumulative mass relative to a baseline or control.

[0094] In some embodiments, the method or the use increases a net weight gain in the subject relative to a baseline or control.

[0095] In some embodiments, the net weight gain is the change in weight between two or more time points.

[0096] In some embodiments, the net weight gain is the change in weight between the start of treatment and the end of treatment with the non-naturally occurring melanocortin analog or the anti-cancer agent.

[0097] In some embodiments, the two or more time points comprises an intermediate time point.

[0098] In some embodiments, the method or the use increases the subject's cumulative food intake relative to a baseline or control.

[0099] In some embodiments, the cumulative food intake is the total food intake between two or more time points.

[0100] In some embodiments, the cumulative food intake is the total in food intake between the start of treatment and the end of treatment with the non-naturally occurring melanocortin analog or the anti-cancer agent.

[0101] In some embodiments, the two or more time points comprises an intermediate time point.

[0102] In some embodiments, the method or the use increases the subject's BMI relative to a baseline or control.

[0103] In some embodiments, the increase in BMI is the change in BMI between two or more time points.

[0104] In some embodiments, the increase in BMI is a change in BMI between the start of treatment and the end of treatment with the non-naturally occurring melanocortin analog or the anti-cancer agent.

[0105] In some embodiments, the two or more time points comprises an intermediate time point.

[0106] In some embodiments, the non-naturally occurring melanocortin analog is administered to the subject based on the subject's BMI at the time of administration.

[0107] In some embodiments, the subject is administered the non-naturally occurring melanocortin analog at two or more doses based on the subject's BMI at the time of each administration.

[0108] In some embodiments, the two or more doses are inversely titrated based on the subject's BMI at the time of each administration.

In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence according to Formula (I),

$X^1X^2X^3R^1R^2R^3R^4R^5R^6R^7R^8R^9R^{10}R^{11}R^{12}R^{13}R^{14}R^{15}R^{16}R^{17}R^{18}R^{19}R^{20}Y^1Y^2Y^3Y^4Y^5Y^6Y^7Y^8$ (I)

wherein:

R^1 is absent or is selected from the group consisting of cysteine, norleucine (Nle), acetylated norleucine (Ac-Nle), *trans*-4-guanidinyl-proline (*trans*Pro(guan)), *cis*-4-guanidinyl-proline (*cis*Pro(guan)), acetylated *trans*-4-guanidinyl-proline (Ac-*trans*Pro(guan)), acetylated *cis*-4-guanidinyl-proline (Ac-*cis*Pro(guan)), tyrosine, D-tyrosine, di-methyl tyrosine (Dmt), aspartic acid, glutaric acid, leucine, isoleucine, valine, norvaline (Nva), alanine, glycine, proline, methionine, lysine, phenylalanine, glutamic acid, asparagine, and acetylated glutamic acid;

R^2 is absent or is selected from the group consisting of proline, histidine, D-hydroxyproline (dHyp), *trans*Pro(guan), *cis*Pro(guan), aspartic acid, glutamic acid, glycine, lysine, alanine, D-alanine, cysteine, norleucine, arginine, succinic acid, glutaric acid, methionine, and phenylalanine;

R^3 is absent or is selected from the group consisting of histidine, L-proline, *trans*Pro(guan), *cis*Pro(guan), D-valine, glutamic acid, tryptylarginine (Trp-Arg), glycine, D-leucine, D-isoleucine, tryptophan, arginine, 4-amino-1,2,4,5-tetrahydro-2-benzazepin-3-one (Aba), 7-amino-7,8-dihydro-4H-(1,2,3)triazolo-(1,5-a)(1,4)diazepin-6(5H)-one (Ata), 4-amino-1,4,5,6-

tetrahydroazepino(4,3-*b*)indol-3(2*H*)-one (Aia), octohydroindole-2-carboxylic acid (Oic), 1-amino-1-cyclohexanecarboxylic acid (Che), tetrahydro-isoquinoline-3-carboxylic acid (Tic), and indoline-2-carboxylic acid (Ioc),

R^4 is selected from the group consisting of histidine, D-phenylalanine, L-phenylalanine, D-Nal(2′), aspartic acid, dBip, glycine, proline, cysteine, para-chloro-D-phenylalanine (p(Cl)dPhe), para-iodo-D-phenylalanine (p(I)dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-trifluoromethyl-D-phenylalanine (p(CF_3)dPhe);

R^5 is absent or is selected from the group consisting of arginine, homoarginine, proline, *trans*Pro(guan), *cis*Pro(guan), Pip, Nip, Tic, Phg, Sar, Azt, phenylalanine, D-Nal(2′), D-histidine, D-alanine, D-aspartic acid, D-glutamic acid, cysteine, and p(I)dPhe;

R^6 is absent or is selected from the group consisting of L-tryptophan, D-phenylalanine, D-Nal(2′), L-Nal(2′), Tic, Bip, arginine, D-histidine, cysteine, D-Nal(1’), Aba, Ata, D-tyrosine, Pen, dPen, and D-alanine;

R^7 is absent or is selected from the group consisting of glycine, aspartic acid, glutamic acid, cysteine, lysine, ornithine, 2,3-diamino-propionic acid (Dap), methionine, proline, tryptophan, D-Nal(2′), and tetrahydro-isoquinoline-3-carboxylic acid (Tic);

R^8 is absent or is lysine;

R^9-R^{20} are absent;

X^1 is absent or is selected from the group consisting of D-cysteine, L-cysteine, D-threonine, D-proline, L-proline, D-alanine, L-alanine, β-alanine, D-arginine, L-arginine, D-valine, L-valine, D-leucine, L-leucine, D-isoleucine, L-isoleucine, norvaline, glycine, methionine, lysine, phenylalanine, tyrosine, glutamic acid, asparagine, aspartic acid, acetylated D-arginine, acetylated L-arginine, acetylated D-valine, and acetylated norleucine;

X^2 is absent or is D-proline;

X^3 is absent;

Y^1 is absent or is selected from the group consisting of D-valine, D-tert-leucine, L-tert-leucine, norleucine, and D-proline;

Y^2 is absent or is selected from the group consisting of D-proline, L-proline, Hyp, D-valine, L-valine, D-tert-leucine, L-tert-leucine, norleucine, and glycine;

Y^3 is absent or is selected from the group consisting of D-lysine, L-lysine, D-proline, L-proline, D-valine, and L-valine;

Y^4 is absent or is D-aspartic acid or aspartic acid;

Y^5-Y^8 are absent;

the non-naturally occurring melanocortin analog is optionally cyclized through a moiety selected from the group consisting of:

a disulfide bond between R^1 and R^7 when R^1 is cysteine and R^7 is cysteine;

a lactam bridge between R^1 and R^7 when R^1 is norleucine and R^7 is glutamic acid;

a side-chain lactam bridge between R^1 or R^2 and R^7 when R^1 or R^2 is glutamic acid or aspartic acid, and R^7 is lysine, Dap, or ornithine;

a side-chain lactam bridge between R^2 and R^7 when R^2 is lysine, and R^7 is glutamic acid or aspartic acid;

a side-chain lactam bridge between R^1 or R^2 and R^8 when R^1 or R^2 is glutamic acid or aspartic acid, R^8 is lysine, and R^7 is proline, glycine or tryptophan;

provided that:

when R^2 is dAsp, then R^7 is not dLys;

when R^2-R^4 is Asp-His-dNal(2'), Asp-Pro-dNal(2') or Asp-Pro-dPhe, then R^5-R^7 is not Arg-Trp-Lys;

when Y^1 is dPro, Y^2 is dVal, and Y^3-Y^8 are absent, then R^4 is not dNal(2') or R^4 is dNal(2') and the C-terminus is not modified;

when R^3 is Aba, Ata, or Aia, R^6 is Aia, or R^7 is Orn, then R^4 is not dNal(2'), or R^4 is dNal(2') and R^5 is not Arg;

when R^4 is p(Cl)dPhe, then R^3 is not Pro or His;

when R^4 is p(I)dPhe then the non-naturally occurring melanocortin analog is cyclized through a side-chain lactam bridge between R^1 and R^7 and at least one of R^2 and R^3 is Pro;

when Y^2-Y^4 are absent, then Y^1 is absent or is norleucine;

when R^2 is Pro or Y^2 is Hyp, then R^3 is not Pro;

when R^3, R^5, or R^6 is absent, then the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between R^1 and R^7 or X^1-X^2 are present and are Ac-dVal-dPro;

when R^2-R^7 is Asp-Pro-dNal(2')-Arg-Trp-Lys (SEQ ID NO: 526) or Cys-Pro-dNal(2')-Arg-Trp-Cys (SEQ ID NO: 527), then R^1 is not Ac-Nle or Y^1-Y^2 is not dVal-dPro, dVal-dVal, dPro-dPro; and

when the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between R^2 and R^8, then R^3 is not His or Y^1 is not dVal.

[0109] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2.

[0110] In some embodiments, the chemotherapy comprises at least one chemotherapeutic agent.

[0111] In some embodiments, the at least one chemotherapeutic agent comprises one or more chemotherapeutic agents selected from the group consisting of a platinum-coordination complex, an antimetabolite, a tubulin binding agent or a plant alkaloid, an alkylating antineoplastic agent, and a cytotoxic antibiotic.

[0112] In some embodiments, the at least one chemotherapeutic agent comprises a platinum-coordination complex.

[0113] In some embodiments, the at least one chemotherapeutic agent comprises an antimetabolite.

[0114] In some embodiments, the at least one chemotherapeutic agent comprises a tubulin binding agent or a plant alkaloid.

[0115] In some embodiments, the at least one chemotherapeutic agent comprises an alkylating antineoplastic agent.

[0116] In some embodiments, the at least one chemotherapeutic agent comprises a cytotoxic antibiotic.

[0117] In some embodiments, the platinum-coordination complex is carboplatin and/or cisplatin.

[0118] In some embodiments, the antimetabolite is at least one selected from the group consisting of 5-fluorouracil (5-FU), 6-mercaptopurine, azacitidine, capecitabine, clofarabine, cytarabine, floxuridine, fludarabine, gemcitabine, methotrexate, pemetrexed, pentostatin, pralatrexate, trifluridine, and tipiracil.

[0119] In some embodiments, the tubulin binding agent or the plant alkaloid is at least one selected from the group consisting of vincristine, vinblastine, vinorelbine, paclitaxel, docetaxel, etoposide, teniposide, irinotecan, and Topotecan.

[0120] In some embodiments, the alkylating antineoplastic agent is at least one selected from the group consisting of altretamine, busulfan, carmustine, cyclophosphamide, dacarbazine, ifosfamide, lomustine, melphalan, temozolomide, and trabectedin.

[0121] In some embodiments, the cytotoxic antibiotic is at least one selected from the group consisting of daunorubicin, doxorubicin, doxorubicin liposomal, epirubicin, idarubicin, and valrubicin.

[0122] In some embodiments, the platinum-coordination complex is cisplatin.

[0123] In some embodiments, the antimetabolite is 5-fluorouracil (5-FU).

[0124] In some embodiments, the tubulin binding agent or the plant alkaloid is vincristine.

[0125] In some embodiments, the alkylating antineoplastic agent is cyclophosphamide.

[0126] In some embodiments, the cancer is at least one selected from the group consisting of bone cancer, testicular cancer, gastric cancer, sarcoma, lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, leukemia, head and neck cancer, squamous cell head and neck cancer, thymic cancer, epithelial cancer, salivary cancer, liver cancer, stomach cancer, thyroid cancer, lung cancer, ovarian cancer, breast cancer, prostate cancer, esophageal cancer, pancreatic cancer, glioma, leukemia, multiple myeloma, renal cell carcinoma, bladder cancer, cervical cancer, choriocarcinoma, colorectal cancer, oral cancer, skin cancer, and melanoma.

[0127] In some embodiments, the cancer is at least one selected from the group consisting of bone cancer, lung cancer, testicular cancer, breast cancer, prostate

cancer, colorectal cancer, non-Hodgkin's lymphoma, ovarian cancer, cervical cancer, bladder cancer, and head and neck cancer.

[0128] In some embodiments, the cancer is breast cancer, and wherein the anti-cancer agent is at least one selected from the group consisting of an anthracycline, cyclophosphamide, epirubicin, fluorouracil, methotrexate, a taxane, and docetaxel.

[0129] In some embodiments, the anthracycline is doxorubicin.

[0130] In some embodiments, the taxane is paclitaxel.

[0131] In some embodiments, the cancer is lung cancer, and the anti-cancer agent is at least one selected from the group consisting of cisplatin, carboplatin, paclitaxel, albumin-bound paclitaxel, docetaxel, gemcitabine, vinorelbine, etoposide, and pemetrexed.

[0132] In some embodiments, the cancer is prostate cancer, and the anti-cancer agent is at least one selected from the group consisting of docetaxel, cabazitaxel, mitoxantrone, and estramustine.

[0133] In some embodiments, the cancer is colorectal cancer, and the anti-cancer agent is at least one selected from the group consisting of 5-FU, capecitabine, irinotecan, oxaliplatin, trifluridine, and tipiracil.

[0134] In some embodiments, the cancer is colorectal cancer, the subject is receiving radiation therapy, and wherein the chemotherapy is at least one selected from the group consisting of cisplatin, cisplatin plus 5-FU, and mitomycin plus 5-FU.

[0135] In some embodiments, the cancer is colorectal cancer, the subject is not receiving radiation therapy, and wherein the chemotherapy is at least one selected from the group consisting of gemcitabine plus cisplatin, methotrexate, vinblastine, doxorubicin, plus cisplatin, cisplatin, methotrexate, plus vinblastine, and gemcitabine plus paclitaxel.

[0136] In some embodiments, the cancer is melanoma, and the anti-cancer agent is dacarbazine and/or temozolomide.

[0137] In some embodiments, the cancer is non-Hodgkin's lymphoma, and the anti-cancer agent is at least one selected from the group consisting of cyclophosphamide, chlorambucil, bendamustine, ifosfamide, prednisone,

dexamethasone, cisplatin, carboplatin, oxaliplatin, fludarabine, pentostatin, cladribine (2-CdA), cytarabine (ara-C), gemcitabine, methotrexate, pralatrexate, doxorubicin, liposomal doxorubicin, hydroxydaunorubicin, vincristine, mitoxantrone, etoposide, and bleomycin.

[0138] In some embodiments, the method or the use does not reduce efficacy of the anti-cancer agent.

[0139] In some embodiments, the subject with a cancer has previously undergone a treatment with the anti-cancer agent.

[0140] In some embodiments, the subject has previously experienced one or more adverse side effects when treated with the anti-cancer agent, wherein the adverse side effects are selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, and appetite reduction or loss of appetite.

[0141] In some embodiments, the subject is a human.

[0142] In some embodiments, the subject is an animal.

[0143] In some embodiments, the muscle mass loss is cardiac muscle mass loss, skeletal muscle mass loss, or both.

[0144] In some embodiments, the cardiac muscle mass loss is determined by measuring change in heart weight.

[0145] In some embodiments, the skeletal muscle mass loss is determined by measuring change in gastrocnemius tissue weight.

[0146] In some embodiments, anorexia is determined by daily food intake, daily food consumption, and/or weekly food intake.

[0147] In some embodiments, the daily food intake is determined by total calories (kcal) consumed in 1 day or mass of food (grams or kilograms) consumed in 1 day.

[0148] In some embodiments, the daily food consumption is determined by the daily food intake normalized to daily body weight of the subject.

[0149] In some embodiments, the weekly food intake is determined total calories (kcal) consumed in 1 day or mass of food (grams or kilograms) consumed in 1 week.

[0150] In some embodiments, the weight loss is determined by daily body weight, and/or daily body weight gain.

[0151] In some embodiments, the fat mass of the subject treated with the method is at least 10% to 100% greater than a baseline or control, and the baseline or control is the subject prior to the administration of the non-naturally occurring melanocortin analog and/or a subject who is receiving or has received the anti-cancer agent without the non-naturally occurring melanocortin analog.

[0152] In some embodiments, the heart weight of the subject treated with the method is at least 0.1% to 10% greater than a baseline or control, and the baseline or control is the subject prior to the administration of the non-naturally occurring melanocortin analog and/or a subject who is receiving or has received the anti-cancer agent without the non-naturally occurring melanocortin analog.

[0153] In some embodiments, the gastrocnemius tissue weight of the subject treated with the method is at least 0.1% to 10% greater than a baseline or control, and the baseline or control is the subject prior to the administration of the non-naturally occurring melanocortin analog and/or a subject who is receiving or has received the anti-cancer agent without the non-naturally occurring melanocortin analog.

[0154] In some embodiments, the daily food intake of the subject treated with the method is at least 5% to 50% greater than a baseline or control, and the baseline or control is the subject prior to the administration of the non-naturally occurring melanocortin analog and/or a subject who is receiving or has received the anti-cancer agent without the non-naturally occurring melanocortin analog.

[0155] In some embodiments, appetite of the subject is increased by at least 10% to 200% after the administration of the non-naturally occurring melanocortin analog.

[0156] In some embodiments, appetite of the subject is increased by at least 25% to 100% after the administration of the non-naturally occurring melanocortin analog.

[0157] In some embodiments, appetite is increased for at least 1 day, 1 week, 1 month, 3 months, 6 months, 1 year, or 5 years during the administration.

[0158] In some embodiments, appetite is increased for at least 1 day, 5 days, 7 days, 14 days, 21 days, 28 days, 35 days, 40 days, 45 days, 50 days, 60 days, 75 days, 90 days, 100 days, 110 days, or 120 days during the administration.

[0159] In some embodiments, the increased appetite is maintained for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks, 3 weeks, 1 month, 3 months, 6 months, 1 year, or 5 years, after the administration is stopped.

[0160] In some embodiments, the appetite is assessed by a scale for measuring desire to eat, feeling of hunger, and/or level of satiety.

[0161] In some embodiments, the appetite is assessed between meals.

[0162] In some embodiments, the subject comprises two or more subjects, and wherein the appetite is an average appetite of the two or more subjects.

[0163] In some embodiments, anorexia is determined by food consumption.

[0164] In some embodiments, the non-naturally occurring melanocortin analog is present in a pharmaceutical composition.

[0165] In some embodiments, the pharmaceutical composition further comprises a pharmaceutical salt.

[0166] In some embodiments, the pharmaceutical composition further comprises a pharmaceutical carrier.

[0167] In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of 0.1 mg/mL to 500 mg/mL, relative to a total volume of the pharmaceutical composition.

[0168] In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of about 50 mg/mL, relative to a total volume of the pharmaceutical composition.

[0169] In some embodiments, the non-naturally occurring melanocortin analog is administered via intraperitoneal, intravenous, parenteral, subcutaneous, intramuscular, intracerebroventricular, intranasal, or oral administration.

[0170] In some embodiments, the pharmaceutical composition comprising the non-naturally occurring melanocortin analog is administered to the subject parenterally.

[0171] In some embodiments, the pharmaceutical composition comprising the non-naturally occurring melanocortin analog is administered to the subject subcutaneously.

[0172] In some embodiments, the non-naturally occurring melanocortin analog crosses the blood-brain-barrier of the subject.

[0173] In some embodiments, the pharmaceutical carrier comprises water.

[0174] In some embodiments, the non-naturally occurring melanocortin analog is administered to a subject prior to or after a meal.

[0175] In some embodiments, the non-naturally occurring melanocortin analog is administered to a subject with a meal.

[0176] In some embodiments, a therapeutically effective amount of the non-naturally occurring melanocortin analog is administered, and wherein the therapeutically effective amount of the non-naturally occurring melanocortin analog is from 0.001 mg/kg to 25 mg/kg per body weight of the subject.

[0177] In some embodiments, the therapeutically effective amount of the non-naturally occurring melanocortin analog is from 0.5 mg/kg to 10 mg/kg per body weight of the subject.

[0178] In some embodiments, the non-naturally occurring melanocortin analog is administered at least once daily in an amount ranging from 0.001 mg/kg to 25 mg/kg per body weight of the subject.

[0179] In some embodiments, the non-naturally occurring melanocortin analog is administered at least once daily in an amount ranging from about 0.5 mg/kg to about 10 mg/kg per body weight of the subject.

[0180] In some embodiments, the non-naturally occurring melanocortin analog is administered to the subject for at least 1 day, 1 week, 1 month, 3 months, 6 months, 1 year, or 5 years.

[0181] In some embodiments, the non-naturally occurring melanocortin analog is administered to the subject for 1 day, 5 days, 7 days, 14 days, 21 days, 28 days, 35 days, 40 days, 45 days, 50 days, 60 days, 75 days, 90 days, 100 days, 110 days, or 120 days.

[0182] In some embodiments, the anti-cancer agent and the non-naturally occurring melanocortin analog are administered simultaneously as a single composition.

[0183] In some embodiments, the non-naturally occurring melanocortin analog is present in the single composition in a concentration of 0.1 mg/mL to 500 mg/mL, relative to a total volume of the single composition.

[0184] In some embodiments, the non-naturally occurring melanocortin analog is present in the single composition in a concentration of about 10 mg/mL, about 20 mg/mL, about 30 mg/mL, about 40 mg/mL, about 50 mg/mL, or about 60 mg/mL, relative to a total volume of the single composition.

[0185] In some embodiments, the non-naturally occurring melanocortin analog is present in the single composition in a concentration of about 50 mg/mL, relative to a total volume of the single composition.

[0186] In some embodiments, the non-naturally occurring melanocortin analog is present in the single composition at a dose of about 5 mg to about 500 mg in a dose volume of about 1 mL to 20 mL, and wherein the administration is performed once, twice, 3 times, 4 times, 5 times, or 10 times per day.

[0187] In some embodiments, the non-naturally occurring melanocortin analog is present in the single composition at a dose of about 50 mg to about 100 mg in a dose volume of about 2 mL to 10 mL, and wherein the administration is performed once, twice, 3 times, 4 times, 5 times, or 10 times per day.

[0188] In some embodiments, the non-naturally occurring melanocortin analog is present in the single composition at a dose of about 75 mg in a dose volume of about 5 mL, and wherein the administration is performed once, twice, 3 times, 4 times, 5 times, or 10 times per day.

[0189] In some embodiments, the administration is performed once per day.

[0190] In some embodiments, the anti-cancer agent is present in a first pharmaceutical composition; and the non-naturally occurring melanocortin analog is present in a second pharmaceutical composition.

[0191] In some embodiments, the first and the second pharmaceutical compositions are different and are administered sequentially.

[0192] In some embodiments, the first and the second pharmaceutical compositions are different and are administered simultaneously but separately.

[0193] In some embodiments, the second pharmaceutical composition is administered subcutaneously.

[0194] In some embodiments, anti-cancer agent comprises a chemotherapy, and the chemotherapy is present in the first pharmaceutical composition in a concentration of 0.001 mg/mL to 1,000 mg/mL, relative to a total volume of the first pharmaceutical composition.

[0195] In some embodiments, the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition in a concentration of 0.1 mg/mL to 500 mg/mL, relative to a total volume of the second pharmaceutical composition.

[0196] In some embodiments, the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition in a concentration of about 10 mg/mL, about 20 mg/mL, about 30 mg/mL, about 40 mg/mL, about 50 mg/mL, or about 60 mg/mL, relative to a total volume of the second pharmaceutical composition.

[0197] In some embodiments, the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition in a concentration of about 50 mg/mL, relative to a total volume of the second pharmaceutical composition.

[0198] In some embodiments, the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition at a dose of about 5 mg to about 500 mg in a dose volume of about 1 mL to 20 mL, and wherein the administration is performed once, twice, 3 times, 4 times, 5 times, or 10 times per day.

[0199] In some embodiments, the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition at a dose of about 50 mg to about 100 mg in a dose volume of about 2 mL to 10 mL, and wherein the administration is performed once, twice, 3 times, 4 times, 5 times, or 10 times per day.

[0200] In some embodiments, the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition at a dose of about 75 mg in a dose volume of about 5 mL, and wherein the administration is performed once, twice, 3 times, 4 times, 5 times, or 10 times per day.

BRIEF DESCRIPTION OF THE DRAWINGS

[0201] FIG. 1A is a graph depicting daily food intake of Sprague Dawley rats in a chemotherapy dose-response study. The graph compares the daily food intakes in the rats administered with saline (Group 1), 2.5 mg/kg/week cisplatin (Group 2), 5 mg/kg/week cisplatin (Group 3), 62.5 mg/kg/week 5-FU (Group 4), and 125 mg/kg/week 5-FU (Group 5), respectively, for 21 days. Mortality was observed in rats treated with high dose of cisplatin (Group 3, 5 mg/kg/week cisplatin) or 5-FU (Group 5, 125 mg/kg/week 5-FU) after the second cycle of chemotherapy. Therefore, the third cycle of chemotherapy was discontinued to ensure survival of both high dose groups.

[0202] FIG. 1B is a graph depicting daily food consumption of Sprague Dawley rats in a chemotherapy dose-response study. The graph compares the daily food consumptions (i.e., daily food intake normalized to daily body weight) in the rats administered with saline (Group 1), 2.5 mg/kg/week cisplatin (Group 2), 5 mg/kg/week cisplatin (Group 3), 62.5 mg/kg/week 5-FU (Group 4), and 125 mg/kg/week 5-FU (Group 5), respectively, for 21 days. Mortality was observed in rats treated with high dose of cisplatin (Group 3, 5 mg/kg/week cisplatin) or 5-FU (Group 5, 125 mg/kg/week 5-FU) after the second cycle of chemotherapy. Therefore, the third cycle of chemotherapy was discontinued to ensure survival of both high dose groups.

[0203] FIG. 1C is a graph depicting daily body weight of Sprague Dawley rats in a chemotherapy dose-response study. The graph compares the daily body weights in the rats administered with saline (Group 1), 2.5 mg/kg/week cisplatin (Group 2), 5 mg/kg/week cisplatin (Group 3), 62.5 mg/kg/week 5-FU (Group 4), and 125 mg/kg/week 5-FU (Group 5), respectively, for 21 days. Mortality was observed in rats treated with high dose of cisplatin (Group 3, 5 mg/kg/week cisplatin) or 5-FU (Group 5, 125 mg/kg/week 5-FU) after the second cycle of chemotherapy. Therefore, the third cycle of chemotherapy was discontinued to ensure survival of both high dose groups.

[0204] FIG. 1D is a graph depicting daily body weight gain of Sprague Dawley rats in a chemotherapy dose-response study. The graph compares the daily body weight gains (% initial) in the rats administered with saline (Group 1), 2.5 mg/kg/week cisplatin (Group 2), 5 mg/kg/week cisplatin (Group 3), 62.5 mg/kg/week 5-FU (Group 4), and 125 mg/kg/week 5-FU (Group 5), respectively, for 21 days. Mortality was observed in rats treated with high dose of cisplatin (Group 3, 5 mg/kg/week cisplatin) or 5-FU (Group 5,

125 mg/kg/week 5-FU) after the second cycle of chemotherapy. Therefore, the third cycle of chemotherapy was discontinued to ensure survival of both high dose groups.

[0205] FIG. 2A is a graph depicting locomotor activity in dark phase of Sprague Dawley rats in a chemotherapy dose-response study. The graph compares the locomotor activities in dark phase in the rats administered with saline (Group 1), 2.5 mg/kg/week cisplatin (Group 2), 5 mg/kg/week cisplatin (Group 3), 62.5 mg/kg/week 5-FU (Group 4), and 125 mg/kg/week 5-FU (Group 5), respectively, for 21 days. The locomotor activities in dark phase are monitored from 5 days prior to the administration until 21 days after administration of the initial dose. Mortality was observed in rats treated with high dose of cisplatin (Group 3, 5 mg/kg/week cisplatin) or 5-FU (Group 5, 125 mg/kg/week 5-FU) after the second cycle of chemotherapy. Therefore, the third cycle of chemotherapy was discontinued to ensure survival of both high dose groups.

[0206] FIG. 2B is a graph depicting locomotor activity in light phase of Sprague Dawley rats in a chemotherapy dose-response study. The graph compares the locomotor activities in light phase in the rats administered with saline (Group 1), 2.5 mg/kg/week cisplatin (Group 2), 5 mg/kg/week cisplatin (Group 3), 62.5 mg/kg/week 5-FU (Group 4), and 125 mg/kg/week 5-FU (Group 5), respectively, for 21 days. The locomotor activities in light phase are monitored from 5 days prior to the administration until 21 days after administration of the initial dose. Mortality was observed in rats treated with high dose of cisplatin (Group 3, 5 mg/kg/week cisplatin) or 5-FU (Group 5, 125 mg/kg/week 5-FU) after the second cycle of chemotherapy. Therefore, the third cycle of chemotherapy was discontinued to ensure survival of both high dose groups.

[0207] FIG. 2C is a graph depicting locomotor activity (% of baseline) in dark phase of Sprague Dawley rats in a chemotherapy dose-response study. The graph compares the locomotor activities (% of baseline) in dark phase in the rats administered with saline (Group 1), 2.5 mg/kg/week cisplatin (Group 2), 5 mg/kg/week cisplatin (Group 3), 62.5 mg/kg/week 5-FU (Group 4), and 125 mg/kg/week 5-FU (Group 5), respectively, for 21 days. The locomotor activities in dark phase are monitored from 5 days prior to the administration until 21 days after administration of the initial dose. Mortality was observed in rats treated with high dose of cisplatin (Group 3, 5 mg/kg/week cisplatin) or 5-FU (Group 5, 125 mg/kg/week 5-FU) after the second cycle of chemotherapy.

Therefore, the third cycle of chemotherapy was discontinued to ensure survival of both high dose groups.

[0208] FIG. 2D is a graph depicting locomotor activity (% of baseline) in light phase of Sprague Dawley rats in a chemotherapy dose-response study. The graph compares the locomotor activities (% of baseline) in light phase in the rats administered with saline (Group 1), 2.5 mg/kg/week cisplatin (Group 2), 5 mg/kg/week cisplatin (Group 3), 62.5 mg/kg/week 5-FU (Group 4), and 125 mg/kg/week 5-FU (Group 5), respectively, for 21 days. The locomotor activities in light phase are monitored from 5 days prior to the administration until 21 days after administration of the initial dose. Mortality was observed in rats treated with high dose of cisplatin (Group 3, 5 mg/kg/week cisplatin) or 5-FU (Group 5, 125 mg/kg/week 5-FU) after the second cycle of chemotherapy. Therefore, the third cycle of chemotherapy was discontinued to ensure survival of both high dose groups.

[0209] FIG. 3 is a bar graph depicting fat mass, lean mass, and total water changes of Sprague Dawley rats after a chemotherapy dose-response study. The graph compares the changes in fat mass, lean mass, and total water of the rats after administration with saline (Group 1), 2.5 mg/kg/week cisplatin (Group 2), 5 mg/kg/week cisplatin (Group 3), 62.5 mg/kg/week 5-FU (Group 4), and 125 mg/kg/week 5-FU (Group 5), respectively, for 21 days.

[0210] FIG. 4 is a bar graph depicting serum GDF-15 (growth differentiation factor-15) concentration of Sprague Dawley rats after a chemotherapy dose-response study. The graph compares the serum GDF-15 concentrations of the rats after administration with saline (Group 1), 2.5 mg/kg/week cisplatin (Group 2), 5 mg/kg/week cisplatin (Group 3), 62.5 mg/kg/week 5-FU (Group 4), and 125 mg/kg/week 5-FU (Group 5), respectively, for 21 days.

[0211] FIG. 5 is a graph depicting the design of studies using one or more compositions of the present technology.

[0212] FIG. 6A is a graph depicting daily food intake of Sprague Dawley rats in a combination therapy study. The graph compares the daily food intakes in the rats administered with 2.5 mg/kg/week cisplatin plus saline (Group 1), 2.5 mg/kg/week cisplatin plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3),

respectively, for 21 days. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0213] FIG. 6B is a graph depicting daily food intake of Sprague Dawley rats in a combination therapy study. The graph compares the daily food intakes in the rats administered with 70 mg/kg/week 5-FU plus saline (Group 1), 70 mg/kg/week 5-FU plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0214] FIG. 6C is a graph depicting daily food consumption of Sprague Dawley rats in a combination therapy study. The graph compares the daily food consumptions (i.e., daily food intake normalized to daily body weight) in the rats administered with 2.5 mg/kg/week cisplatin plus saline (Group 1), 2.5 mg/kg/week cisplatin plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0215] FIG. 6D is a graph depicting daily food consumption of Sprague Dawley rats in a combination therapy study. The graph compares the daily food consumptions (i.e., daily food intake normalized to daily body weight) in the rats administered with 70 mg/kg/week 5-FU plus saline (Group 1), 70 mg/kg/week 5-FU plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0216] FIG. 7A is a graph depicting cumulative food intake of Sprague Dawley rats in a combination therapy study. The graph compares the cumulative food intakes in the rats administered with 2.5 mg/kg/week cisplatin plus saline (Group 1), 2.5 mg/kg/week cisplatin plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0217] FIG. 7B is a graph depicting cumulative food intake of Sprague Dawley rats in a combination therapy study. The graph compares the cumulative food intakes in the rats administered with 70 mg/kg/week 5-FU plus saline (Group 1), 70 mg/kg/week 5-FU plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0218] FIG. 7C is a graph depicting weekly food intake of Sprague Dawley rats in a combination therapy study. The graph compares the weekly food intakes in the rats administered with 2.5 mg/kg/week cisplatin plus saline (Group 1), 2.5 mg/kg/week cisplatin plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days.

[0219] FIG. 7D is a graph depicting weekly food intake of Sprague Dawley rats in a combination therapy study. The graph compares the weekly food intakes in the rats administered with 70 mg/kg/week 5-FU plus saline (Group 1), 70 mg/kg/week 5-FU plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days.

[0220] FIG. 8A is a graph depicting daily food intake of Sprague Dawley rats in a combination therapy study. The graph compares the daily food intakes in the rats administered with 65 mg/kg/week cyclophosphamide plus saline (Group 1), 65 mg/kg/week cyclophosphamide plus 3 mg/kg/day TCMCB07 (Group 2), saline plus saline, (Group 3), and saline plus 3 mg/kg/day TCMCB07 (Group 4), respectively, for 21 days. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0221] FIG. 8B is a graph depicting cumulative food intake of Sprague Dawley rats in a combination therapy study. The graph compares the cumulative food intakes in the rats administered with 65 mg/kg/week cyclophosphamide plus saline (Group 1), 65 mg/kg/week cyclophosphamide plus 3 mg/kg/day TCMCB07 (Group 2), saline plus saline, (Group 3), and saline plus 3 mg/kg/day TCMCB07 (Group 4), respectively, for 21 days. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0222] FIG. 9A is a graph depicting daily food intake of Sprague Dawley rats in a combination therapy study. The graph compares the daily food intakes in the rats administered with 0.27 mg/kg/week vincristine plus saline (Group 1), 0.27 mg/kg/week vincristine plus 3 mg/kg/day TCMCB07 (Group 2), saline plus saline, (Group 3), and saline plus 3 mg/kg/day TCMCB07 (Group 4), respectively, for 21 days. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0223] FIG. 9B is a graph depicting cumulative food intake of Sprague Dawley rats in a combination therapy study. The graph compares the cumulative food intakes in the rats administered with 0.27 mg/kg/week vincristine plus saline (Group 1), 0.27 mg/kg/week vincristine plus 3 mg/kg/day TCMCB07 (Group 2), saline plus saline,

(Group 3), and saline plus 3 mg/kg/day TCMCB07 (Group 4), respectively, for 21 days. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0224] FIG. 10A is a graph depicting daily food intake of Sprague Dawley rats in a combination therapy study. The graph compares the daily food intakes in the rats administered cisplatin, saline, and IgG (Group 1), cisplatin plus saline plus an anti-GDF-15 monoclonal antibody (mAb) comprising a human ponsegromab Fab region ("ponsegromab"; Group 2), and cisplatin plus 3 mg/kg/day TCMCB07 plus the anti-GDF-15 mAb (Group 3). Cisplatin was administered at 5 mg/kg on day 0, 3 mg/kg on day 7, and 3 mg/kg on day 14. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0225] FIG. 10B is a graph depicting weekly food intake of Sprague Dawley rats in a combination therapy study. The graph compares the weekly food intakes in the rats administered cisplatin plus saline plus IgG (IgG (Group 1), cisplatin plus saline plus the anti-GDF-15 mAb (Group 2), and cisplatin plus 3 mg/kg/day TCMCB07 plus GDF15 the anti-GDF-15 mAb (Group 3). Cisplatin was administered at 5 mg/kg on day 0, 3 mg/kg on day 7, and 3 mg/kg on day 14. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0226] FIG. 10C is a graph depicting cumulative food intake of Sprague Dawley rats in a combination therapy study. The graph compares the cumulative food intakes in the rats administered cisplatin plus saline plus IgG (Group 1), cisplatin plus saline plus the anti-GDF-15 mAb (Group 2), and cisplatin plus 3 mg/kg/day TCMCB07 plus the anti-GDF-15 mAb (Group 3). Cisplatin was administered at 5 mg/kg on day 0, 3 mg/kg on day 7, and 3 mg/kg on day 14. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0227] FIG. 10D is a graph depicting total food intake of Sprague Dawley rats in a combination therapy study over 21 days. The graph compares total food intakes in the rats administered cisplatin plus saline plus IgG (Group 1), cisplatin plus saline plus the anti-GDF-15 mAb (Group 2), and cisplatin plus 3 mg/kg/day TCMCB07 plus the anti-GDF-15 mAb (Group 3). Cisplatin was administered at 5 mg/kg on day 0, 3 mg/kg on day 7, and 3 mg/kg on day 14. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0228] FIG. 11A is a graph depicting daily body weight of Sprague Dawley rats in a combination therapy study. The graph compares the daily body weights in the rats administered with 2.5 mg/kg/week cisplatin plus saline (Group 1), 2.5 mg/kg/week cisplatin plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0229] FIG. 11B is a graph depicting daily body weight of Sprague Dawley rats in a combination therapy study. The graph compares the daily body weights in the rats administered with 70 mg/kg/week 5-FU plus saline (Group 1), 70 mg/kg/week 5-FU plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0230] FIG. 11C is a graph depicting daily body weight gain of Sprague Dawley rats in a combination therapy study. The graph compares the daily body weight gains (% initial) in the rats administered with 2.5 mg/kg/week cisplatin plus saline (Group 1), 2.5 mg/kg/week cisplatin plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0231] FIG. 11D is a graph depicting daily body weight gain of Sprague Dawley rats in a combination therapy study. The graph compares the daily body weight gains (% initial) in the rats administered with 70 mg/kg/week 5-FU plus saline (Group 1), 70 mg/kg/week 5-FU plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0232] FIG. 11E is a graph depicting daily body weight gain of Sprague Dawley rats in a combination therapy study. The graph compares the daily body weight gains (% of day 0) in the rats administered with 2.5 mg/kg/week cisplatin plus saline (Group 1), 2.5 mg/kg/week cisplatin plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively. Daily body weight gains are shown from day -10 to day 21, where day 0 signifies initiation of cisplatin administration. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0233] FIG. 12A is a graph depicting cumulative body weight gain of Sprague Dawley rats in a combination therapy study. The graph compares the cumulative body

weight gains (% of initial) in the rats administered with 2.5 mg/kg/week cisplatin plus saline (Group 1), 2.5 mg/kg/week cisplatin plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days.

[0234] FIG. 12B is a graph depicting cumulative body weight gain of Sprague Dawley rats in a combination therapy study. The graph compares the cumulative body weight gains (% of initial) in the rats administered with 70 mg/kg/week 5-FU plus saline (Group 1), 70 mg/kg/week 5-FU plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days.

[0235] FIG. 13A is a graph depicting daily body weight gain of Sprague Dawley rats in a combination therapy study. The graph compares the daily body weight gains in the rats administered with 65 mg/kg/week cyclophosphamide plus saline (Group 1), 65 mg/kg/week cyclophosphamide plus 3 mg/kg/day TCMCB07 (Group 2), saline plus saline (Group 3), and saline plus 3 mg/kg/day TCMCB07 (Group 4), respectively, for 21 days. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0236] FIG. 13B is a graph depicting daily body weight change of Sprague Dawley rats in a combination therapy study. The graph compares the daily body weight gains (% of initial) in the rats administered with 65 mg/kg/week cyclophosphamide plus saline (Group 1), 65 mg/kg/week cyclophosphamide plus 3 mg/kg/day TCMCB07 (Group 2), saline plus saline (Group 3), and saline plus 3 mg/kg/day TCMCB07 (Group 4), respectively, for 21 days. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0237] FIG. 14A is a graph depicting daily body weight gain of Sprague Dawley rats in a combination therapy study. The graph compares the daily body weight gain in the rats administered with 0.27 mg/kg/week vincristine plus saline (Group 1), 65 0.27 mg/kg/week vincristine plus 3 mg/kg/day TCMCB07 (Group 2), saline plus saline (Group 3), and saline plus 3 mg/kg/day TCMCB07 (Group 4), respectively, for 21 days. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0238] FIG. 14B is a graph depicting daily body weight change of Sprague Dawley rats in a combination therapy study. The graph compares the daily body weight gains (% of initial) in the rats administered with 0.27 mg/kg/week vincristine plus saline (Group 1), 65 0.27 mg/kg/week vincristine plus 3 mg/kg/day TCMCB07 (Group 2), saline plus

saline (Group 3), and saline plus 3 mg/kg/day TCMCB07 (Group 4), respectively, for 21 days. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0239] FIG. 15A is a graph depicting daily body weight gain of Sprague Dawley rats in a combination therapy study. The graph compares the daily body weight gain in the rats administered cisplatin plus saline plus IgG (Group 1), cisplatin plus saline plus the anti-GDF-15 mAb of FIG. 10 (Group 2), and cisplatin plus 3 mg/kg/day TCMCB07 the anti-GDF-15 mAb of FIG. 10 (Group 3). Cisplatin was administered at 5 mg/kg on day 0, 3 mg/kg on day 7, and 3 mg/kg on day 14. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0240] FIG. 15B is a graph depicting cumulative body weight gain of Sprague Dawley rats in a combination therapy study. The graph compares the body weight change (% of initial) in the rats administered cisplatin plus saline plus (Group 1), cisplatin plus saline plus the anti-GDF-15 mAb of FIG. 10 (Group 2), and cisplatin plus 3 mg/kg/day TCMCB07 plus the anti-GDF-15 mAb of FIG. 10 (Group 3). Cisplatin was administered at 5 mg/kg on day 0, 3 mg/kg on day 7, and 3 mg/kg on day 14. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0241] FIG. 15C is a graph depicting daily body weight gain of Sprague Dawley rats in a combination therapy study. The graph compares the daily body weight change (% of initial) in the rats administered cisplatin plus saline plus IgG (Group 1), cisplatin plus saline plus the anti-GDF-15 mAb of FIG. 10 (Group 2), and cisplatin plus 3 mg/kg/day TCMCB07 plus the anti-GDF-15 mAb of FIG. 10 (Group 3). Cisplatin was administered at 5 mg/kg on day 0, 3 mg/kg on day 7, and 3 mg/kg on day 14. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0242] FIG. 15D is a graph depicting total body weight gain of Sprague Dawley rats in a combination therapy study. The graph compares the net body weight gain (% of baseline) in the rats administered cisplatin plus saline plus IgG (Group 1), cisplatin plus saline plus the anti-GDF-15 mAb of FIG. 10 (Group 2), and cisplatin plus 3 mg/kg/day TCMCB07 plus the anti-GDF-15 mAb of FIG. 10 (Group 3). Cisplatin was administered at 5 mg/kg on day 0, 3 mg/kg on day 7, and 3 mg/kg on day 14. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0243] FIG. 16A is a graph depicting daily body weight of Sprague Dawley rats in a combination therapy study. The graph compares the daily body weight in the rats

administered 2 mg/kg/week doxorubicin plus saline (Group 1), 2 mg/kg/week doxorubicin plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0244] FIG. 16B is a graph depicting daily body weight gain of Sprague Dawley rats in a combination therapy study. The graph compares the daily body weight gain (% of initial) in the rats administered 2 mg/kg/week doxorubicin plus saline (Group 1), 2 mg/kg/week doxorubicin plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0245] FIG. 16C is a graph depicting daily body weight of Sprague Dawley rats in a combination therapy study. The graph compares the daily body weight in the rats administered 2 mg/kg/week doxorubicin plus saline (Group 1), 2 mg/kg/week doxorubicin plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 63 days. Administration occurred on days 0, 7, 14, 21, 28, and 35.

[0246] FIG. 16D is a graph depicting daily body weight gain of Sprague Dawley rats in a combination therapy study. The graph compares the daily body weight gain (% of initial) in the rats administered 2 mg/kg/week doxorubicin plus saline (Group 1), 2 mg/kg/week doxorubicin plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 63 days. Administration occurred on days 0, 7, 14, 21, 28, and 35.

[0247] FIG. 17A is a bar graph depicting heart weight of Sprague Dawley rats after combination therapy. The graph compares the heart weights of the rats after administration with 2.5 mg/kg/week cisplatin plus saline (Group 1), 2.5 mg/kg/week cisplatin plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days.

[0248] FIG. 17B is a bar graph depicting heart weight of Sprague Dawley rats after combination therapy. The graph compares the heart weights of the rats after administration with 70 mg/kg/week 5-FU plus saline (Group 1), 70 mg/kg/week 5-FU plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days.

[0249] FIG. 17C is a bar graph depicting gastrocnemius weight of Sprague Dawley rats after combination therapy. The graph compares the gastrocnemius weights of the rats after administration with 2.5 mg/kg/week cisplatin plus saline (Group 1), 2.5 mg/kg/week cisplatin plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days.

[0250] FIG. 17D is a bar graph depicting gastrocnemius weight of Sprague Dawley rats after combination therapy. The graph compares the gastrocnemius weights of the rats after administration with 70 mg/kg/week 5-FU plus saline (Group 1), 70 mg/kg/week 5-FU plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days.

[0251] FIG. 17E is a bar graph depicting spleen weight of Sprague Dawley rats after combination therapy. The graph compares the spleen weights of the rats after administration with 2.5 mg/kg/week cisplatin plus saline (Group 1), 2.5 mg/kg/week cisplatin plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days.

[0252] FIG. 17F is a bar graph depicting spleen weight of Sprague Dawley rats after combination therapy. The graph compares the spleen weights of the rats after administration with 70 mg/kg/week 5-FU plus saline (Group 1), 70 mg/kg/week 5-FU plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days.

[0253] FIG. 18A is a bar graph depicting heart weight of Sprague Dawley rats after combination therapy. The graph compares heart weights of rats administered with 65 mg/kg/week cyclophosphamide plus saline (Group 1), 65 mg/kg/week cyclophosphamide plus 3 mg/kg/day TCMCB07 (Group 2), saline plus saline (Group 3), and saline plus 3 mg/kg/day TCMCB07 (Group 4), respectively, for 21 days. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0254] FIG. 18B is a bar graph depicting gastrocnemius weight of Sprague Dawley rats after combination therapy. The graph compares gastrocnemius weights of rats administered with 65 mg/kg/week cyclophosphamide plus saline (Group 1), 65 mg/kg/week cyclophosphamide plus 3 mg/kg/day TCMCB07 (Group 2), saline plus saline (Group 3), and saline plus 3 mg/kg/day TCMCB07 (Group 4), respectively, for 21 days. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0255] FIG. 19A is a bar graph depicting heart weight of Sprague Dawley rats after combination therapy. The graph compares heart weights of rats administered with 0.27 mg/kg/week vincristine plus saline (Group 1), 0.27 mg/kg/week vincristine plus 3 mg/kg/day TCMCB07 (Group 2), saline plus saline (Group 3), and saline plus 3 mg/kg/day TCMCB07 (Group 4), respectively, for 21 days. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0256] FIG. 19B is a bar graph depicting gastrocnemius weight of Sprague Dawley rats after combination therapy. The graph compares gastrocnemius weights of rats administered with 0.27 mg/kg/week vincristine plus saline (Group 1), 0.27 mg/kg/week vincristine plus 3 mg/kg/day TCMCB07 (Group 2), saline plus saline (Group 3), and saline plus 3 mg/kg/day TCMCB07 (Group 4), respectively, for 21 days. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0257] FIG. 20A is a bar graph depicting fat mass gain of Sprague Dawley rats after combination therapy. The graph compares the fat mass gains of the rats after administration with 2.5 mg/kg/week cisplatin plus saline (Group 1), 2.5 mg/kg/week cisplatin plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days.

[0258] FIG. 20B is a bar graph depicting fat mass gain of Sprague Dawley rats after combination therapy. The graph compares the fat mass gains of the rats after administration with 70 mg/kg/week 5-FU plus saline (Group 1), 70 mg/kg/week 5-FU plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days.

[0259] FIG. 20C is a bar graph depicting lean mass gain of Sprague Dawley rats after combination therapy. The graph compares the lean mass gains of the rats after administration with 2.5 mg/kg/week cisplatin plus saline (Group 1), 2.5 mg/kg/week cisplatin plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days.

[0260] FIG. 20D is a bar graph depicting lean mass gain of Sprague Dawley rats after combination therapy. The graph compares the lean mass gains of the rats after administration with 70 mg/kg/week 5-FU plus saline (Group 1), 70 mg/kg/week 5-FU plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days.

[0261] FIG. 21A is a bar graph depicting fat mass of Sprague Dawley rats after combination therapy. The graph compares the fat mass of the rats before and after administration with 65 mg/kg/week cyclophosphamide plus saline (Group 1), 65 mg/kg/week cyclophosphamide plus 3 mg/kg/day TCMCB07 (Group 2), saline plus saline (Group 3), and saline plus 3 mg/kg/day TCMCB07 (Group 4), respectively, for 21 days. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0262] FIG. 21B is a bar graph depicting fat mass gain of Sprague Dawley rats after combination therapy. The graph compares the fat mass gain (% of initial) of the rats after administration with 65 mg/kg/week cyclophosphamide plus saline (Group 1), 65 mg/kg/week cyclophosphamide plus 3 mg/kg/day TCMCB07 (Group 2), saline plus saline (Group 3), and saline plus 3 mg/kg/day TCMCB07 (Group 4), respectively, for 21 days. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0263] FIG. 21C is a bar graph depicting lean mass of Sprague Dawley rats after combination therapy. The graph compares the lean mass of the rats before and after administration with 65 mg/kg/week cyclophosphamide plus saline (Group 1), 65 mg/kg/week cyclophosphamide plus 3 mg/kg/day TCMCB07 (Group 2), saline plus saline (Group 3), and saline plus 3 mg/kg/day TCMCB07 (Group 4), respectively, for 21 days. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0264] FIG. 21D is a bar graph depicting lean mass gain of Sprague Dawley rats after combination therapy. The graph compares the lean mass gain (% of initial) of the rats after administration with 65 mg/kg/week cyclophosphamide plus saline (Group 1), 65 mg/kg/week cyclophosphamide plus 3 mg/kg/day TCMCB07 (Group 2), saline plus saline (Group 3), and saline plus 3 mg/kg/day TCMCB07 (Group 4), respectively, for 21 days. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0265] FIG. 22A is a bar graph depicting fat mass of Sprague Dawley rats after combination therapy. The graph compares the fat mass of the rats before and after administration with 0.27 mg/kg/week vincristine plus saline (Group 1), 0.27 mg/kg/week vincristine plus 3 mg/kg/day TCMCB07 (Group 2), saline plus saline (Group 3), and saline plus 3 mg/kg/day TCMCB07 (Group 4), respectively, for 21 days. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0266] FIG. 22B is a bar graph depicting fat mass gain of Sprague Dawley rats after combination therapy. The graph compares the fat mass gain (% of initial) of the

rats after administration with 0.27 mg/kg/week vincristine plus saline (Group 1), 0.27 mg/kg/week vincristine plus 3 mg/kg/day TCMCB07 (Group 2), saline plus saline (Group 3), and saline plus 3 mg/kg/day TCMCB07 (Group 4), respectively, for 21 days. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0267] FIG. 22C is a bar graph depicting lean mass of Sprague Dawley rats after combination therapy. The graph compares the lean mass of the rats before and after administration with 0.27 mg/kg/week vincristine plus saline (Group 1), 0.27 mg/kg/week vincristine plus 3 mg/kg/day TCMCB07 (Group 2), saline plus saline (Group 3), and saline plus 3 mg/kg/day TCMCB07 (Group 4), respectively, for 21 days. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0268] FIG. 22D is a bar graph depicting lean mass gain of Sprague Dawley rats after combination therapy. The graph compares the lean mass gain (% of initial) of the rats after administration with 0.27 mg/kg/week vincristine plus saline (Group 1), 0.27 mg/kg/week vincristine plus 3 mg/kg/day TCMCB07 (Group 2), saline plus saline (Group 3), and saline plus 3 mg/kg/day TCMCB07 (Group 4), respectively, for 21 days. The cutoffs for significance are * (or #, &)<.05, **<.01, ***<.001 ****<.0001.

[0269] FIG. 23A is a graph depicting locomotor activity in dark phase of Sprague Dawley rats in combination therapy. The graph compares the locomotor activities in dark phase in the rats administered with 2.5 mg/kg/week cisplatin plus saline (Group 1), 2.5 mg/kg/week cisplatin plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days. The locomotor activities in dark phase are monitored from 4 days prior to the administration until 21 days after administration of the initial dose.

[0270] FIG. 23B is a graph depicting locomotor activity in dark phase of Sprague Dawley rats in combination therapy. The graph compares the locomotor activities in dark phase in the rats administered with 70 mg/kg/week 5-FU plus saline (Group 1), 70 mg/kg/week 5-FU plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days. The locomotor activities in dark phase are monitored from 4 days prior to the administration until 21 days after administration of the initial dose.

[0271] FIG. 23C is a graph depicting locomotor activity (% of baseline) in dark phase of Sprague Dawley rats in combination therapy. The graph compares the locomotor activities (% of baseline) in dark phase in the rats administered with 2.5

mg/kg/week cisplatin plus saline (Group 1), and 2.5 mg/kg/week cisplatin plus 3 mg/kg/day TCMCB07 (Group 2), respectively, for 21 days. The locomotor activities in dark phase are monitored from 4 days prior to the administration until 21 days after administration of the initial dose.

[0272] FIG. 23D is a graph depicting locomotor activity (% of baseline) in dark phase of Sprague Dawley rats in combination therapy. The graph compares the locomotor activities (% of baseline) in dark phase in the rats administered with 70 mg/kg/week 5-FU plus saline (Group 1), and 70 mg/kg/week 5-FU plus 3 mg/kg/day TCMCB07 (Group 2), respectively, for 21 days. The locomotor activities in dark phase are monitored from 4 days prior to the administration until 21 days after administration of the initial dose.

[0273] FIG. 24A is a graph depicting locomotor activity in light phase of Sprague Dawley rats in combination therapy. The graph compares the locomotor activities in light phase in the rats administered with 2.5 mg/kg/week cisplatin plus saline (Group 1), 2.5 mg/kg/week cisplatin plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days. The locomotor activities in light phase are monitored from 4 days prior to the administration until 21 days after administration of the initial dose.

[0274] FIG. 24B is a graph depicting locomotor activity in light phase of Sprague Dawley rats in combination therapy. The graph compares the locomotor activities in dark phase in the rats administered with 70 mg/kg/week 5-FU plus saline (Group 1), 70 mg/kg/week 5-FU plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days. The locomotor activities in dark phase are monitored from 4 days prior to the administration until 21 days after administration of the initial dose.

[0275] FIG. 24C is a graph depicting locomotor activity (% of baseline) in light phase of Sprague Dawley rats in combination therapy. The graph compares the locomotor activities (% of baseline) in light phase in the rats administered with 2.5 mg/kg/week cisplatin plus saline (Group 1), and 2.5 mg/kg/week cisplatin plus 3 mg/kg/day TCMCB07 (Group 2), respectively, for 21 days. The locomotor activities in light phase are monitored from 4 days prior to the administration until 21 days after administration of the initial dose.

[0276] FIG. 24D is a graph depicting locomotor activity (% of baseline) in light phase of Sprague Dawley rats in combination therapy. The graph compares the locomotor activities (% of baseline) in light phase in the rats administered with 70 mg/kg/week 5-FU plus saline (Group 1), and 70 mg/kg/week 5-FU plus 3 mg/kg/day TCMCB07 (Group 2), respectively, for 21 days. The locomotor activities in light phase are monitored from 4 days prior to the administration until 21 days after administration of the initial dose.

[0277] FIG. 25A is a bar graph depicting leukocyte counts (total leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, and basophils) of Sprague Dawley rats after combination therapy. The graph compares the leukocyte counts (total leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, and basophils) of the rats after administration with 2.5 mg/kg/week cisplatin plus saline (Group 1), 2.5 mg/kg/week cisplatin plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days.

[0278] FIG. 25B is a bar graph depicting leukocyte counts (total leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, and basophils) of Sprague Dawley rats after combination therapy. The graph compares the leukocyte counts (total leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, and basophils) of the rats after administration with 70 mg/kg/week 5-FU plus saline (Group 1), 70 mg/kg/week 5-FU plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days.

[0279] FIG. 25C is a bar graph depicting leukocyte ratios of neutrophils, lymphocytes, monocytes, eosinophils, and basophils of Sprague Dawley rats after combination therapy. The graph compares the leukocyte ratios of neutrophils, lymphocytes, monocytes, eosinophils, and basophils of the rats after administration with 2.5 mg/kg/week cisplatin plus saline (Group 1), 2.5 mg/kg/week cisplatin plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days.

[0280] FIG. 25D is a bar graph depicting leukocyte ratios of neutrophils, lymphocytes, monocytes, eosinophils, and basophils of Sprague Dawley rats after combination therapy. The graph compares the leukocyte ratios of neutrophils, lymphocytes, monocytes, eosinophils, and basophils of the rats after administration with

70 mg/kg/week 5-FU plus saline (Group 1), 70 mg/kg/week 5-FU plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days.

[0281] FIG. 26A is a bar graph depicting erythrocytes (RBC, Hb, HCT, MCV, MCH, and MCHC) of Sprague Dawley rats after combination therapy. The graph compares the erythrocytes (RBC, Hb, HCT, MCV, MCH, and MCHC) of the rats after administration with 2.5 mg/kg/week cisplatin plus saline (Group 1), 2.5 mg/kg/week cisplatin plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days.

[0282] FIG. 26B is a bar graph depicting erythrocytes (RBC, Hb, HCT, MCV, MCH, and MCHC) of Sprague Dawley rats after combination therapy. The graph compares the erythrocytes (RBC, Hb, HCT, MCV, MCH, and MCHC) of the rats after administration with 70 mg/kg/week 5-FU plus saline (Group 1), 70 mg/kg/week 5-FU plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days.

[0283] FIG. 26C is a bar graph depicting concentration of thrombocytes of Sprague Dawley rats after combination therapy. The graph compares the concentrations of thrombocytes of the rats after administration with 2.5 mg/kg/week cisplatin plus saline (Group 1), 2.5 mg/kg/week cisplatin plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days.

[0284] FIG. 26D is a bar graph depicting concentration of thrombocytes of Sprague Dawley rats after combination therapy. The graph compares the concentrations of thrombocytes of the rats after administration with 70 mg/kg/week 5-FU plus saline (Group 1), 70 mg/kg/week 5-FU plus 3 mg/kg/day TCMCB07 (Group 2), and saline plus saline (Group 3), respectively, for 21 days.

[0285] FIG. 27A is a bar graph depicting total body weight change (as a percentage of baseline) after combination therapy for 7 days in a doxorubicin chemotherapy Sprague Dawley rat model. The graph compares the total body weight gains (as a percentage of baseline) of the rats after administration with saline vehicle (Group 1) 2 mg/kg/week doxorubicin (DOX) plus saline (Group 2), and 2 mg/kg/week doxorubicin plus 3 mg/kg/day TCMCB07 (Group 3), respectively, for 7 days. N=10, 16, and 12 rats for Group 1, Group 2, and Group 3, respectively. DOX was administered

by intraperitoneal injection and TCMCB07 was administered by subcutaneous injection. The cutoffs for significance are * <.05, **<.01, ***<.001 ****<.0001.

[0286] FIG. 27B is a bar graph depicting total body weight change (as a percentage of baseline) after combination therapy for 14 days in a doxorubicin chemotherapy Sprague Dawley rat model. The graph compares the total body weight gains (as a percentage of baseline) of the rats after administration with saline vehicle (Group 1) 2 mg/kg/week doxorubicin plus saline (Group 2), and 2 mg/kg/week doxorubicin plus 3 mg/kg/day TCMCB07 (Group 3), respectively, for 14 days. N=10, 16, and 12 rats for Group 1, Group 2, and Group 3, respectively. DOX was administered by intraperitoneal injection and TCMCB07 was administered by subcutaneous injection. The cutoffs for significance are * <.05, **<.01, ***<.001 ****<.0001.

[0287] FIG. 27C is a bar graph depicting total body weight change (as a percentage of baseline) after combination therapy for 21 days in a doxorubicin chemotherapy Sprague Dawley rat model. The graph compares the total body weight gains (as a percentage of baseline) of the rats after administration with saline vehicle (Group 1) 2 mg/kg/week doxorubicin plus saline (Group 2), and 2 mg/kg/week doxorubicin plus 3 mg/kg/day TCMCB07 (Group 3), respectively, for 21 days. N=10, 16, and 12 rats for Group 1, Group 2, and Group 3, respectively. DOX was administered by intraperitoneal injection and TCMCB07 was administered by subcutaneous injection.

[0288] FIG. 27D is a bar graph depicting total body weight change (as a percentage of baseline) after combination therapy for 28 days in a doxorubicin chemotherapy Sprague Dawley rat model. The graph compares the total body weight gains (as a % of baseline) of the rats after administration with saline vehicle (Group 1) 2 mg/kg/week doxorubicin plus saline (Group 2), and 2 mg/kg/week doxorubicin plus 3 mg/kg/day TCMCB07 (Group 3), respectively, for 28 days. N=10, 16, and 12 rats for Group 1, Group 2, and Group 3, respectively. DOX was administered by intraperitoneal injection and TCMCB07 was administered by subcutaneous injection. The cutoffs for significance are * <.05, **<.01, ***<.001 ****<.0001.

[0289] FIG. 28A is a graph depicting daily body weight after combination therapy in a doxorubicin chemotherapy Sprague Dawley rat model. The graph compares the daily body weights in the rats administered with saline vehicle (Group 1) 2 mg/kg/week

doxorubicin plus saline (Group 2), and 2 mg/kg/week doxorubicin plus 3 mg/kg/day TCMCB07 (Group 3), respectively, for 17 days.

[0290] FIG. 28B is a graph depicting daily body weight after combination therapy in a doxorubicin chemotherapy Sprague Dawley rat model. The graph compares the daily body weights in the rats administered with saline vehicle (Group 1), 2 mg/kg/week doxorubicin plus saline (Group 2), and 2 mg/kg/week doxorubicin plus 3 mg/kg/day TCMCB07 (Group 3), respectively, for 26 days. N = 12 rats per group. TCMCB07 was administered subcutaneously.

[0291] FIGS. 29A-C are graphs from a post treatment study (TCMCB07 post treatment after cisplatin administration) in a Sprague Dawley rat model. Rats were administered with cisplatin plus TCMCB07 followed by saline vehicle (Group 1), cisplatin plus TCMCB07 followed by TCMCB07 post treatment (Group 2), cisplatin followed by saline vehicle (Group 3), and cisplatin followed by TCMCB07 post treatment (Group 4) respectively. N = 10 rats per group. FIG. 29A depicts daily body weight. FIG. 29B depicts body weight gain (% of initial). FIG. 29C depicts daily cumulative food intake (g). TCMCB07 was administered subcutaneously.

[0292] FIGS. 30A-YY illustrate percent activation of the melanocortin 3 receptor (MC3R) following stimulation with non-naturally occurring melanocortin analogs as measured by cAMP levels in accordance with embodiments of the present technology. Example non-naturally occurring melanocortin analogs included HS024(TFA) (FIG. 30A; SEQ ID NO: 525), E1 (FIG. 30B; SEQ ID NO: 15), E2 (FIG. 30C; SEQ ID NO: 16), E3 (FIG. 30D; SEQ ID NO: 17), E4 (FIG. 30E; SEQ ID NO: 18), E5 (FIG. 30F; SEQ ID NO: 19), E6 (FIG. 30G; SEQ ID NO: 20), E7 (FIG. 30H; SEQ ID NO: 21), E8 (FIG. 30I; SEQ ID NO: 22), E9 (FIG. 30J; SEQ ID NO: 23), E10 (FIG. 30K; SEQ ID NO: 24), E11 (FIG. 30L; SEQ ID NO: 25), E12 (FIG. 30M; SEQ ID NO: 26), E13 (FIG. 30N; SEQ ID NO: 27), E14 (FIG. 30O; SEQ ID NO: 28), E15 (FIG. 30P; SEQ ID NO: 29), E16 (FIG. 30Q; SEQ ID NO: 30), E17 (FIG. 30R; SEQ ID NO: 31), E18 (FIG. 30S; SEQ ID NO: 32), E19 (FIG. 30T; SEQ ID NO: 35), E20 (FIG. 30U; SEQ ID NO: 36), E21 (FIG. 30V; SEQ ID NO: 37), F1 (FIG. 30W; SEQ ID NO: 40), F2 (FIG. 30X; SEQ ID NO: 41), F3 (FIG. 30Y; SEQ ID NO: 42), F4 (FIG. 30Z; SEQ ID NO: 43), F5 (FIG. 30AA; SEQ ID NO: 44), F6 (FIG. 30BB; SEQ ID NO: 50), F7 (FIG. 30CC; SEQ ID NO: 51), F8 (FIG. 30DD; SEQ ID NO: 52), F9 (FIG. 30EE; SEQ ID NO: 53), F10 (FIG. 30FF; SEQ ID NO:

54), F11 (FIG. 30GG; SEQ ID NO: 55), F12 (FIG. 30HH; SEQ ID NO: 56), F13 (FIG. 30II; SEQ ID NO: 57), F14 (FIG. 30JJ; SEQ ID NO: 58), F15 (FIG. 30KK; SEQ ID NO: 59), F16 (FIG. 30LL; SEQ ID NO: 60), F17 (FIG. 30MM; SEQ ID NO: 61), F18 (FIG. 30NN; SEQ ID NO: 62), F19 (FIG. 30OO; SEQ ID NO: 63), F20 (FIG. 30PP; SEQ ID NO: 64), F21 (FIG. 30QQ; SEQ ID NO: 65), F22 (FIG. 30RR; SEQ ID NO: 45), F23 (FIG. 30SS; SEQ ID NO: 46), F24 (FIG. 30TT; SEQ ID NO: 47), F25 (FIG. 30UU; SEQ ID NO: 48), F26 (FIG. 30VV; SEQ ID NO: 49), F28 (FIG. 30WW; SEQ ID NO: 67), F29 (FIG. 30XX; SEQ ID NO: 68), and F30 (FIG. 30YY; SEQ ID NO: 69).

[0293] FIGS. 31A-OO illustrate percent activation of the MC3R following stimulation with non-naturally occurring melanocortin analogs as measured by cAMP levels in accordance with embodiments of the present technology. Example non-naturally occurring melanocortin analogs included Example non-naturally occurring melanocortin analogs included G5 (FIG. 31A; SEQ ID NO: 77), G6 (FIG. 31B; SEQ ID NO: 78), G7 (FIG. 31C; SEQ ID NO: 75), G8 (FIG. 31D; SEQ ID NO: 74), G9 (FIG. 31E; SEQ ID NO: 79), G10 (FIG. 31F; SEQ ID NO: 80), G11 (FIG. 31G; SEQ ID NO: 81), G12 (FIG. 31H; SEQ ID NO: 82), G13 (FIG. 31I; SEQ ID NO: 83), G15 (FIG. 31J; SEQ ID NO: 85), G17 (FIG. 31K; SEQ ID NO: 211), G18 (FIG. 31L; SEQ ID NO: 212), G19 (FIG. 31M; SEQ ID NO: 213), G 20 (FIG. 31N; SEQ ID NO: 214), H1 (FIG. 31O; SEQ ID NO: 97), H2 (FIG. 31P; SEQ ID NO: 98), H3 (FIG. 31Q; SEQ ID NO: 99), H4 (FIG. 31R; SEQ ID NO: 100), H5 (FIG. 31S; SEQ ID NO: 101), H6 (FIG. 31T; SEQ ID NO: 102), H7 (FIG. 31U; SEQ ID NO: 103), H8 (FIG. 31V; SEQ ID NO: 104), H9 (FIG. 31W; SEQ ID NO: 105), H10 (FIG. 31X; SEQ ID NO: 106), H11 (FIG. 31Y; SEQ ID NO: 107), H12 (FIG. 31Z; SEQ ID NO: 108), H13 (FIG. 31AA; SEQ ID NO: 109), H14 (FIG. 31BB; SEQ ID NO: 110), H15 (FIG. 31CC; SEQ ID NO: 111), I1 (FIG. 31DD; SEQ ID NO: 112), I2 (FIG. 31EE; SEQ ID NO: 113), I3 (FIG. 31FF; SEQ ID NO: 119), I4 (FIG. 31GG; SEQ ID NO: 115), I5 (FIG. 31HH; SEQ ID NO: 120), I6 (FIG. 31II; SEQ ID NO: 121), I7 (FIG. 31JJ; SEQ ID NO: 116), I8 (FIG. 31KK; SEQ ID NO: 117), I9 (FIG. 31LL; SEQ ID NO: 122), I10 (FIG. 31MM; SEQ ID NO: 123), I11 (FIG. 31NN; SEQ ID NO: 118), and I12 (FIG. 31OO; SEQ ID NO: 124).

[0294] FIGS. 32A-ZZ illustrate percent inhibition of the MC3R following stimulation with non-naturally occurring melanocortin analogs as measured by cAMP levels in accordance with embodiments of the present technology. Example non-naturally occurring melanocortin analogs included Example non-naturally occurring

melanocortin analogs included J1 (FIG. 32A; SEQ ID NO: 126), J4 (FIG. 32B; SEQ ID NO: 129), J5 (FIG. 32C; SEQ ID NO: 130), J6 (FIG. 32D; SEQ ID NO: 131), J7 (FIG. 32E; SEQ ID NO: 132), J8 (FIG. 32F; SEQ ID NO: 133), J9 (FIG. 32G; SEQ ID NO: 134), J10 (FIG. 32H; SEQ ID NO: 135), J11 (FIG. 32I; SEQ ID NO: 136), J12 (FIG. 32J; SEQ ID NO: 137), J13 (FIG. 32K; SEQ ID NO: 138), J14 (FIG. 32L; SEQ ID NO: 139), J15 (FIG. 32M; SEQ ID NO: 140), J16 (FIG. 32N; SEQ ID NO: 141), J17 (FIG. 32O; SEQ ID NO: 142), J18 (FIG. 32P; SEQ ID NO: 143), J19 (FIG. 32Q; SEQ ID NO: 144), J20 (FIG. 32R; SEQ ID NO: 145), J21 (FIG. 32S; SEQ ID NO: 146), J22 (FIG. 32T; SEQ ID NO: 147), J23 (FIG. 32U; SEQ ID NO: 148), J24 (FIG. 32V; SEQ ID NO: 149), J25 (FIG. 32W; SEQ ID NO: 150), J26 (FIG. 32X; SEQ ID NO: 151), J27 (FIG. 32Y; SEQ ID NO: 152), J28 (FIG. 32Z; SEQ ID NO: 153), J29 (FIG. 32AA; SEQ ID NO: 154), J30 (FIG. 32BB; SEQ ID NO: 155), J31 (FIG. 32CC; SEQ ID NO: 156), J32 (FIG. 32DD; SEQ ID NO: 157), J33 (FIG. 32EE; SEQ ID NO: 158), J34 (FIG. 32FF; SEQ ID NO: 159), J35 (FIG. 32GG; SEQ ID NO: 160), J36 (FIG. 32HH; SEQ ID NO: 161), J37 (FIG. 32II; SEQ ID NO: 162), J38 (FIG. 32JJ; SEQ ID NO: 163), J39 (FIG. 32KK; SEQ ID NO: 164), J40 (FIG. 32LL; SEQ ID NO: 165), J41 (FIG. 32MM; SEQ ID NO: 166), J42 (FIG. 32NN; SEQ ID NO: 167), J43 (FIG. 32OO; SEQ ID NO: 168), J44 (FIG. 32PP; SEQ ID NO: 169), J45 (FIG. 32QQ; SEQ ID NO: 170), J46 (FIG. 32RR; SEQ ID NO: 171), J47 (FIG. 32SS; SEQ ID NO: 172), J48 (FIG. 32TT; SEQ ID NO: 173), J49 (FIG. 32UU; SEQ ID NO: 174), J60 (FIG. 32VV; SEQ ID NO: 185), J63 (FIG. 32WW; SEQ ID NO: 188), J65 (FIG. 32XX; SEQ ID NO: 190), J68 (FIG. 32YY; SEQ ID NO: 193), and J69 (FIG. 32ZZ; SEQ ID NO: 194).

[0295] FIGS. 33A-SS illustrate percent inhibition of the MC3R following stimulation with non-naturally occurring melanocortin analogs as measured by cAMP levels in accordance with embodiments of the present technology. Example non-naturally occurring melanocortin analogs included Example non-naturally occurring melanocortin analogs included K2 (FIG. 33A; SEQ ID NO: 394), K3 (FIG. 33B; SEQ ID NO: 396), K4 (FIG. 33C; SEQ ID NO: 398), K5 (FIG. 33D; SEQ ID NO: 399), K6 (FIG. 33E; SEQ ID NO: 392), K7 (FIG. 33F; SEQ ID NO: 393), K8 (FIG. 33G; SEQ ID NO: 395), K9 (FIG. 33H; SEQ ID NO: 397), K10 (FIG. 33I; SEQ ID NO: 400), K13 (FIG. 33J; SEQ ID NO: 403), K16 (FIG. 33K; SEQ ID NO: 376), K17 (FIG. 33L; SEQ ID NO: 377), K18 (FIG. 33M; SEQ ID NO: 378), K20 (FIG. 33N; SEQ ID NO: 380), K23 (FIG. 33O; SEQ ID NO: 388), L4 (FIG. 33P; SEQ ID NO: 217), M1 (FIG. 33Q; SEQ ID NO: 225),

M2 (FIG. 33R; SEQ ID NO: 234), M3 (FIG. 33S; SEQ ID NO: 226), M4 (FIG. 33T; SEQ ID NO: 235), M5 (FIG. 33U; SEQ ID NO: 227), M6 (FIG. 33V; SEQ ID NO: 228), M7 (FIG. 33W; SEQ ID NO: 229), M8 (FIG. 33X; SEQ ID NO: 230), M9 (FIG. 33Y; SEQ ID NO: 231), M11 (FIG. 33Z; SEQ ID NO: 233), N1 (FIG. AA; SEQ ID NO: 236), N2 (FIG. 33BB; SEQ ID NO: 237), N3 (FIG. 33CC; SEQ ID NO: 240), N4 (FIG. 33DD; SEQ ID NO: 241), N5 (FIG. 33EE; SEQ ID NO: 242), N6 (FIG. 33FF; SEQ ID NO: 243), N7 (FIG. 33GG; SEQ ID NO: 244), N8 (FIG. 33HH; SEQ ID NO: 245), O1 (FIG. 33II; SEQ ID NO: 246), O2 (FIG. 33JJ; SEQ ID NO: 247), O3 (FIG. 33KK; SEQ ID NO: 248), O4 (FIG. 33LL; SEQ ID NO: 249), O5 (FIG. 33MM; SEQ ID NO: 250), O6 (FIG. 33NN; SEQ ID NO: 255), O7 (FIG. 33OO; SEQ ID NO: 256), O9 (FIG. 33PP; SEQ ID NO: 258), O10 (FIG. 33QQ; SEQ ID NO: 259), O11 (FIG. 33RR; SEQ ID NO: 260), and TCMCB07 (FIG. 33SS; SEQ ID NO: 3).

[0296] FIGS. 34A-DDD illustrate percent activation of the melanocortin 4 receptor (MC4R) following stimulation with non-naturally occurring melanocortin analogs as measured by cAMP levels in accordance with embodiments of the present technology. Example non-naturally occurring melanocortin analogs included HS024(TFA) (FIG. 34A; SEQ ID NO: 525), E1 (FIG. 34B; SEQ ID NO: 15), E2 (FIG. 34C; SEQ ID NO: 16), E3 (FIG. 34D; SEQ ID NO: 17), E4 (FIG. 34E; SEQ ID NO: 18), E5 (FIG. 34F; SEQ ID NO: 19), E6 (FIG. 34G; SEQ ID NO: 20), E7 (FIG. 34H; SEQ ID NO: 21), E8 (FIG. 34I; SEQ ID NO: 22), E9 (FIG. 34J; SEQ ID NO: 23), E10 (FIG. 34K; SEQ ID NO: 24), E11 (FIG. 34L; SEQ ID NO: 25), E12 (FIG. 34M; SEQ ID NO: 26), E13 (FIG. 34N; SEQ ID NO: 27), E14 (FIG. 34O; SEQ ID NO: 28), E15 (FIG. 34P; SEQ ID NO: 29), E16 (FIG. 34Q; SEQ ID NO: 30), E17 (FIG. 34R; SEQ ID NO: 31), E18 (FIG. 34S; SEQ ID NO: 32), E20 (FIG. 34T; SEQ ID NO: 36), E21 (FIG. 34U; SEQ ID NO: 37), E22 (FIG. 34V; SEQ ID NO: 195), E23 (FIG. 34W; SEQ ID NO: 196), E24 (FIG. 34X; SEQ ID NO: 197), F1 (FIG. 34Y; SEQ ID NO: 40), F2 (FIG. 34Z; SEQ ID NO: 41), F3 (FIG. 34AA; SEQ ID NO: 42), F4 (FIG. 34BB; SEQ ID NO: 43), F5 (FIG. 34CC; SEQ ID NO: 44), F6 (FIG. 34DD; SEQ ID NO: 50), F7 (FIG. 34EE; SEQ ID NO: 51), F8 (FIG. 34FF; SEQ ID NO: 52), F9 (FIG. 34GG; SEQ ID NO: 53), F10 (FIG. 34HH; SEQ ID NO: 54), F11 (FIG. 34II; SEQ ID NO: 55), F12 (FIG. 34JJ; SEQ ID NO: 56), F13 (FIG. 34KK; SEQ ID NO: 57), F14 (FIG. 34LL; SEQ ID NO: 58), F15 (FIG. 34MM; SEQ ID NO: 59), F16 (FIG. 34NN; SEQ ID NO: 60), F17 (FIG. 34OO; SEQ ID NO: 61), F18 (FIG. 34PP; SEQ ID NO: 62), F19 (FIG. 34QQ; SEQ ID NO: 63), F20 (FIG. 34RR; SEQ ID NO: 64), F21 (FIG. 34SS;

SEQ ID NO: 65), F22 (FIG. 34TT; SEQ ID NO: 45), F23 (FIG. 34UU; SEQ ID NO: 46), F24 (FIG. 34VV; SEQ ID NO: 47), F25 (FIG. 34WW; SEQ ID NO: 48), F26 (FIG. 34XX; SEQ ID NO: 49), F27 (FIG. 34YY; SEQ ID NO: 66), F28 (FIG. 34ZZ; SEQ ID NO: 67), F29 (FIG. 34AAA; SEQ ID NO: 68), F30 (FIG. 34BBB; SEQ ID NO: 69), F31 (FIG. 34CCC; SEQ ID NO: 201), and F32 (FIG. 34DDD; SEQ ID NO: 205).

[0297] FIGS. 35A-ZZ illustrate percent activation of the MC4R following stimulation with non-naturally occurring melanocortin analogs as measured by cAMP levels in accordance with embodiments of the present technology. Example non-naturally occurring melanocortin analogs included G1 (FIG. 35A; SEQ ID NO: 71), G2 (FIG. 35B; SEQ ID NO: 72), G3 (FIG. 35C; SEQ ID NO: 73), G4 (FIG. 35D; SEQ ID NO: 76), G5 (FIG. 35E; SEQ ID NO: 77), G6 (FIG. 35F; SEQ ID NO: 78), G7 (FIG. 35G; SEQ ID NO: 75), G8 (FIG. 35H; SEQ ID NO: 74), G9 (FIG. 35I; SEQ ID NO: 79), G10 (FIG. 35J; SEQ ID NO: 80), G11 (FIG. 35K; SEQ ID NO: 81), G12 (FIG. 35L; SEQ ID NO: 82), G13 (FIG. 35M; SEQ ID NO: 83), G14 (FIG. 35N; SEQ ID NO: 84), G15 (FIG. 35O; SEQ ID NO: 85), G16 (FIG. 35P; SEQ ID NO: 86), G17 (FIG. 35Q; SEQ ID NO: 211), G18 (FIG. 35R; SEQ ID NO: 212), G19 (FIG. 35S; SEQ ID NO: 213), G20 (FIG. 35T; SEQ ID NO: 214), G21 (FIG. 35U; SEQ ID NO: 215), G22 (FIG. 35V; SEQ ID NO: 202), G23 (FIG. 35W; SEQ ID NO: 203), G24 (FIG. 35X; SEQ ID NO: 204), H1 (FIG. 35Y; SEQ ID NO: 97), H2 (FIG. 35Z; SEQ ID NO: 98), H3 (FIG. 35AA; SEQ ID NO: 99), H4 (FIG. 35BB; SEQ ID NO: 100), H5 (FIG. 35CC; SEQ ID NO: 101), H6 (FIG. 35DD; SEQ ID NO: 102), H7 (FIG. 35EE; SEQ ID NO: 103), H8 (FIG. 35FF; SEQ ID NO: 104), H9 (FIG. 35GG; SEQ ID NO: 105), H10 (FIG. 35HH; SEQ ID NO: 106), H11 (FIG. 35II; SEQ ID NO: 107), H12 (FIG. 35JJ; SEQ ID NO: 108), H13 (FIG. 35KK; SEQ ID NO: 109), H14 (FIG. 35LL; SEQ ID NO: 110), H15 (FIG. 35MM; SEQ ID NO: 111), I1 (FIG. 35NN; SEQ ID NO: 112), I2 (FIG. 35OO; SEQ ID NO: 113), I3 (FIG. 35PP; SEQ ID NO: 119), I4 (FIG. 35QQ; SEQ ID NO: 115), I5 (FIG. 35RR; SEQ ID NO: 120), I6 (FIG. 35SS; SEQ ID NO: 121), I7 (FIG. 35TT; SEQ ID NO: 116), I8 (FIG. 35UU; SEQ ID NO: 117), I9 (FIG. 35VV; SEQ ID NO: 122), I10 (FIG. 35WW; SEQ ID NO: 123), I11 (FIG. 35XX; SEQ ID NO: 118), I12 (FIG. 35YY; SEQ ID NO: 124), and I13 (FIG. 35ZZ; SEQ ID NO: 200).

[0298] FIGS. 36A-RRR illustrate percent inhibition of the MC4R following stimulation with non-naturally occurring melanocortin analogs as measured by cAMP levels in accordance with embodiments of the present technology. Example non-

naturally occurring melanocortin analogs included J1 (FIG. 36A; SEQ ID NO: 126), J2 (FIG. 36B; SEQ ID NO: 127), J3 (FIG. 36C; SEQ ID NO: 128), J4 (FIG. 36D; SEQ ID NO: 129), J5 (FIG. 36E; SEQ ID NO: 130), J6 (FIG. 36F; SEQ ID NO: 131), J7 (FIG. 36G; SEQ ID NO: 132), J8 (FIG. 36H; SEQ ID NO: 133), J9 (FIG. 36I; SEQ ID NO: 136), J10 (FIG. 36J; SEQ ID NO: 135), J11 (FIG. 36K; SEQ ID NO: 136), J12 (FIG. 36L; SEQ ID NO: 137), J13 (FIG. 36M; SEQ ID NO: 138), J14 (FIG. 36N; SEQ ID NO: 139), J15 (FIG. 36O; SEQ ID NO: 140), J16 (FIG. 36P; SEQ ID NO: 141), J17 (FIG. 36Q; SEQ ID NO: 142), J18 (FIG. 36R; SEQ ID NO: 143), J19 (FIG. 36S; SEQ ID NO: 144), J20 (FIG. 36T; SEQ ID NO: 145), J21 (FIG. 36U; SEQ ID NO: 146), J22 (FIG. 36V; SEQ ID NO: 147), J23 (FIG. 36W; SEQ ID NO: 148), J24 (FIG. 36X; SEQ ID NO: 149), J25 (FIG. 36Y; SEQ ID NO: 150), J26 (FIG. 36Z; SEQ ID NO: 151), J27 (FIG. 36AA; SEQ ID NO: 152), J28 (FIG. 36BB; SEQ ID NO: 153), J29 (FIG. 36CC; SEQ ID NO: 154), J30 (FIG. 36DD; SEQ ID NO: 155), J31 (FIG. 36EE; SEQ ID NO: 156), J32 (FIG. 36FF; SEQ ID NO: 157), J33 (FIG. 36GG; SEQ ID NO: 158), J34 (FIG. 36HH; SEQ ID NO: 159), J35 (FIG. 36II; SEQ ID NO: 160), J36 (FIG. 36JJ; SEQ ID NO: 161), J37 (FIG. 36KK; SEQ ID NO: 126; SEQ ID NO: 162), J38 (FIG. 36LL; SEQ ID NO: 163), J39 (FIG. 36MM; SEQ ID NO: 164), J40 (FIG. 36NN; SEQ ID NO: 165), J41 (FIG. 36OO; SEQ ID NO: 166), J42 (FIG. 36PP; SEQ ID NO: 167), J43 (FIG. 36QQ; SEQ ID NO: 168), J44 (FIG. 36RR; SEQ ID NO: 169), J45 (FIG. 36SS; SEQ ID NO: 170), J46 (FIG. 36TT; SEQ ID NO: 171), J47 (FIG. 36UU; SEQ ID NO: 172), J48 (FIG. 36VV; SEQ ID NO: 173), J49 (FIG. 36WW; SEQ ID NO: 174), J50 (FIG. 36XX; SEQ ID NO: 175), J51 (FIG. 36YY; SEQ ID NO: 176), J52 (FIG. 36ZZ; SEQ ID NO: 177), J53 (FIG. 36AAA; SEQ ID NO: 178), J54 (FIG. 36BBB; SEQ ID NO: 179), J55 (FIG. 36CCC; SEQ ID NO: 180), J56 (FIG. 36DDD; SEQ ID NO: 181), J57 (FIG. 36EEE; SEQ ID NO: 182), J58 (FIG. 36FFF; SEQ ID NO: 183), J59 (FIG. 36GGG; SEQ ID NO: 184), J60 (FIG. 36HHH; SEQ ID NO: 185), J61 (FIG. 36III; SEQ ID NO: 186), J62 (FIG. 36JJJ; SEQ ID NO: 187), J63 (FIG. 36KKK; SEQ ID NO: 188), J64 (FIG. 36LLL; SEQ ID NO: 189), J65 (FIG. 36MMM; SEQ ID NO: 190), J66 (FIG. 36NNN; SEQ ID NO: 191), J67 (FIG. 36OOO; SEQ ID NO: 192), J68 (FIG. 36PPP; SEQ ID NO: 193), J69 (FIG. 36QQQ; SEQ ID NO: 194), and J70 (FIG. 36RRR; SEQ ID NO: 206).

[0299] FIGS. 37A-GGG illustrate percent inhibition of the MC4R following stimulation with non-naturally occurring melanocortin analogs as measured by cAMP levels in accordance with embodiments of the present technology. Example non-

naturally occurring melanocortin analogs included Example non-naturally occurring melanocortin analogs included K1 (FIG. 37A; SEQ ID NO: 391), K2 (FIG. 37B; SEQ ID NO: 394), K3 (FIG. 37C; SEQ ID NO: 396), K4 (FIG. 37D; SEQ ID NO: 398), K5 (FIG. 37E; SEQ ID NO: 399), K6 (FIG. 37F; SEQ ID NO: 392), K7 (FIG. 37G; SEQ ID NO: 393), K8 (FIG. 37H; SEQ ID NO: 395), K9 (FIG. 37I; SEQ ID NO: 397), K10 (FIG. 37J; SEQ ID NO: 400), K11 (FIG. 37K; SEQ ID NO: 401), K12 (FIG. 37L; SEQ ID NO: 402), K13 (FIG. 37M; SEQ ID NO: 403), K14 (FIG. 37N; SEQ ID NO: 406), K15 (FIG. 37O; SEQ ID NO: 375), K16 (FIG. 37P; SEQ ID NO: 376), K17 (FIG. 37Q; SEQ ID NO: 377), K18 (FIG. 37R; SEQ ID NO: 378), K19 (FIG. 37S; SEQ ID NO: 379), K20 (FIG. 37T; SEQ ID NO: 380), K21 (FIG. 37U; SEQ ID NO: 381), K22 (FIG. 37V; SEQ ID NO: 125), K23 (FIG. 37W; SEQ ID NO: 388), L1 (FIG. 37X; SEQ ID NO: 198), L2 (FIG. 37Y; SEQ ID NO: 199), L3 (FIG. 37Z; SEQ ID NO: 216), L4 (FIG. 37AA; SEQ ID NO: 217), L5 (FIG. 37BB; SEQ ID NO: 220), M1 (FIG. 37CC; SEQ ID NO: 225), M2 (FIG. 37DD; SEQ ID NO: 234), M3 (FIG. 37EE; SEQ ID NO: 226), M4 (FIG. 37FF; SEQ ID NO: 237), M5 (FIG. 37GG; SEQ ID NO: 227), M6 (FIG. 37HH; SEQ ID NO: 228), M7 (FIG. 37II; SEQ ID NO: 229), M8 (FIG. 37JJ; SEQ ID NO: 230), M9 (FIG. 37KK; SEQ ID NO: 231), M10 (FIG. 37LL; SEQ ID NO: 232), M11 (FIG. 37MM; SEQ ID NO: 233), N1 (FIG. 37NN; SEQ ID NO: 236), N2 (FIG. 37OO; SEQ ID NO: 237), N3 (FIG. 37PP; SEQ ID NO: 239), N4 (FIG. 37QQ; SEQ ID NO: 241), N5 (FIG. 37RR; SEQ ID NO: 242), N6 (FIG. 37SS; SEQ ID NO: 243), N7 (FIG. 37TT; SEQ ID NO: 244), N8 (FIG. 37UU; SEQ ID NO: 245), O1 (FIG. 37VV; SEQ ID NO: 246), O2 (FIG. 37WW; SEQ ID NO: 247), O3 (FIG. 37XX; SEQ ID NO: 248), O4 (FIG. 37YY; SEQ ID NO: 249), O5 (FIG. 37ZZ; SEQ ID NO: 250), O6 (FIG. 37AAA; SEQ ID NO: 255), O7 (FIG. 37BBB; SEQ ID NO: 256), O8 (FIG. 37CCC; SEQ ID NO: 257), O9 (FIG. 37DDD; SEQ ID NO: 258), O10 (FIG. 37EEE; SEQ ID NO: 259), O11 (FIG. 37FFF; SEQ ID NO: 260), and TCMCB07 (FIG. 37GGG; SEQ ID NO: 3).

[0300] FIG. 38 illustrates proinflammatory gene expression in the hypothalamus of cancer cachectic rats administered either TCMCB07 or saline control as measured by mRNA levels.

[0301] FIGS. 39A-C illustrate changes in cAMP levels following activation of the human (FIG. 39A), rat (FIG. 39B), and dog (FIG. 39C) melanocortin 1 receptor (MC1R) under various concentrations of TCMCB07.

[0302] FIG. 40 illustrates a dosing schema for administering TCMCB07 in a chronic kidney disease model.

[0303] FIG. 41 illustrates daily body weight measurements in rats having chronic kidney disease induced cachexia (G2) and control rats (G1) administered TCMCB07 under 3 different dosing schemas (G3, G4, and G5).

[0304] FIGS. 42A-G illustrate that subcutaneous administration of the non-naturally occurring melanocortin analogs of the present technology ameliorate anorexia, body weight loss, and lean mass loss in rats with chronic kidney disease (CKD) cachexia. FIG. 42A is a graph depicting design of an *in vivo* renal failure model (5/6 nephrectomy model) in rats using one or more non-naturally occurring melanocortin analogs of the present technology. FIG. 42B is a graph comparing the daily body weights in rats who received the nephrectomy according to the *in vivo* renal failure model of FIG. 42A administered with saline (Neph/saline) or TCMCB07 (Neph/TCMCB07), respectively, and rat on sham operation administered with saline (Sham/saline), for 28 days. FIG. 42C is a graph comparing the daily food intakes in rats who received the nephrectomy according to the *in vivo* renal failure model of FIG. 42A administered with saline (Neph/saline) or TCMCB07 (Neph/TCMCB07), respectively, and rat on sham operation administered with saline (Sham/saline), for 28 days. FIG. 42D is a bar graph depicting fat mass gain in rats who received the nephrectomy according to the *in vivo* renal failure model of FIG. 42A administered with saline (Neph/saline) or TCMCB07 (Neph/TCMCB07), respectively, and rat on sham operation administered with saline (Sham/saline), for 28 days. FIG. 42E is a graph showing body weight gain (%, net gain normalized to baseline) post-nephrectomy and post-treatment. FIG. 42F is a graph showing cumulative food intake post-treatment. FIG. 42G is a graph showing lean mass were determined by MR pre- (day 14) and post- (day 28) treatment, and gain (%) was calculated (net gain normalized to baseline). All data are expressed as mean ± SEM for each group. Two-way ANOVA in (42B-42E), Unpaired Student's t-Test in (42D & 42G), * & # $p < 0.05$, ## $p < 0.01$, ***& ### $p < 0.001$ and **** $p < 0.0001$. Stars in (42B & 42C): Neph/saline group versus Sham/saline group, and red pounds in (42B & 42C): Neph/TCMCB07 group versus Neph/saline group

[0305] FIGS. 43A-F illustrate effects of continued treatment with TCMCB07 in CKD model after the rat meets the equivalence point, where the weight of the rat treated

with TCMCB07 is no different from a sham rat. FIG. 43A shows a schematic diagram of the experimental method. FIG. 43B shows daily body weight of CKD model rats treated with TCMCB07 with a change in dosing at the equivalence point. FIG. 43C shows daily body weight gain compared to day 1 of CKD model rats treated with TCMCB07 with a change in dosing at the equivalence point. FIG. 43D shows body weight gain, measured as % of initial weight compared to day 1 of CKD model rats treated with TCMCB07 with a change in dosing at the equivalence point. FIG. 43E shows body weight gain, measured as % of initial weight compared to day 14 of CKD model rats treated with TCMCB07 with a change in dosing at the equivalence point. FIG. 43F shows the cumulative food intake of CKD model rats treated with TCMCB07 with a change in dosing at the equivalence point.

[0306] FIGS. 44A-F illustrate body compositions of CKD model rats treated with TCMCB07 with a change in dosing at the equivalence point. FIG. 44A illustrates fat mass; FIG. 44B illustrates lean mass; FIG. 44C illustrates fluid mass; FIG. 44D illustrates fat mass gained; FIG. 44E illustrates lean mass gained; and FIG. 44F illustrates fluid mass gained.

[0307] FIGS. 45A-D illustrates tissue weight and length of the rats treated with TCMCB07 with a change in dosing at the equivalence point. FIG. 45A illustrates heart weight; FIG. 45B illustrates gastrocnemii weight; FIG. 45C illustrates spleen weight; and FIG. 45D illustrates body length.

[0308] FIGS. 46A and 46B illustrate serum creatinine and urea in rats treated with TCMCB07 with a change in dosing at the equivalence point. FIG. 46A illustrates serum creatinine and FIG. 46B illustrates serum blood urea nitrogen (BUN).

DETAILED DESCRIPTION

[0309] Described herein are methods of treating, preventing, or reducing one or more conditions, including but not limited to side effects and iatrogenic injury, associated with an anti-cancer agent (e.g., chemotherapy agent) in a subject in need thereof using non-naturally occurring melanocortin analogs, as well as methods of treating subjects with having one or more such conditions. In some embodiments, the present technology includes methods for preventing or reducing one or more of the conditions associated with an anti-cancer agent by administering a non-naturally

occurring melanocortin analog to the subject in need thereof prior to administration of the anti-cancer agent. In some embodiments, the non-naturally occurring melanocortin analog is administered to the subject after an anti-cancer agent. In some embodiments, the non-naturally occurring melanocortin analog is administered to the subject concurrently with an anti-cancer agent or during an anti-cancer agent dosing regimen. In any of the embodiments of the present technology, the subject has cancer, or the subject has another condition (e.g., not cancer) which may be treated with an anti-cancer agent such as, but not limited to, a chemotherapy agent.

[0310] Some of the non-naturally occurring melanocortin analogs may bind only the MC3R or MC4R. Other non-naturally occurring melanocortin analogs may bind the MC3R with greater affinity than the MC4R, whereas other non-naturally occurring melanocortin analogs may bind the MC4R with greater affinity than the MC3R. some non-naturally occurring melanocortin analogs may bind the MC3R with the same or generally similar affinity as the MC4R.

[0311] Each of the non-naturally occurring melanocortin analogs may have one or more beta hairpin (β-hairpin) and/or beta turn (β-turn) structures. The presence of amino acids that are structurally rigid, such as, for example, Aia, Aba, Ata, Hyp, D-Hyp, Pro, D-Pro, *trans*Pro(guan), and *cis*Pro(guan), may lead to formation of β-hairpin and/or β-turn structures in the peptide. Additionally, D-Met and disulfide bridges (cyclization via a disulfide bridge) may induce and/or stabilize beta-turn structures of the non-naturally occurring melanocortin analogs. Pro-Gly and Gly-Gly linkers may also induce and/or stabilize beta-turns. In general, cyclization may stabilize beta-turns, and D-amino acids may induce and/or stabilize beta-turns. The non-naturally occurring melanocortin analogs include D-valine-D-proline (dV-dP) or D-proline-D-valine (dP-dV) chain as their C-terminus, which may provide enhanced transport and resistance to degradation. The non-naturally occurring melanocortin analogs may be linear or optionally cyclized via a disulfide bridge or a lactam bond at various positions of the peptide chain. Each of the non-naturally occurring melanocortin analogs may include one or more of the foregoing features.

[0312] The following description is merely exemplary in nature and is not intended to limit the present technology, its applications, or its uses. It should be understood that throughout the drawings, corresponding reference numerals indicate like or

corresponding parts and features. The description of specific examples indicated in various embodiments of the present technology are intended for purposes of illustration only and are not intended to limit the scope of the present technology described herein. Moreover, recitation of multiple embodiments having stated features is not intended to exclude other embodiments having additional features or other embodiments incorporating different combinations of the stated features.

[0313] Furthermore, the detailed description of various embodiments herein makes reference to the accompanying drawing/FIGS, which show various embodiments by way of illustration. While the embodiments are described in sufficient detail to enable those skilled in the art to practice the present technology, it should be understood that other embodiments may be realized and that logical and mechanical changes may be made without departing from the spirit and scope of the present technology. Thus, the detailed description herein is presented for purposes of illustration only and not of limitation. For example, steps or functions recited in descriptions, any method, system, or process, may be executed in any order and are not limited to the order presented. Moreover, any of the step or functions thereof may be outsourced to or performed by one or more third parties.

Definitions

[0314] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by those of ordinary skill in the art to which the present technology belongs. For the purposes of the present technology, the following terms are defined below.

[0315] The articles "a" and "an" are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

[0316] The term "about" means a quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length that varies by acceptable levels in the art. In some embodiments, such variation may be as much as 30, 25, 20, 15, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1% to a reference quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length. When the term "about" is used

in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth.

[0317] "Melanocortin analogs," "non-naturally occurring melanocortin analogs," "melanocortin peptides," "melanocortin receptor peptides," or "melanocortins," are used interchangeably and refer to melanocortin-receptor ligands, which are macromolecules containing at least one melanocortin pharmacophore. Melanocortin analogs are typically peptides that bind melanocortin receptors under physiological conditions. Melanocortin analogs include naturally occurring non-naturally occurring melanocortin analogs (i.e., "synthetic peptides" or "synthetic analogs") and truncated and/or modified versions of melanocortin full-length protein or peptides. For example, the full-length pro-opiomelanocortin protein (POMC), prior to proteolytic cleavage of "sub-peptides," consists of 241 amino acids. Tissue-specific proteolytic cleavage of POMC yields peptides ranging in size from 13 amino acids to 76 amino acids. See Bicknell and Lawry, *Encyclopedia of Stress*, vol. 3, 257-265, Academic Press (2000). Synthesized, non-naturally occurring melanocortin analogs having increased melanocortin receptor activity as discussed herein are approximately 7-12 amino acids in size. Melanocortin analogs exhibit binding functionality with melanocortin receptors. The binding to the melanocortin receptor is inhibitory (antagonist). In addition to peptides, the non-naturally occurring melanocortin analogs include small molecule analogs of melanocortin or portions thereof comprised of organic compounds, inorganic compounds, or combinations of peptide and small molecule—i.e., peptide mimetics, or various combinations thereof. "Non-naturally occurring melanocortin analogs" may be structurally similar and/or functionally similar to biological melanocortin proteins in their ability to bind melanocortin receptors. Further, the non-naturally occurring melanocortin analogs generally contain the pharmacophore: His-Phe-Arg-Trp (SEQ ID NO: 1) or a modified version thereof, or a structural or functional peptide mimetic thereof.

[0318] A "pharmacophore" is the minimum set of amino acid residues necessary to achieve a physiological effect; or a small molecule that is (with respect to a receptor) a structural mimic of the amino acid residues required for binding to and activation of a receptor. His-Phe-Arg-Trp (SEQ ID NO: 1) and their analogs are the pharmacophore of melanocortin for the regulated physiological effect. Therefore, non-naturally occurring melanocortin pharmacophore analogs may be small peptides or organic molecules designed to mimic the appearance or function (including activation or

deactivation of receptor activity) of the melanocortin pharmacophore core sequence peptide.

[0319] "Potentiated therapeutic activity" refers to an increase in melanocortin activity in a non-naturally occurring melanocortin analog that has undergone derivatization at the N- and/or C-terminus. Such derivatizations do not necessarily involve the pharmacophore but do imply a relative increase in in vivo biological half-life.

[0320] A melanocortin receptor "antagonist" is a naturally occurring substance or manufactured drug substance or composition that opposes the melanocortin receptor-associated responses normally induced by a melanocortin receptor agonist agent.

[0321] The terms "bind," "binding," "complex," and "complexing," refer to all types of physical and chemical binding, reactions, complexing, attraction, chelating and the like.

[0322] The "peptides" described herein may be (a) naturally-occurring, (b) produced by chemical synthesis, (c) produced by recombinant DNA technology, (d) produced by biochemical or enzymatic fragmentation of larger molecules, (e) produced by methods resulting from a combination of methods (a) through (d) listed above, or (f) produced by any other means for producing peptides.

[0323] The term "peptide" as used herein includes any structure comprised of two or more amino acids, including chemical modifications and derivatives of amino acids. The amino acids forming all or a part of a peptide may be naturally occurring amino acids, stereoisomers and modifications of such amino acids, non-protein amino acids, post-translationally modified amino acids, enzymatically modified amino acids, constructs or structures designed to mimic amino acids, and the like, so that the term "peptide" includes pseudopeptides and peptidomimetics, including structures which have a non-peptidic backbone. The term "peptide" also includes dimers or multimers of peptides. A "manufactured" peptide includes a peptide produced by chemical synthesis, recombinant DNA technology, biochemical, or enzymatic fragmentation of larger molecules, combinations of the foregoing or, in general, made by any other method. The term "peptide" includes peptides containing a variable number of amino acid residues, optionally with non-amino acid residue groups at the N- and C-termini, such groups including acyl, acetyl, alkenyl, alkyl, N-alkyl, amine, or amide groups, among others.

[0324] By employing chemical synthesis, a useful means of production, it is possible to introduce various amino acids which do not naturally occur along the chain, modify the N- or C-terminus, and the like, thereby providing for improved stability and formulation, resistance to protease degradation, and the like.

[0325] "Amino acids" are molecules containing an amine group, a carboxylic acid group, and a side-chain that is specific to each amino acid. The key elements of an amino acid are carbon, hydrogen, oxygen, and nitrogen and have the generic formula H_2N—CHR—COOH, wherein R represents a side chain group. The various α-amino acids differ in the side-chain moiety that is attached to the α-carbon. The "amino acids" of the present technology include the known naturally occurring protein amino acids, which are referred to by both their common three letter abbreviation and single letter abbreviation. See generally *Non-naturally occurring melanocortin analogs: A User's Guide*, G. A. Grant, editor, W.H. Freeman & Co., New York (1992), the teachings of which are incorporated herein by reference, including the text and table set forth at pages 11 through 24. As set forth above, the term "amino acid" also includes stereoisomers and modifications of naturally occurring protein amino acids, non-protein amino acids, post-translationally modified amino acids, enzymatically synthesized amino acids, derivatized amino acids, constructs or structures designed to mimic amino acids, and the like. Modified and unusual amino acids are described generally in *Non-naturally occurring melanocortin analogs: A User's Guide*, supra; Hruby et al., *Biochem. J.* 268:249-262 (1990); and Toniolo, *Int. J. Peptide Protein Res.* 35:287-300 (1990); the teachings of all of which are incorporated herein by reference.

[0326] The phrase "amino acid side chain moiety" used herein, including as used in the specification and claims, includes any side chain of any amino acid, as the term "amino acid" is defined herein. This thus includes the side chain moiety present in naturally occurring amino acids. It further includes side chain moieties in modified naturally occurring amino acids, such as glycosylated amino acids. It further includes side chain moieties in stereoisomers and modifications of naturally occurring protein amino acids, non-protein amino acids, post-translationally modified amino acids, enzymatically synthesized amino acids, derivatized amino acids, constructs, or structures designed to mimic amino acids, and the like. For example, the side chain moiety of any amino acid described herein is included within the definition. A

"derivative" of an amino acid side chain moiety is included within the definition of an amino acid side chain moiety.

[0327] The "derivative" of an amino acid side chain moiety includes any modification to or variation in any amino acid side chain moieties, including a modification of naturally occurring amino acid side chain moieties. By way of example, derivatives of amino acid side chain moieties include straight chain or branched, cyclic or noncyclic, substituted or unsubstituted, saturated or unsaturated, alkyl, aryl or aralkyl moieties.

[0328] In the peptides described herein, conventional amino acid residues have their conventional meaning as given in Chapter 2400, of the *Manual of Patent Examining Procedure,* 8th Ed. Thus, "Ala" is alanine; "Arg" is arginine; "Asn" is asparagine; "Asp" is aspartic acid; "Cys" is cysteine; "Gln" is glutamine; "Glu" is glutamic acid; "His" is histidine; "Ile" is isoleucine; "Leu" is leucine; "Lys" is lysine; "Met" is methionine; "Phe" is phenylalanine; "Pro" is proline; "Ser" is serine; "Thr" is threonine; "Trp" is tryptophan; "Tyr" is tryosine; and "Val" is valine. Unless otherwise indicated, all amino acids abbreviations represent either isomer, i.e., the L-isomer, the D-isomer, or combinations thereof may be used. Thus, for example, "L-Phe" or "lPhe" is L-phenylalanine; "D-Phe" or "dPhe" is D-phenylalanine; dVal is D-valine; dPro is D-proline; "D-/L-Phe" or "d/lPhe" is D-phenylalanine, L-phenylalanine, or combinations thereof; "Phe" is also D-phenylalanine, L-phenylalanine, or combinations thereof, and so on. Non-standard amino acids are "Nle" is norleucine; "Nal" is naphthylalanine; "D-Nal" is D-naphthylalanine; D-Nal(2′) or DNal(2') is D-2′-naphthylalanine; L-Nal(2') or LNal(2') is L-2′-naphthylalanine; L-Nal(1') is L-1′-naphthylalanine; D-Nal(1') or DNal(1') is D-1′-naphthylalanine; Tle is tert-Leucine; Nva is norvaline; Orn is ornithine; and so on.

[0329] An alpha (α)-amino acid has the generic formula $H_2N—C_\alpha HR—COOH$, where R is a side chain moiety and the amino group is attached to the carbon atom immediately adjacent to the carboxylate group (i.e., the α-carbon). Other types of amino acids exist when the amino group is attached to a different carbon atom. For example, 253 (β)-amino acids, the carbon atom to which the amino group is attached is separated from the carboxylate group by one carbon atom, C_β. For example, α-alanine has the formula $H_2N—C_\alpha H(CH_3)—COOH$. In contrast, β-alanine has the general formula $H_2N—C_\beta H_2—C_\alpha H_2—COOH$ (i.e., 3-aminopropanoic acid).

[0330] When β-amino acids are incorporated into peptides, two main types of β-peptides exist: those with the side chain residue, R, on the carbon next to the amine are called β^3 peptides and those with the side chain residue on the carbon next to the carbonyl group are called β^2 amino acids. As a non-limiting example, "β-valine" may refer to:

—NH—$C_\beta H_2$—$C_\alpha H(CH_3)_2$—CO—, i.e., β^2-valine (R on carboxy side);

—NH—$C_\beta H(CH_3)_2$—$C_\alpha H_2$—CO—, i.e., β^3-valine (R on amino side); or

—NH—$C_\beta H(CH_3)_2$—$C_\alpha H(CH_3)_2$—CO—, i.e., $\beta^{2,3}$-valine (R at both positions).

[0331] Further, β-amino acids may adopt L- or D- stereochemistry. Unless otherwise indicated, all β-amino acid abbreviations represent either isomer, i.e., the L-isomer, the D-isomer, or a combination thereof.

[0332] Gamma (γ)-amino acids are amino acids with the carbon atom to which the amino group attaches is separated from the carboxylate moiety by two carbon atoms. For example, γ-amino butyric acid has the formula, H_2N—$C_\gamma H_2$—$C_\beta H_2$—$C_\alpha H_2$—COOH.

[0333] For additional modified and unusual amino acids, see §2422 of the MPEP, particularly Table 4 at 2400-24. Additionally, "Ac" indicates N-acetyl and "cyclo" refers to a cyclic structure, which is also shown in the literature as "c" or referred to as a "lactam." "NH_2" indicates an amine group, typically added on the C-terminus of a polypeptide. Accordingly, as used herein, an —NH_2 moiety on the C-terminus of a peptide indicates an amidated C-terminus. In addition, the following abbreviations are used herein: Harg is Homo arginine; Hlys is Homo lysine.

[0334] Additional abbreviations are used as follows: tBu is tert-butyl; Hyp(Bzl) is benzyl-L-hydroxy-proline; glutaric acid linker is CO—$(CH_2)_3$—CO; Pen is L-Penicillamine; Aib is 2-Aminoisobutyric acid; Aba is 4-amino-1,2,4,5-tetra-hydro-2-benzazepin-3-one; Pip is piperidine-2-carboxylic acid; Nip is piperidine-3-carboxylic acid; Tic is tetrahydroquinoline-3-carboxylic acid; Bip is biphenylalanine; Phg is α-Phenyl-glycine; Sar is Sarcosine; Azt is 3′-azido-3′-deoxythymidine; Oic is Octohydroindole-2-carboxylic acid; Ata is 7-amino-7,8-dihydro4H-(1,2,3)triazolo(1,5-a)(1,4)diazepin-6(5H)-one; Aia is 4-amino-1,4,5,6-tetrahydroazepino(4,3-*b*)indol-3(*2H*)-one; Mamb is 3-aminomethylbenzoic acid; Atc is 2-Aminotetraline-2-carboxylic acid; APC is 1-Amino-4-phenylcyclohexane-carboxylic acid; ACC is 4-

Aminophenylpiperidine-4-carboxylic acid (APPC); Acpc is 1-aminocyclo-propane-1-carboxylic acid; Aic is 2-aminoindone-2-carboxylic acid; p(Cl)Phe is para-chloro-phenylalanine (I – iodo, Br- bromo, F- fluoro, CF_3 - trifluoromethyl); and p(Cl)dPhe is para-chloro-D-phenylalanine (I – iodo, Br- bromo, F- fluoro, CF_3 - trifluoromethyl).

[0335] The term "alkene" includes unsaturated hydrocarbons that contain one or more double carbon-carbon bonds. Examples of such alkene groups include ethylene, propene, and the like.

[0336] The term "alkenyl" includes a linear monovalent hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbon atoms containing at least one double bond; examples thereof include ethenyl, 2-propenyl, and the like.

[0337] The "alkyl" groups specified herein include those alkyl radicals of the designated length in either a straight or branched configuration. Examples of such alkyl radicals include methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, isohexyl, and the like.

[0338] The term "alkynyl" includes a linear monovalent hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbon atoms containing at least one triple bond; examples thereof include ethynyl, propynyl, butynyl, and the like.

[0339] The term "aryl" includes a monovalent or bicyclic aromatic hydrocarbon radical of 6-to-12 ring atoms, and optionally substituted independently with one or more substituents selected from alkyl, haloalkyl, cycloalkyl, alkoxy, alkythio, halo, nitro, acyl, cyano, amino, monosubstituted amino, disubstituted amino, hydroxy, carboxy, or alkoxy-carbonyl. Examples of an aryl group include phenyl, biphenyl, naphthyl, 1-naphthyl, and 2-naphthyl, derivatives thereof, and the like.

[0340] The term "aliphatic" includes compounds with hydrocarbon chains, such as for example alkanes, alkenes, alkynes, and derivatives thereof.

[0341] The term "acyl" includes a group RCO—, where R is an organic group. An example is the acetyl group CH_3CO—, referred to herein as "Ac."

[0342] The term "fatty acid" describes a carboxylic acid with an aliphatic chain, which may be fully saturated or partially unsaturated, and optionally attached to a

functional group such as a hydroxyl group or a carboxyl group. The aliphatic chain may contain e.g., from 6 to 26 carbon atoms and hydrogen atoms.

[0343] A peptide or aliphatic moiety is "acylated" when an alkyl or substituted alkyl group as defined above is bonded through one or more carbonyl {—(C=O)—} groups. A peptide is most usually acylated at the N-terminus.

[0344] An "omega amino derivative" includes an aliphatic moiety with a terminal amino group. Examples of omega amino derivatives include aminoheptanoyl and the amino acid side chain moieties of ornithine and lysine.

[0345] The term "heteroaryl" includes mono- and bicyclic aromatic rings containing from 1 to 4 heteroatoms selected from nitrogen, oxygen, and sulfur. Five- or six-membered heteroaryl are monocyclic heteroaromatic rings; examples thereof include thiazole, oxazole, thiophene, furan, pyrrole, imidazole, isoxazole, pyrazole, triazole, thiadiazole, tetrazole, oxadiazole, pyridine, pyridazine, pyrimidine, pyrazine, and the like. Bicyclic heteroaromatic rings include, but are not limited to, benzothiadiazole, indole, benzothiophene, benzofuran, benzimidazole, benzisoxazole, benzothiazole, quinoline, benzotriazole, benzoxazole, isoquinoline, purine, furopyridine, and thienopyridine.

[0346] An "amine" includes compounds that contain an amine group (—NH_2).

[0347] An "amide" includes compounds that have a trivalent nitrogen attached to a carbonyl group (i.e., —CO—NH_2), such as for example methylamide, ethylamide, propylamide, and the like. A peptide is most usually amidated at the C-terminus by the addition of an amine (—NH_2) moiety to the C-terminal carboxyl group.

[0348] An "imine" includes compounds that have a carbon-nitrogen double bond, with the nitrogen also attached to a hydrogen (NH=CH—R).

[0349] An "imide" includes compounds containing an imido group (—OC—NH—CO—).

[0350] A "nitrile" includes compounds that are carboxylic acid derivatives and contain a (—CN) group bound to an organic group.

[0351] The term "halogen" is intended to include the halogen atoms fluorine, chlorine, bromine and iodine, and groups including one or more halogen atoms, such as —CF_3 and the like.

[0352] Amino acids, including stereoisomers and modifications of naturally occurring amino acids, protein amino acids, non-protein amino acids, post-translationally modified amino acids, enzymatically synthesized amino acids, derivatized amino acids, constructs, or structures designed to mimic amino acids (peptide mimetics), and the like, including all of the foregoing, are sometimes referred to herein as "residues."

[0353] A peptide or amino acid "mimetic" is a non-amino acid molecule that mimics a peptide (a chain of amino acids) or one amino acid residue.

[0354] "Substantial degradation" refers to the degradation of the N-terminal extension, the C-terminal extension, both N- and C-terminal degradation or degradation to other regions of the non-naturally occurring melanocortin analog by physiological enzymes and other factors, in such a manner or to a degree that side effects appear. According to one aspect, a non-naturally occurring melanocortin analog having a C-terminal extension that resists substantial degradation is one where no more than 50% of the administered peptide causes side effects and/or displays a low half-life. In some aspects, no more than 25% of the administered peptide causes side effects and/or displays a low half-life. More preferably, in some aspects, less than 10% of the administered peptide causes side effects and/or displays a low half-life, as compared to a non-naturally occurring melanocortin analog that lacks a C-terminal extension.

[0355] The terms "administering" or "administer" include delivery of therapies (e.g., combination therapies, non-naturally occurring melanocortin analogs (also referred to herein as peptides), anti-cancer agents) of the present technology to a subject either by local or systemic administration. Administration may be topical (including ophthalmic and to mucous membranes including vaginal and rectal delivery), pulmonary (e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer), intratracheal, intranasal, epidermal and transdermal, oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; or intracranial, e.g., intrathecal or intraventricular, administration.

[0356] The terms "active ingredient" and "active compound" refer to a biologically active substance, whether naturally or non-naturally occurring, that is the main component of the pharmaceutical composition which elicits the intended effect of an administered therapeutic. This may be any component that drives the pharmacological

activity or direct effect in the diagnosis, cure, mitigation, treatment, or prevention of the conditions associated with the present technology, such as but not limited to, reduced appetite and weight loss.

[0357] As used herein, a "composition" or a "pharmaceutical composition" refers to a mixture of the active ingredient with other chemical components, such as pharmaceutically acceptable carriers and/or excipients.

[0358] As used herein, a "pharmaceutically acceptable carrier" of the first or the second pharmaceutical composition refers to a carrier or diluent that does not cause significant irritation to an organism, does not abrogate the biological activity and properties of the administered active ingredient, and/or does not interact in a deleterious manner with the other components of the composition in which it is contained. The term "carrier" encompasses any excipient, binder, diluent, filler, salt, buffer, solubilizer, lipid, stabilizer, or other material well known in the art for use in pharmaceutical formulations. The choice of a carrier for use in a composition will depend upon the intended route of administration for the composition. The preparation of pharmaceutically acceptable carriers and formulations containing these materials is described in, e.g., Remington's Pharmaceutical Sciences, 21st Edition, ed. University of the Sciences in Philadelphia, Lippincott, Williams & Wilkins, Philadelphia Pa., 2005, which is incorporated herein by reference in its entirety). Some examples of physiologically acceptable carriers include antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN® (ICI, Inc.; Bridgewater, N.J.), polyethylene glycol (PEG), and PLURONICS™ (BASF; Florham Park, N.J.). An "excipient" of the first or the second pharmaceutical composition refers to an inert substance added to a composition to further facilitate administration of a compound. Examples, without limitation, of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils, and polyethylene glycols.

[0359] As used herein, "a side effect associated with the anti-cancer agent", "an adverse side-effect associated with the anti-cancer agent", or "a side effect induced by the anti-cancer agent", refers to any unwanted, undesirable, or deleterious biological activity occurs during or after independent use of the anti-cancer agent. Examples of such side effects include, but are not limited to, anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite. Such anti-cancer agents may also be administered to subjects for therapeutic uses besides cancer, for example, to treat, reduce, or prevent a condition or disease in a subject not having cancer.

[0360] The terms "treat," "treatment," and "treating" refer to a manner of providing a pharmaceutical composition and/or melanocortin analog to alleviate disease outcomes. This includes utilizing administration techniques as described in the context of the present technology. Efficacy of treatment may be determined by various assessment methods as described in the context of the present technology (e.g., assessment of appetite, food consumption, body weight, muscle mass, fat mass, and measurement of biomarkers). The term "biomarker" refers to a biological output that is used as a measure of cellular response, whether that be to assess response to therapeutics, disease status, such as cachexia, or as a predictor of clinical outcomes. Biomarkers evaluated in the context of cells, tissue, or whole organisms. The term "disease" herein refers to any disorder adversely affecting biological status. This includes weight-related disorders, such as cachexia. Disease also may be in the context of human and animal health.

[0361] The terms "treat", "treatment", and "treating" may also refer to the reduction or inhibition of the progression and/or duration of a disease (e.g., cancer), the reduction or amelioration of the severity of the disease, and/or the amelioration of one or more symptoms thereof resulting from the administration of one or more therapies. Specifically, these terms may refer to: (1) a stabilization, reduction (e.g. by more than 10%, 20%, 30%, 40%, 50%, or more than 60% of the population of cancer cells and/or tumor size before administration), or elimination of the cancer cells, (2) inhibiting cancerous cell division and/or cancerous cell proliferation, (3) relieving to some extent (or, preferably, eliminating) one or more symptoms associated with a pathology related to or caused in part by unregulated or aberrant cellular division, (4) an increase in disease-free, relapse-free, progression-free, and/or overall survival, duration, or rate,

(5) a decrease in hospitalization rate, (6) a decrease in hospitalization length, (7) eradication, removal, or control of primary, regional and/or metastatic cancer, (8) a stabilization or reduction (e.g. by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, or at least 80% relative to the initial growth rate) in the growth of a tumor or neoplasm, (9) an impairment in the formation of a tumor, (10) a reduction in mortality, (11) an increase in the response rate, the durability of response, or number of patients who respond or are in remission, (12) the size of the tumor is maintained and does not increase or increases by less than 10%, less than 5%, less than 4%, or less than 2%, (13) a decrease in the need for surgery (e.g. colectomy, mastectomy), (14) preventing or reducing the metastasis of cancer cells, and (15) promoting mass gain and/or mass maintenance by the subject or otherwise preventing mass loss or reducing mass loss by the subject prior to, during, or after administration of an anti-cancer agent. The terms "treat", "treatment", and "treating" include prophylactic and/or therapeutic treatments. If it is administered prior to clinical manifestation of a condition, the treatment is considered prophylactic. Therapeutic treatment includes, e.g., ameliorating or reducing the severity of a disease, or shortening the length or frequency of the disease.

[0362] As used herein, the terms "effective amount" or "therapeutically effective amount", refer to that amount of the active ingredient being administered which will relieve to some extent one or more of the symptoms of the disease being treated. The result may be a reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. An appropriate "effective amount" may differ from one individual to another. An appropriate "effective amount" in any individual case may be determined using techniques, such as a dose escalation study.

[0363] The term "after administration" refers to any duration of time after the non-naturally occurring melanocortin analog or pharmaceutical composition thereof, and/or the anti-cancer agent has been administered to a subject. "After administration" may also refer to the duration of time after one dose has been completed or after more than one dose has been completed, such as two doses, three doses, four doses, and the like. In some embodiments, "after administration" refers to completion of dosing regimen that includes one or more doses. Likewise, the term "prior to" refers to any duration of time before the non-naturally occurring melanocortin analog or pharmaceutical composition thereof, and/or the anti-cancer agent has been

administered to a subject. Unless otherwise specified, durations of time encompassed by "after administration" or "prior to administration" may include seconds, minutes, hours, days, weeks, months, and years.

[0364] "Appetite" in a subject and/or patient is typically assessed by their desire to eat and/or the amount of food they consume. As used herein, appetite may be assessed through a daily questionnaire given at specified or random times of the day. In the questionnaire, subjects or patients rate their hunger and/or desire to eat greater varieties of food using scales ranging from 0 (not at all) to 100 (extremely).

[0365] "Cachexia" refers to a state of general ill health and malnutrition characterized by loss of body mass including loss of weight, loss of muscle mass (skeletal, smooth, and/or cardiac muscle), loss of fat mass, or a combination thereof, and wasting. It is often associated with and induced by certain diseases or conditions such as, but not limited to, cancer, cystic fibrosis, or AIDS. The term "cancer cachexia" refers to cachexia induced by cancer. Diagnostic criterion for cachexia may include (i) weight loss of greater than 5% over past 6 months; (ii) weight loss of greater than 2% in patients with a body mass index (BMI) less than 20 kg/m^2; or (iii) weight loss of greater than 2% in patients with sarcopenia (or appendicular skeletal muscle index consistent with sarcopenia). See Fearon K, et al., *Lancet Oncol.* 12(5):489-95 (2011). Cachexia may be used interchangeably with the term "Protein-Energy Wasting" (i.e., PEW).

[0366] "Anorexia" refers to a loss of appetite, whether brought on by medical, physiological, or psychological factors. Anorexia is often closely associated with, and generally contributes to, cachexia seen in patients with advanced cancers and other conditions.

[0367] The term "Body Mass Index" or "BMI" refers to a value derived from an individual's body weight and height. Specifically, BMI is determined by body weight (kilograms) divided by the square of height (m^2) and is expressed in units of "kg/m^2". "Normal" BMI ranges are known to a person of ordinary skill in the art and consider factors such as patient sex, age, height, race, and body type. Typically, a normal BMI range is about 18.5 kg/m^2 to about 25 kg/m^2.

[0368] The terms "subject" and "patient" refer to anyone being evaluated for disease or condition or being administered a therapeutic or pharmaceutical composition. This includes people without diagnosed or confirmed disease or condition.

This also includes people with diagnosed or confirmed disease or condition, such as cancer, loss of appetite, nausea, emesis, anorexia, or cachexia.

[0369] The term "control," as used herein, refers to any basis for comparison to the subject (e.g., test subject). A control includes, but is not limited to, a given measurement at baseline in a subject, any subject who has not been administered the therapeutic or pharmaceutical composition (e.g., the non-naturally occurring melanocortin analog, a therapeutically effective amount of the non-naturally occurring melanocortin analog or a pharmaceutical composition thereof) or administered a placebo. A control may reference to a measurement from the same subject as the subject being treated (e.g., a measurement at baseline or an intermediate timepoint), or from a different subject (e.g., a subject not having the same treatment or condition as the subject being treated).

[0370] The disclosure of all publications, patents, and published patent applications listed herein are hereby incorporated by reference in their entireties, including but not limited to U.S. Patent Nos. 8,541,545 and 9,534,018.

Non-naturally Occurring Melanocortin Analogs

[0371] The present technology provides non-naturally occurring melanocortin analogs that may be administered to a subject in need thereof. The present technology also provides methods of treating, preventing, or reducing unwanted side effects induced by anti-cancer agents (e.g., chemotherapeutic agents) as well as symptoms associated with cancer via administration of a non-naturally occurring melanocortin analog, which may be the non-naturally occurring melanocortin analog as described herein in any of its embodiments.

[0372] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence according to Formula (I),

$X^1X^2X^3R^1R^2R^3R^4R^5R^6R^7R^8R^9R^{10}R^{11}R^{12}R^{13}R^{14}R^{15}R^{16}R^{17}R^{18}R^{19}R^{20}Y^1Y^2Y^3Y^4Y^5Y^6Y^7Y^8$ (I)

wherein:

R^1 is absent or is selected from the group consisting of cysteine, norleucine (Nle), acetylated norleucine (Ac-Nle), acetylated *trans*-4-guanidinyl-proline (Ac-*trans*Pro(guan)), acetylated *cis*-4-guanidinyl-proline (Ac-*cis*Pro(guan)), *trans*-4-

guanidinyl-proline (*trans*Pro(guan)), *cis*-4-guanidinyl-proline (*cis*Pro(guan)), acetylated cysteine, methylated D-phenylalanine, succinic acid, o-phthalic acid, tyrosine, D-tyrosine, di-methyl tyrosine (Dmt), aspartic acid, glutaric acid, CO-cis-CH=CH—CO, an n-pentanoyl group, an n-hexanoyl group, leucine, isoleucine, valine, norvaline, alanine, glycine, proline, methionine, lysine, phenylalanine, glutamic acid, asparagine, acetylated D-arginine, acetylated arginine, acetylated D-methionine, acetylated D-isoleucine, acetylated D-leucine, acetylated D-valine, acetylated alanine, acetylated D-alanine, acetylated tert-leucine (Ac-Tle), acetylated D-tert-leucine (Ac-dTle), acetylated norvaline (Ac-Nva), acetylated glycine, acetylated D-proline, acetylated D-phenylalanine, acetylated glutamic acid, acetylated D-tyrosine, acetylated D-glutamine, and acetylated D-asparagine;

R^2 is absent or is selected from the group consisting of proline, histidine, D-hydroxyproline (dHyp), hydroxyproline (Hyp), *trans*Pro(guan), *cis*Pro(guan), D-aspartic acid, aspartic acid, D-glutamic acid, glutamic acid, glycine, lysine, alanine, D-alanine, tryptophan, cysteine, D-cysteine, norleucine, arginine, succinic acid, glutaric acid, CO-cis-CH=CH—CO, an n-pentanoyl group, an n-hexanoyl group, methionine, phenylalanine, penicillamine (Pen), and D-penicillamine (dPen);

R^3 is absent or is selected from the group consisting of histidine, histidine methylated at positions 1 or 3, D-proline, L-proline, hydroxyproline (Hyp), D-hydroxyproline (dHyp), *trans*Pro(guan), *cis*Pro(guan), alanine, D-alanine, D-methionine, valine, D-valine, glutamic acid, prolylglycine (Pro-Gly), glycylglycine (Gly-Gly), tryptylarginine (Trp-Arg), glycine, phenylalanine, D-phenylalanine, succinic acid, D-leucine, leucine, D-isoleucine, isoleucine, tryptophan, D-tryptophan, arginine, 4-amino-1,2,4,5-tetrahydro-2-benzazepin-3-one (Aba), beta-alanine (β-Ala), 3-aminomethylbenzoic acid (Mamb), 1-aminocyclo-propane-1-carboxylic acid (Acpc), 2-aminotetraline-2-carboxylic acid (Atc), 7-amino-7,8-dihydro-4H-(1,2,3)triazolo-(1,5-a)(1,4)diazepin-6(5H)-one (Ata), 4-amino-1,4,5,6-tetrahydroazepino(4,3-*b*)indol-3(*2H*)-one (Aia), 1-amino-4-phenylcyclohexane-carboxylic acid (APC), 4-aminophenylpiperidine-4-carboxylic acid (APPC), octohydroindole-2-carboxylic acid (Oic), 1-amino-1-cyclohexanecarboxylic acid (Che), tetrahydro-isoquinoline-3-carboxylic acid (Tic), indoline-2-carboxylic acid (Ioc), 2-aminoindone-2-carboxylic acid (Aic), and 1-amino-1-cyclopentane carboxylic (Cpe);

R^4 is selected from the group consisting of histidine, D-phenylalanine, L-phenylalanine, D-Nal(2'), (o-Phe)Phe, aspartic acid, biphenylalanine (Bip), dBip, glycine, proline, cysteine, para-chloro-D-phenylalanine (p(Cl)dPhe), para-bromo-D-phenylalanine (p(Br)dPhe), para-iodo-D-phenylalanine (p(I)dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-trifluoromethyl-D-phenylalanine (p(CF_3)dPhe);

R^5 is absent or is selected from the group consisting of arginine, homoarginine, ornithine, histidine, alanine, proline, *trans*Pro(guan), *cis*Pro(guan), Pip, Nip, Tic, Phg, Sar, Azt, phenylalanine, D-Nal(2'), lysine, D-arginine, D-ornithine, D-histidine, D-alanine, D-lysine, glycine, aspartic acid, D-aspartic acid, glutamic acid, D-glutamic acid, cysteine, and p(I)dPhe;

R^6 is absent or is selected from the group consisting of D-tryptophan, L-tryptophan, D-Nal(2'), L-Nal(2'), Tic, Bip, arginine, histidine, D-histidine, cysteine, Nal(1'), D-Nal(1'), Aia, D-phenylalanine, phenylalanine, Aba, Ata, tyrosine, D-tyrosine, Pen, dPen, alanine, and D-alanine;

R^7 is absent or is selected from the group consisting of glycine, aspartic acid, glutamic acid, cysteine, lysine, D-cysteine, D-lysine, 2,3-diamino-propionic acid (Dap), methionine, proline, tryptophan, D-Nal(2'), ornithine, D-ornithine, Pen, dPen, and tetrahydro-isoquinoline-3-carboxylic acid (Tic);

R^8 is absent or is lysine or arginine;

R^9 is absent or is tryptophan;

R^{10} is absent or is lysine;

R^{11}-R^{20} are each independently absent or selected from the group consisting of cysteine, norleucine, tyrosine, aspartic acid, leucine, isoleucine, valine, norvaline, alanine, glycine, proline, methionine, lysine, phenylalanine, glutamic acid, arginine, histidine, hydroxyproline, D-hydroxyproline, D-proline, prolylglycine (Pro-Gly), D-Nal(2'), L-Nal(2'), Bip, ornithine, and tryptophan;

wherein if R^2 is an n-pentanoyl group or an n-hexanoyl group, then R^1, X^1, X^2 and X^3 are absent;

X^1 is absent or is selected from the group consisting of D-cysteine, L-cysteine, D-threonine, D-proline, L-proline, β-homo proline, D-alanine, L-alanine, β-alanine, D-arginine, L-arginine, D-valine, L-valine, β-valine, D-leucine, L-leucine, β-leucine, D-

isoleucine, L-isoleucine, β-isoleucine, a piperazin-2-one ring, norvaline, glycine, methionine, lysine, phenylalanine, tyrosine, glutamic acid, asparagine, aspartic acid, acetylated D-arginine, acetylated L-arginine, acetylated D-valine, and acetylated norleucine;

X^2 is absent or is selected from the group consisting of D-threonine, D-proline, L-proline, β-homo proline, D-alanine, L-alanine, β-alanine, D-valine, L-valine, β-valine, D-leucine, L-leucine, β-leucine, D-isoleucine, L-isoleucine, β-isoleucine, a piperazin-2-one ring, norvaline, glycine, methionine, lysine, phenylalanine, tyrosine, glutamic acid, asparagine, aspartic acid, and norleucine;

X^3 is absent or is selected from the group consisting of D-cysteine, L-cysteine, D-threonine, D-proline, L-proline, β-homo proline, D-alanine, L-alanine, D-valine, L-valine, β-valine, D-leucine, L-leucine, β-leucine, D-isoleucine, L-isoleucine, β-isoleucine, a piperazin-2-one ring, norvaline, glycine, methionine, lysine, phenylalanine, tyrosine, glutamic acid, asparagine, aspartic acid, and norleucine;

Y^1 is selected from the group consisting of D-alanine, L-alanine, β-alanine, D-threonine, L-threonine, β-threonine, D-valine, L-valine, β-valine, (3-methyl)-β-valine, D-leucine, L-leucine, β-leucine, D-isoleucine, L-isoleucine, β-isoleucine, D-tert-leucine, L-tert-leucine, norleucine, L-proline, D-proline, β-homo proline, a piperazin-2-one ring, Hyp, dHyp, glycine, aspartic acid, D-aspartic acid, L-arginine, D-arginine, L-asparagine, D-asparagine, L-lysine, D-lysine, and L-tryptophan;

Y^2 is absent or is selected from the group consisting of D-proline, L-proline, β-homo proline, a piperazin-2-one ring, D-threonine, L-threonine, β-threonine, D-valine, L-valine, β-valine, (3-methyl)-β-valine, D-leucine, L-leucine, β-leucine, D-isoleucine, L-isoleucine, β-isoleucine, D-tert-leucine, L-tert-leucine, norleucine, Hyp, dHyp, D-alanine, L-alanine, β-alanine, glycine, aspartic acid, D-aspartic acid, arginine, D-arginine, asparagine, and D-asparagine;

Y^3 is absent or is selected from the group consisting of D-cysteine, L-cysteine, D-threonine, L-threonine, D-alanine, L-alanine, D-lysine, L-lysine, D-proline, L-proline, D-valine, L-valine, β-valine, (3-methyl)-β-valine, D-leucine, L-leucine, β-leucine, D-isoleucine, L-isoleucine, β-isoleucine, and a piperazin-2-one ring;

Y^4 is absent or is D-aspartic acid, aspartic acid, D-proline or D-valine;

Y^5 is absent or is D-proline or D-valine;

Y^6 is absent or is D-proline or D-valine;

Y^7 is absent or is D-proline or D-valine;

Y^8 is absent or is D-proline or D-valine;

the non-naturally occurring melanocortin analog is optionally cyclized through a moiety selected from the group consisting of:

a disulfide bond between R^1 or R^2 and R^7 or X^1 when R^1 or R^2 is cysteine and R^7 or X^1 is cysteine;

a disulfide bond between R^2 and any one of R^5-R^{20} when R^2 and the any one of R^5-R^{20} are selected from the group consisting of D-cysteine, cysteine, Pen, and dPen;

a lactam bridge between R^1 and R^7 when R^1 is norleucine and R^7 is glutamic acid;

a side-chain lactam bridge between R^1 or R^2 and R^7 when R^1 or R^2 is glutamic acid, aspartic acid, or CO-cis-CH=CH—CO, and R^7 is lysine, D-lysine, Dap, D-ornithine, or ornithine;

a side-chain lactam bridge between R^2 and R^7 when R^2 is lysine, and R^7 is glutamic acid or aspartic acid;

a side-chain lactam bridge between R^1 or R^2 and R^8 when R^1 or R^2 is glutamic acid or aspartic acid, R^8 is lysine, and R^7 is glycine, proline or tryptophan;

a side-chain lactam bridge between R^2 or R^4 and R^{10} when R^2 is glutamic acid or aspartic acid and R^{10} is lysine;

a lactam closure between R^1 and R^7 when R^1 is succinic acid or o-phthalic acid and R^7 is lysine; and

a lactam closure between R^2 and R^7 when R^2 is succinic acid and R^7 is 2,3-diamino-propionic acid;

$X^1X^2X^3$ represents an optionally present N-terminus; and

$Y^1Y^2Y^3Y^4Y^5Y^6Y^7Y^8$ represents a C-terminus.

[0373] In some embodiments of Formula (I):

R^1 is absent or is selected from the group consisting of cysteine, norleucine (Nle), acetylated norleucine (Ac-Nle), *trans*-4-guanidinyl-proline (*trans*Pro(guan)), *cis*-4-guanidinyl-proline (*cis*Pro(guan)), acetylated *trans*-4-guanidinyl-proline (Ac-*trans*Pro(guan)), acetylated *cis*-4-guanidinyl-proline (Ac-*cis*Pro(guan)), acetylated cysteine, methylated D-phenylalanine, succinic acid, o-phthalic acid, tyrosine, D-tyrosine, di-methyl tyrosine (Dmt), aspartic acid, glutaric acid, CO-cis-CH=CH—CO, an n-pentanoyl group, an n-hexanoyl group, leucine, isoleucine, valine, norvaline, alanine, glycine, proline, methionine, lysine, phenylalanine, glutamic acid, asparagine, acetylated D-arginine, acetylated arginine, acetylated D-methionine, acetylated D-isoleucine, acetylated D-leucine, acetylated D-valine, acetylated alanine, acetylated D-alanine, acetylated tert-leucine (Tle), acetylated D-tert-leucine (dTle), acetylated norvaline (Nva), acetylated glycine, acetylated D-proline, acetylated D-phenylalanine, acetylated glutamic acid, acetylated D-tyrosine, acetylated D-glutamine, and acetylated D-asparagine;

R^2 is absent or is selected from the group consisting of proline, histidine, D-hydroxyproline (dHyp), hydroxyproline (Hyp), *trans*Pro(guan), *cis*Pro(guan), D-asprtic acid, aspartic acid, D-glutamic acid, glutamic acid, glycine, lysine, alanine, D-alanine, tryptophan, D-cysteine, cysteine, norleucine, arginine, succinic acid, glutaric acid, CO-cis-CH=CH—CO, an n-pentanoyl group, an n-hexanoyl group, methionine, phenylalanine, penicillamine (Pen), and D-penicillamine (dPen);

R^3 is absent or is selected from the group consisting of histidine, histidine methylated at positions 1 or 3, D-proline, L-proline, hydroxyproline (Hyp), D-hydroxyproline (dHyp), *trans*Pro(guan), *cis*Pro(guan), alanine, D-alanine, D-methionine, valine, D-valine, glutamic acid, prolylglycine (Pro-Gly), glycylglycine (Gly-Gly), tryptylarginine (Trp-Arg), glycine, phenylalanine, D-phenylalanine, succinic acid, D-leucine, leucine, D-isoleucine, isoleucine, tryptophan, D-tryptophan, arginine, 4-amino-1,2,4,5-tetrahydro-2-benzazepin-3-one (Aba), beta-alanine (β-Ala), 3-aminomethylbenzoic acid (Mamb), 1-aminocyclo-propane-1-carboxylic acid (Acpc), 2-aminotetraline-2-carboxylic acid (Atc), 7-amino-7,8-dihydro-4H-(1,2,3)triazolo-(1,5-a)(1,4)diazepin-6(5H)-one (Ata), 4-amino-1,4,5,6-tetrahydroazepino(4,3-*b*)indol-3(*2H*)-one (Aia), 1-amino-4-phenylcyclohexane-carboxylic acid (APC), 4-aminophenylpiperidine-4-carboxylic acid (APPC), octohydroindole-2-carboxylic acid (Oic), 1-amino-1-cyclohexanecarboxylic acid (Che), tetrahydro-isoquinoline-3-

carboxylic acid (Tic), indoline-2-carboxylic acid (Ioc), 2-aminoindone-2-carboxylic acid (Aic), and 1-amino-1-cyclopentane carboxylic (Cpe);

R^4 is selected from the group consisting of histidine, D-phenylalanine, L-phenylalanine, D-Nal(2'), (o-Phe)Phe, aspartic acid, biphenylalanine (Bip), dBip, glycine, proline, cysteine, para-chloro-D-phenylalanine (p(Cl)dPhe), para-bromo-D-phenylalanine (p(Br)dPhe), para-iodo-D-phenylalanine (p(I)dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-trifluoromethyl-D-phenylalanine ($p(CF_3)$dPhe);

R^5 is absent or is selected from the group consisting of arginine, homoarginine, ornithine, histidine, alanine, proline, *trans*Pro(guan), *cis*Pro(guan), Pip, Nip, Tic, Phg, Sar, Azt, phenylalanine, D-Nal(2'), lysine, D-arginine, D-ornithine, D-histidine, D-alanine, D-lysine, glycine, aspartic acid, D-aspartic acid, glutamic acid, D-glutamic acid, cysteine, and p(I)dPhe;

R^6 is absent or is selected from the group consisting of D-tryptophan, L-tryptophan, D-Nal(2'), L-Nal(2'), Tic, Bip, arginine, histidine, D-histidine, cysteine, Nal(1'), D-Nal(1'), Aia, D-phenylalanine, phenylalanine, Aba, Ata, tyrosine, D-tyrosine, Pen, dPen, alanine, and D-alanine;

R^7 is absent or is selected from the group consisting of glycine, aspartic acid, glutamic acid, cysteine, lysine, D-cysteine, D-lysine, 2,3-diamino-propionic acid (Dap), methionine, proline, tryptophan, D-Nal(2'), ornithine, D-ornithine, Pen, dPen, and tetrahydro-isoquinoline-3-carboxylic acid (Tic);

R^8 is absent or is lysine or arginine;

R^9 is absent or is tryptophan;

R^{10} is absent or is lysine;

R^{11}-R^{20} are each independently absent or selected from the group consisting of cysteine, norleucine, tyrosine, aspartic acid, leucine, isoleucine, valine, norvaline, alanine, glycine, proline, methionine, lysine, phenylalanine, glutamic acid, arginine, histidine, hydroxyproline, D-hydroxyproline, D-proline, prolylglycine (Pro-Gly), D-Nal(2'), L-Nal(2'), Bip, ornithine, and tryptophan;

wherein if R^2 is an n-pentanoyl group or an n-hexanoyl group, then R^1, X^1, X^2 and X^3 are absent;

X^1 is absent or is selected from the group consisting of D-cysteine, L-cysteine, D-threonine, D-proline, L-proline, β-homo proline, D-alanine, L-alanine, β-alanine, D-arginine, L-arginine, D-valine, L-valine, β-valine, D-leucine, L-leucine, β-leucine, D-isoleucine, L-isoleucine, β-isoleucine, a piperazin-2-one ring, norvaline, glycine, methionine, lysine, phenylalanine, tyrosine, glutamic acid, asparagine, aspartic acid, acetylated D-arginine, acetylated L-arginine, acetylated D-valine, and acetylated norleucine;

X^2 is absent or is selected from the group consisting of D-threonine, D-proline, L-proline, β-homo proline, D-alanine, L-alanine, β-alanine, D-valine, L-valine, β-valine, D-leucine, L-leucine, β-leucine, D-isoleucine, L-isoleucine, β-isoleucine, a piperazin-2-one ring, norvaline, glycine, methionine, lysine, phenylalanine, tyrosine, glutamic acid, asparagine, aspartic acid, and norleucine;

X^3 is absent or is selected from the group consisting of D-cysteine, L-cysteine, D-threonine, D-proline, L-proline, β-homo proline, D-alanine, L-alanine, D-valine, L-valine, β-valine, D-leucine, L-leucine, β-leucine, D-isoleucine, L-isoleucine, β-isoleucine, a piperazin-2-one ring, norvaline, glycine, methionine, lysine, phenylalanine, tyrosine, glutamic acid, asparagine, aspartic acid, and norleucine;

Y^1 is selected from the group consisting of D-alanine, L-alanine, D-valine, L-valine, D-leucine, L-leucine, D-isoleucine, L-isoleucine, D-tert-leucine, L-tert-leucine, norleucine, L-proline, D-proline, Hyp, dHyp, glycine, aspartic acid, D-aspartic acid, arginine, D-arginine, asparagine, D-asparagine, lysine, D-lysine, and tryptophan;

Y^2 is absent or is selected from the group consisting of D-proline, L-proline, D-valine, L-valine, D-tert-leucine, L-tert-leucine, norleucine, Hyp, dHyp, D-alanine, L-alanine, glycine, aspartic acid, D-aspartic acid, arginine, D-arginine, asparagine, and D-asparagine;

Y^3 is absent or is selected from the group consisting of D-lysine, L-lysine, D-proline, L-proline, D-valine, and L-valine;

Y^4 is absent or is D-aspartic acid, aspartic acid, D-proline or D-valine;

Y^5 is absent or is D-proline or D-valine;

Y^6 is absent or is D-proline or D-valine;

Y^7 is absent or is D-proline or D-valine;

Y^8 is absent or is D-proline or D-valine;

the non-naturally occurring melanocortin analog is optionally cyclized through a moiety selected from the group consisting of:

a disulfide bond between R^1 or R^2 and R^7 or X^1 when R^1 or R^2 is cysteine and R^7 or X^1 is cysteine;

a disulfide bond between R^2 and any one of R^5-R^{20} when R^2 and the any one of R^5-R^{20} are selected from the group consisting of D-cysteine, cysteine, Dap, Pen, and dPen;

a lactam bridge between R^1 and R^7 when R^1 is norleucine and R^7 is glutamic acid;

a side-chain lactam bridge between R^1 or R^2 and R^7 when R^1 or R^2 is glutamic acid, aspartic acid, or CO-cis-CH=CH—CO, and R^7 is lysine, D-lysine, D-ornithine, or ornithine;

a side-chain lactam bridge between R^2 and R^7 when R^2 is lysine, and R^7 is glutamic acid or aspartic acid;

a side-chain lactam bridge between R^1 or R^2 and R^8 when R^1 or R^2 is glutamic acid or aspartic acid, R^8 is lysine, and R^7 is proline, glycine or tryptophan;

a side-chain lactam bridge between R^2 or R^4 and R^{10} when R^2 is glutamic acid or aspartic acid and R^{10} is lysine;

a lactam closure between R^1 and R^7 when R^1 is succinic acid or o-phthalic acid and R^7 is lysine; and

a lactam closure between R^2 and R^7 when R^2 is succinic acid and R^7 is 2,3-diamino-propionic acid;

$X^1X^2X^3$ represents an optionally present N-terminus; and

$Y^1Y^2Y^3Y^4Y^5Y^6Y^7Y^8$ represents a C-terminus.

[0374] In some embodiments of Formula (I):

R^1 is absent or is selected from the group consisting of cysteine, norleucine (Nle), acetylated norleucine (Ac-Nle), *trans*-4-guanidinyl-proline (*trans*Pro(guan)), *cis*-4-guanidinyl-proline (*cis*Pro(guan)), acetylated *trans*-4-guanidinyl-proline (Ac-

*trans*Pro(guan)), acetylated *cis*-4-guanidinyl-proline (Ac-*cis*Pro(guan)), acetylated cysteine, tyrosine, D-tyrosine, di-methyl tyrosine (Dmt), aspartic acid, glutaric acid, leucine, isoleucine, valine, norvaline (Nva), alanine, glycine, proline, methionine, lysine, phenylalanine, glutamic acid, asparagine, acetylated D-arginine, acetylated arginine, acetylated D-methionine, acetylated D-isoleucine, acetylated D-leucine, acetylated D-valine, acetylated alanine, acetylated D-alanine, acetylated tert-leucine (Tle), acetylated D-tert-leucine (dTle), acetylated norvaline (Ac-Nva), acetylated glycine, acetylated D-proline, acetylated D-phenylalanine, acetylated glutamic acid, acetylated D-tyrosine, acetylated D-glutamine, and acetylated D-asparagine;

R^2 is absent or is selected from the group consisting of proline, histidine, D-hydroxyproline (dHyp), hydroxyproline (Hyp), *trans*Pro(guan), *cis*Pro(guan), D-aspartic acid, aspartic acid, D-glutamic acid, glutamic acid, glycine, lysine, alanine, D-alanine, tryptophan, D-cysteine, cysteine, norleucine, arginine, succinic acid, glutaric acid, CO-cis-CH=CH—CO, methionine, phenylalanine, penicillamine (Pen), and D-penicillamine (dPen);

R^3 is absent or is selected from the group consisting of histidine, D-proline, L-proline, hydroxyproline (Hyp), D-hydroxyproline (dHyp), *trans*Pro(guan), *cis*Pro(guan), alanine, D-alanine, D-methionine, valine, D-valine, glutamic acid, prolylglycine (Pro-Gly), glycylglycine (Gly-Gly), tryptylarginine (Trp-Arg), glycine, phenylalanine, D-phenylalanine, D-leucine, leucine, D-isoleucine, isoleucine, tryptophan, D-tryptophan, arginine, 4-amino-1,2,4,5-tetrahydro-2-benzazepin-3-one (Aba), beta-alanine (β-Ala), 3-aminomethylbenzoic acid (Mamb), 1-aminocyclo-propane-1-carboxylic acid (Acpc), 2-aminotetraline-2-carboxylic acid (Atc), 7-amino-7,8-dihydro-4H-(1,2,3)triazolo-(1,5-a)(1,4)diazepin-6(5H)-one (Ata), 4-amino-1,4,5,6-tetrahydroazepino(4,3-*b*)indol-3(*2H*)-one (Aia), 1-amino-4-phenylcyclohexane-carboxylic acid (APC), 4-aminophenylpiperidine-4-carboxylic acid (APPC), octohydroindole-2-carboxylic acid (Oic), 1-amino-1-cyclohexanecarboxylic acid (Che), tetrahydro-isoquinoline-3-carboxylic acid (Tic), indoline-2-carboxylic acid (Ioc), 2-aminoindone-2-carboxylic acid (Aic), and 1-amino-1-cyclopentane carboxylic (Cpe);

R^4 is selected from the group consisting of histidine, D-phenylalanine, L-phenylalanine, D-Nal(2'), aspartic acid, biphenylalanine (Bip), dBip, glycine, proline, cysteine, para-chloro-D-phenylalanine (p(Cl)dPhe), para-bromo-D-phenylalanine

(p(Br)dPhe), para-iodo-D-phenylalanine (p(I)dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-trifluoromethyl-D-phenylalanine (p(CF_3)dPhe);

R^5 is absent or is selected from the group consisting of arginine, homoarginine, ornithine, histidine, alanine, proline, *trans*Pro(guan), *cis*Pro(guan), Pip, Nip, Tic, Phg, Sar, Azt, phenylalanine, D-Nal(2′), lysine, D-arginine, D-ornithine, D-histidine, D-alanine, D-lysine, glycine, aspartic acid, D-aspartic acid, glutamic acid, D-glutamic acid, cysteine, and p(I)dPhe;

R^6 is absent or is selected from the group consisting of L-tryptophan, D-Nal(2′), L-Nal(2′), Tic, Bip, arginine, histidine, D-histidine, cysteine, Nal(1′), D-Nal(1′), Aia, D-phenylalanine, phenylalanine, Aba, Ata, tyrosine, D-tyrosine, Pen, dPen, alanine, and D-alanine;

R^7 is absent or is selected from the group consisting of glycine, aspartic acid, glutamic acid, cysteine, lysine, D-cysteine, D-lysine, 2,3-diamino-propionic acid (Dap), methionine, proline, tryptophan, D-Nal(2′), ornithine, D-ornithine, Pen, dPen, and tetrahydro-isoquinoline-3-carboxylic acid (Tic);

R^8 is absent or is lysine or arginine;

R^9 is absent or is tryptophan;

R^{10} is absent or is lysine;

R^{11}-R^{20} are absent;

X^1 is absent or is selected from the group consisting of D-cysteine, L-cysteine, D-threonine, D-proline, L-proline, D-alanine, L-alanine, β-alanine, D-arginine, L-arginine, D-valine, L-valine, D-leucine, L-leucine, D-isoleucine, L-isoleucine, norvaline, glycine, methionine, lysine, phenylalanine, tyrosine, glutamic acid, asparagine, aspartic acid, acetylated D-arginine, acetylated L-arginine, acetylated D-valine, and acetylated norleucine;

X^2 is absent or is selected from the group consisting of D-threonine, D-proline, L-proline, D-alanine, L-alanine, β-alanine, D-valine, L-valine, β-valine, D-leucine, L-leucine, D-isoleucine, L-isoleucine, norvaline, glycine, methionine, lysine, phenylalanine, tyrosine, glutamic acid, asparagine, aspartic acid, and norleucine;

X^3 is absent or is selected from the group consisting of D-cysteine, L-cysteine, D-threonine, D-proline, L-proline, D-alanine, L-alanine, D-valine, L-valine, D-leucine, L-leucine, D-isoleucine, L-isoleucine, norvaline, glycine, methionine, lysine, phenylalanine, tyrosine, glutamic acid, asparagine, aspartic acid, and norleucine;

Y^1 is absent or is selected from the group consisting of D-alanine, L-alanine, D-valine, L-valine, D-tert-leucine, L-tert-leucine, norleucine, L-proline, D-proline, Hyp, dHyp, glycine, aspartic acid, D-aspartic acid, arginine, D-arginine, asparagine, D-asparagine, lysine, D-lysine, and tryptophan;

Y^2 is absent or is selected from the group consisting of D-proline, L-proline, D-valine, L-valine, D-tert-leucine, L-tert-leucine, norleucine, Hyp, dHyp, D-alanine, L-alanine, glycine, aspartic acid, D-aspartic acid, arginine, D-arginine, asparagine, and D-asparagine;

Y^3 is absent or is selected from the group consisting of D-lysine, L-lysine, D-proline, L-proline, D-valine, and L-valine;

Y^4 is absent or is D-aspartic acid, aspartic acid, D-proline or D-valine;

Y^5 is absent or is D-proline or D-valine;

Y^6 is absent or is D-proline or D-valine;

Y^7 is absent or is D-proline or D-valine;

Y^8 is absent or is D-proline or D-valine;

the non-naturally occurring melanocortin analog is optionally cyclized through a moiety selected from the group consisting of:

a disulfide bond between R^1 or R^2 and R^7 or X^1 when R^1 or R^2 is cysteine and R^7 or X^1 is cysteine;

a disulfide bond between R^2 and any one of R^5-R^{20} when R^2 and the any one of R^5-R^{20} are selected from the group consisting of D-cysteine, cysteine, Dap, Pen, and dPen;

a lactam bridge between R^1 and R^7 when R^1 is norleucine and R^7 is glutamic acid;

a side-chain lactam bridge between R^1 or R^2 and R^7 when R^1 or R^2 is glutamic acid, aspartic acid, or CO-cis-CH=CH—CO, and R^7 is lysine, D-lysine, D-ornithine, or ornithine;

a side-chain lactam bridge between R^2 and R^7 when R^2 is lysine, and R^7 is glutamic acid or aspartic acid;

a side-chain lactam bridge between R^1 or R^2 and R^8 when R^1 or R^2 is glutamic acid or aspartic acid, R^8 is lysine, and R^7 is proline, glycine or tryptophan;

a side-chain lactam bridge between R^2 or R^4 and R^{10} when R^2 is glutamic acid or aspartic acid and R^{10} is lysine;

provided that:

when R^2 is dAsp, then R^7 is not dLys;

when R^2-R^4 is Asp-His-dNal(2'), Asp-Pro-dNal(2') or Asp-Pro-dPhe, then R^5-R^7 is not Arg-Trp-Lys; and

when Y^1 is dPro, Y^2 is dVal, Y^3-Y^8 are absent, then R^4 is not dNal(2') or R^4 is dNal(2') and the C-terminus is not modified.

[0375] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (I), wherein:

R^1 is absent or is selected from the group consisting of cysteine, norleucine (Nle), acetylated norleucine (Ac-Nle), *trans*-4-guanidinyl-proline (*trans*Pro(guan)), *cis*-4-guanidinyl-proline (*cis*Pro(guan)), acetylated *trans*-4-guanidinyl-proline (Ac-*trans*Pro(guan)), acetylated *cis*-4-guanidinyl-proline (Ac-*cis*Pro(guan)), tyrosine, D-tyrosine, di-methyl tyrosine (Dmt), aspartic acid, glutaric acid, leucine, isoleucine, valine, norvaline (Nva), alanine, glycine, proline, methionine, lysine, phenylalanine, glutamic acid, asparagine, and acetylated glutamic acid;

R^2 is absent or is selected from the group consisting of proline, histidine, D-hydroxyproline (dHyp), *trans*Pro(guan), *cis*Pro(guan), aspartic acid, glutamic acid, glycine, lysine, alanine, D-alanine, cysteine, norleucine, arginine, succinic acid, glutaric acid, methionine, and phenylalanine;

R^3 is absent or is selected from the group consisting of histidine, L-proline, *trans*Pro(guan), *cis*Pro(guan), D-valine, glutamic acid, tryptylarginine (Trp-Arg), glycine,

D-leucine, D-isoleucine, tryptophan, arginine, 4-amino-1,2,4,5-tetrahydro-2-benzazepin-3-one (Aba), 7-amino-7,8-dihydro-4H-(1,2,3)triazolo-(1,5-a)(1,4)diazepin-6(5H)-one (Ata), 4-amino-1,4,5,6-tetrahydroazepino(4,3-*b*)indol-3(*2H*)-one (Aia), octohydroindole-2-carboxylic acid (Oic), 1-amino-1-cyclohexanecarboxylic acid (Che), tetrahydro-isoquinoline-3-carboxylic acid (Tic), and indoline-2-carboxylic acid (Ioc),

R^4 is selected from the group consisting of histidine, D-phenylalanine, L-phenylalanine, D-Nal(2′), aspartic acid, dBip, glycine, proline, cysteine, para-chloro-D-phenylalanine (p(Cl)dPhe), para-iodo-D-phenylalanine (p(I)dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-trifluoromethyl-D-phenylalanine (p(CF_3)dPhe);

R^5 is absent or is selected from the group consisting of arginine, homoarginine, proline, *trans*Pro(guan), *cis*Pro(guan), Pip, Nip, Tic, Phg, Sar, Azt, phenylalanine, D-Nal(2′), D-histidine, D-alanine, D-aspartic acid, D-glutamic acid, cysteine, and p(I)dPhe;

R^6 is absent or is selected from the group consisting of L-tryptophan, D-phenylalanine, D-Nal(2′), L-Nal(2′), Tic, Bip, arginine, D-histidine, cysteine, D-Nal(1′), Aba, Ata, D-tyrosine, Pen, dPen, and D-alanine;

R^7 is absent or is selected from the group consisting of glycine, aspartic acid, glutamic acid, cysteine, lysine, 2,3-diamino-propionic acid (Dap), methionine, proline, tryptophan, D-Nal(2′), and tetrahydro-isoquinoline-3-carboxylic acid (Tic);

R^8 is absent or is lysine;

R^9-R^{20} are absent;

X^1 is absent or is selected from the group consisting of D-cysteine, L-cysteine, D-threonine, D-proline, L-proline, D-alanine, L-alanine, β-alanine, D-arginine, L-arginine, D-valine, L-valine, D-leucine, L-leucine, D-isoleucine, L-isoleucine, norvaline, glycine, methionine, lysine, phenylalanine, tyrosine, glutamic acid, asparagine, aspartic acid, acetylated D-arginine, acetylated L-arginine, acetylated D-valine, and acetylated norleucine;

X^2 is absent or is D-proline;

X^3 is absent;

Y^1 is absent or is selected from the group consisting of D-valine, D-tert-leucine, L-tert-leucine, norleucine, and D-proline;

Y^2 is absent or is selected from the group consisting of D-proline, L-proline, Hyp, D-valine, L-valine, D-tert-leucine, L-tert-leucine, norleucine, and glycine;

Y^3 is absent or is selected from the group consisting of D-lysine, L-lysine, D-proline, L-proline, D-valine, and L-valine;

Y^4 is absent or is D-aspartic acid or aspartic acid;

Y^5-Y^8 are absent;

the non-naturally occurring melanocortin analog is optionally cyclized through a moiety selected from the group consisting of:

a disulfide bond between R^1 and R^7 when R^1 is cysteine and R^7 is cysteine;

a lactam bridge between R^1 and R^7 when R^1 is norleucine and R^7 is glutamic acid;

a side-chain lactam bridge between R^1 or R^2 and R^7 when R^1 or R^2 is glutamic acid or aspartic acid, and R^7 is lysine or Dap;

a side-chain lactam bridge between R^2 and R^7 when R^2 is lysine, and R^7 is glutamic acid or aspartic acid;

a side-chain lactam bridge between R^1 or R^2 and R^8 when R^1 or R^2 is glutamic acid or aspartic acid, R^8 is lysine, and R^7 is proline, glycine or tryptophan;

provided that:

when R^2 is dAsp, then R^7 is not dLys;

when R^2-R^4 is Asp-His-dNal(2'), Asp-Pro-dNal(2') or Asp-Pro-dPhe, then R^5-R^7 is not Arg-Trp-Lys;

when Y^1 is dPro, Y^2 is dVal, and Y^3-Y^8 are absent, then R^4 is not dNal(2') or R^4 is dNal(2') and the C-terminus is not modified;

when R^3 is Aba, Ata, or Aia, R^6 is Aia, then R^4 is not dNal(2'), or R^4 is dNal(2') and R^5 is not Arg;

when R^4 is p(Cl)dPhe, then R^3 is not Pro or His;

when R^4 is p(I)dPhe then the non-naturally occurring melanocortin analog is cyclized through a side-chain lactam bridge between R^1 and R^7 and at least one of R^2 and R^3 is Pro;

when Y^2-Y^4 are absent, then Y^1 is absent or is norleucine;

when R^2 is Pro or Y^2 is Hyp, then R^3 is not Pro;

when R^3, R^5, or R^6 is absent, then the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between R^1 and R^7 or X^1-X^2 are present and are Ac-dVal-dPro;

when R^2-R^7 is Asp-Pro-dNal(2')-Arg-Trp-Lys (SEQ ID NO: 526) or Cys-Pro-dNal(2')-Arg-Trp-Cys (SEQ ID NO: 527), then R^1 is not Ac-Nle or Y^1-Y^2 is not dVal-dPro, dVal-dVal, dPro-dPro; and

when the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between R^2 and R^8, then R^3 is not His or Y^1 is not dVal.

[0376] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (I), wherein:

R^1 is absent or is selected from the group consisting of cysteine, norleucine (Nle), acetylated norleucine (Ac-Nle), *trans*-4-guanidinyl-proline (*trans*Pro(guan)), *cis*-4-guanidinyl-proline (*cis*Pro(guan)), acetylated *trans*-4-guanidinyl-proline (Ac-*trans*Pro(guan)), acetylated *cis*-4-guanidinyl-proline (Ac-*cis*Pro(guan)), tyrosine, D-tyrosine, di-methyl tyrosine (Dmt), aspartic acid, glutaric acid, leucine, isoleucine, valine, norvaline (Nva), alanine, glycine, proline, methionine, lysine, phenylalanine, glutamic acid, asparagine, and acetylated glutamic acid;

R^2 is absent or is selected from the group consisting of proline, histidine, D-hydroxyproline (dHyp), *trans*Pro(guan), *cis*Pro(guan), aspartic acid, glutamic acid, glycine, lysine, alanine, D-alanine, cysteine, norleucine, arginine, succinic acid, glutaric acid, methionine, and phenylalanine;

R^3 is absent or is selected from the group consisting of histidine, L-proline, *trans*Pro(guan), *cis*Pro(guan), D-valine, glutamic acid, tryptylarginine (Trp-Arg), glycine, D-leucine, D-isoleucine, tryptophan, arginine, 4-amino-1,2,4,5-tetrahydro-2-benzazepin-3-one (Aba), 7-amino-7,8-dihydro-4H-(1,2,3)triazolo-(1,5-a)(1,4)diazepin-6(5H)-one (Ata), 4-amino-1,4,5,6-tetrahydroazepino(4,3-*b*)indol-3(*2H*)-one (Aia), octohydroindole-2-carboxylic acid (Oic), 1-amino-1-cyclohexanecarboxylic acid (Che), tetrahydro-isoquinoline-3-carboxylic acid (Tic), and indoline-2-carboxylic acid (Ioc),

R^4 is selected from the group consisting of histidine, D-phenylalanine, L-phenylalanine, D-Nal(2′), aspartic acid, dBip, glycine, proline, cysteine, para-chloro-D-phenylalanine (p(Cl)dPhe), para-iodo-D-phenylalanine (p(I)dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-trifluoromethyl-D-phenylalanine (p(CF_3)dPhe);

R^5 is absent or is selected from the group consisting of arginine, homoarginine, proline, *trans*Pro(guan), *cis*Pro(guan), Pip, Nip, Tic, Phg, Sar, Azt, phenylalanine, D-Nal(2′), D-histidine, D-alanine, D-aspartic acid, D-glutamic acid, cysteine, and p(I)dPhe;

R^6 is absent or is selected from the group consisting of L-tryptophan, D-phenylalanine, D-Nal(2′), L-Nal(2′), Tic, Bip, arginine, D-histidine, cysteine, D-Nal(1’), Aba, Ata, D-tyrosine, Pen, dPen, and D-alanine;

R^7 is absent or is selected from the group consisting of glycine, aspartic acid, glutamic acid, cysteine, lysine, 2,3-diamino-propionic acid (Dap), methionine, proline, tryptophan, D-Nal(2′), and tetrahydro-isoquinoline-3-carboxylic acid (Tic);

R^8 is absent or is lysine;

R^9-R^{20} are absent;

X^1 is absent or is selected from the group consisting of D-cysteine, L-cysteine, D-threonine, D-proline, L-proline, D-alanine, L-alanine, β-alanine, D-arginine, L-arginine, D-valine, L-valine, D-leucine, L-leucine, D-isoleucine, L-isoleucine, norvaline, glycine, methionine, lysine, phenylalanine, tyrosine, glutamic acid, asparagine, aspartic acid, acetylated D-arginine, acetylated L-arginine, acetylated D-valine, and acetylated norleucine;

X^2 is absent or is D-proline;

X^3 is absent;

Y^1 is absent or is selected from the group consisting of D-valine, D-tert-leucine, L-tert-leucine, norleucine, and D-proline;

Y^2 is absent or is selected from the group consisting of D-proline, L-proline, Hyp, D-valine, L-valine, D-tert-leucine, L-tert-leucine, norleucine, and glycine;

Y^3 is absent or is selected from the group consisting of D-lysine, L-lysine, D-proline, L-proline, D-valine, and L-valine;

Y^4 is absent or is D-aspartic acid or aspartic acid;

Y^5-Y^8 are absent;

the non-naturally occurring melanocortin analog is optionally cyclized through a moiety selected from the group consisting of:

a disulfide bond between R^1 and R^7 when R^1 is cysteine and R^7 is cysteine;

a lactam bridge between R^1 and R^7 when R^1 is norleucine and R^7 is glutamic acid;

a side-chain lactam bridge between R^1 or R^2 and R^7 when R^1 or R^2 is glutamic acid or aspartic acid, and R^7 is lysine or Dap;

a side-chain lactam bridge between R^2 and R^7 when R^2 is lysine, and R^7 is glutamic acid or aspartic acid;

a side-chain lactam bridge between R^1 or R^2 and R^8 when R^1 or R^2 is glutamic acid or aspartic acid, R^8 is lysine, and R^7 is proline, glycine or tryptophan;

provided that the non-naturally occurring melanocortin analog does not comprise a sequence selected from the group consisting of:

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-NH_2 (SEQ ID NO: 139);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dPro-NH_2 (SEQ ID NO: 140);

Ac-Nle-c(Asp-Aba-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 207);

Ac-Nle-c(Asp-Aia-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 208);

Ac-Nle-c(Asp-Ata-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 209),

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dVal-dVal-dPro-NH_2 (SEQ ID NO: 192);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-dVal-dPro-NH_2 (SEQ ID NO: 193);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dVal-dPro-NH_2 (SEQ ID NO: 190);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dPro-dVal-dPro-NH_2 (SEQ ID NO: 191);

Ac-Nle-c(Asp-Pro-p(Cl)dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 391);

Ac-Nle-c(Asp-His-p(Cl)dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 396);

Ac-Nle-c(Asp-His-Arg-p(I)dPhe-Arg-Tic-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 376);

Ac-Nle-c(Asp-Pro-p(I)dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 392);

Ac-Nle-c(Asp-His-p(I)dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 397);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dVal-NH_2 (SEQ ID NO: 137);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dPro-dPro-NH_2 (SEQ ID NO: 138);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-OH (SEQ ID NO: 127);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-Hyp-NH_2 (SEQ ID NO: 129);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Val-Hyp-NH_2 (SEQ ID NO: 131);

Ac-Nle-c(Asp-Pro-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 198);

Ac-Nle-c(Asp-Pro-Pro-dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 401);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Aia-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 114);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3; B07);

Ac-Nle-Asp-Pro-dNal(2')-Arg-Trp-Lys-dVal-dPro-NH_2 (SEQ ID NO: 13; A1);

Ac-Nle-c(Asp-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 71);

Ac-Nle-c(Cys-dNal(2')-Arg-Trp-Cys)-dVal-dPro-NH_2 (SEQ ID NO: 46);

Ac-Nle-c(Asp-Pro-dNal(2')-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 97);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 112);

Ac-Nle-c(Asp-Pro-His-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 5; D1);

Ac-Nle-c(Asp-His-dNal(2')-Arg-Trp-Pro-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 8; D2);

Ac-Nle-c(Cys-Pro-dNal(2')-Arg-Trp-Cys)-dVal-dPro-NH_2 (SEQ ID NO: 42);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dPro-dVal-NH_2 (SEQ ID NO: 286);

Ac-Nle-c(Asp-His-dNal(2')-Arg-Trp-Lys)-dPro-dVal-NH_2 (SEQ ID NO: 287);

Ac-Nle-c(dAsp-Pro-dNal(2')-Arg-Trp-dLys)-dPro-dVal-NH_2 (SEQ ID NO: 288);

Ac-Nle-c(dAsp-His-dNal(2')-Arg-Trp-dLys)-dPro-dVal-NH_2 (SEQ ID NO: 289);

Ac-Nle-c(Asp-His-dNal(2′)-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 291);

Ac-Nle-c(dAsp-Pro-dNal(2′)-Arg-Trp-dLys)-dVal-dPro-NH_2 (SEQ ID NO: 292);

Ac-Nle-c(dAsp-His-dNal(2′)-Arg-Trp-dLys)-dVal-dPro-NH_2 (SEQ ID NO: 293);

Ac-Nle-c(Asp-Pro-dPhe-Arg-Trp-Lys)-dPro-dVal-NH_2 (SEQ ID NO: 420);

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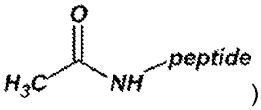
Ac-Nle-c(Asp-Pro-dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 424);

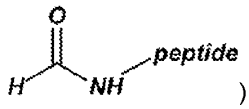
Ac-Nle-c(Asp-His-dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 425); and

Ac-Nle-c(dAsp-Pro-dPhe-Arg-Trp-dLys)-dVal-dPro-NH_2 (SEQ ID NO: 426).

[0377] In some embodiments, the non-naturally occurring melanocortin analog has one or more beta hairpin (β-hairpin) and/or beta turn (β-turn) structures. In some embodiments, R3 of the sequence according to Formula (I), which may be D-proline, L-proline, hydroxyproline, D-hydroxyproline, D-alanine, D-methionine, D-valine, prolylglycine (Pro-Gly), glycine, transPro(guan), cisPro(guan), provides the β-hairpin and/or β-turn structures of the non-naturally occurring melanocortin analog. In some embodiments, the disulfide bond of the sequence according to Formula (I), if present, provides the β-hairpin and/or β-turn structures of the non-naturally occurring melanocortin analog.

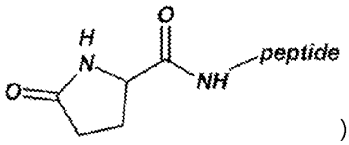
[0378] In some embodiments, the N-terminus of the non-naturally occurring melanocortin analog, if present, is modified by a functional group selected from the group consisting of an acyl group, an imine group, an amide group, a urea group, a carbamate group, a sulfonamide group, and an alkylamine group.

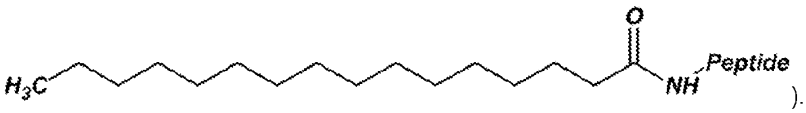
[0379] In some embodiments, the N-terminus of the non-naturally occurring melanocortin analog, if present, is modified by an acyl group. In some embodiments, the acyl group is acetyl group (e.g., 

). In some embodiments, the acyl group is formyl group (e.g., 

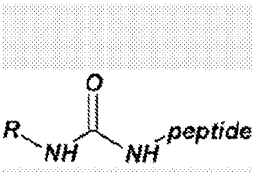
).

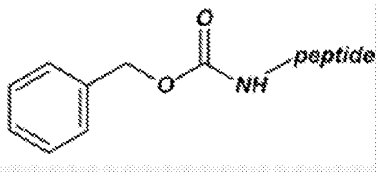
[0380] In some embodiments, the N-terminus of the non-naturally occurring melanocortin analog, if present, is modified by an imine group.

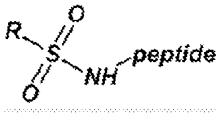
[0381] In some embodiments, the N-terminus of the non-naturally occurring melanocortin analog, if present, is modified by an amide group. In some embodiments, the amide group is a pyroglutamyl (pGlu) group (e.g., 

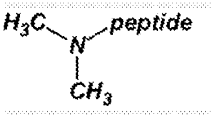
). In some embodiments, the amide group is derived from a fatty acid (e.g., 

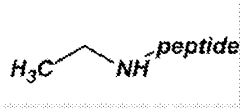
).

[0382] Other examples of the N-terminal modifications include, but are not limited to, 

(urea group), 

(carbamate group), 

(sulfonamide group), 

and 

(alkylamine group).

[0383] In some embodiments, the N-terminus of the non-naturally occurring melanocortin analog, if present, is not modified.

[0384] As discussed above, $Y^1Y^2Y^3Y^4Y^5Y^6Y^7Y^8$ represents a C-terminus of the non-naturally occurring melanocortin analog. In some embodiments, Y^1-Y^8 are absent. In some embodiments, Y^1 is present and Y^2-Y^8 are absent.

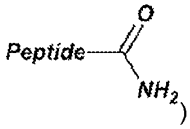
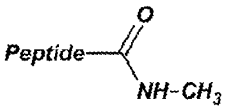
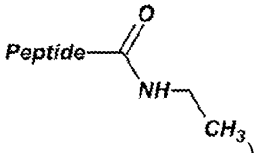
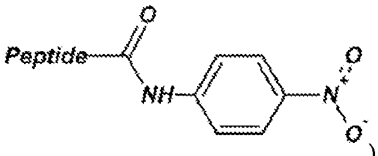
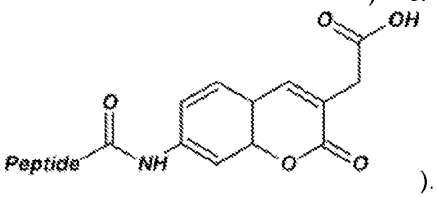
[0385] In some embodiments, Y^1 and Y^2 are present and Y^3-Y^8 are absent. In some embodiments, Y^3-Y^8 are absent, and Y^1 is D-valine and Y^2 is D-proline, or Y^1 is D-proline and Y^2 is D-valine.

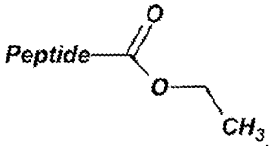
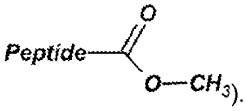
[0386] In some embodiments, Y^3 is present and Y^4-Y^8 are absent. In some embodiments, Y^3 is present and Y^4-Y^8 are absent, and (i) Y^1 is D-valine or D-proline, (ii) Y^2 is D-valine or D-proline, and/or (iii) Y^3 is D-valine or D-proline. In some embodiments, Y^3 is present and Y^4-Y^8 are absent, and (i) Y^1 is D-valine, Y^2 is D-valine, and Y^3 is D-proline, (ii) Y^1 is D-proline, Y^2 is D-valine, and Y^3 is D-valine, or (iii) Y^1 is D-valine, Y^2 is D-proline, and Y^3 is D-valine.

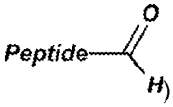
[0387] In some embodiments, Y^3 and Y^4 are present, and Y^5-Y^8 are absent. In some embodiments, Y^3 and Y^4 are present, and Y^5-Y^8 are absent, and (i) Y^1 is D-valine or D-proline, (ii) Y^2 is D-valine or D-proline, (iii) Y^3 is D-valine or D-proline, and/or (iv) Y^4 is D-valine or D-proline. In some embodiments, Y^3 and Y^4 are present, and Y^5-Y^8 are absent, and (i) Y^1 is D-valine, Y^2 is D-valine, Y^3 is D-valine, and Y^4 is D-proline, (ii) Y^1 is D-proline, Y^2 is D-valine, Y^3 is D-valine, and Y^4 is D-valine, (iii) Y^1 is D-valine, Y^2 is D-proline, Y^3 is D-valine, and Y^4 is D-valine, or (iv) Y^1 is D-valine, Y^2 is D-valine, Y^3 is D-proline, and Y^4 is D-valine.

[0388] In some embodiments, the C-terminus includes additional derivatives to extend the length of C-terminus of the non-naturally occurring melanocortin analog. Exemplary additional C-terminus include, but are not limited to, $Y^1Y^2Y^3Y^4Y^5Y^6Y^7Y^8Y^9$, $Y^1Y^2Y^3Y^4Y^5Y^6Y^7Y^8Y^9Y^{10}$, $Y^1Y^2Y^3Y^4Y^5Y^6Y^7Y^8Y^9Y^{10}Y^{11}$, $Y^1Y^2Y^3Y^4Y^5Y^6Y^7Y^8Y^9Y^{10}Y^{11}Y^{12}$, $Y^1Y^2Y^3Y^4Y^5Y^6Y^7Y^8Y^9Y^{10}Y^{11}Y^{12}Y^{13}$, $Y^1Y^2Y^3Y^4Y^5Y^6Y^7Y^8Y^9Y^{10}Y^{11}Y^{12}Y^{13}Y^{14}$, $Y^1Y^2Y^3Y^4Y^5Y^6Y^7Y^8Y^9Y^{10}Y^{11}Y^{12}Y^{13}Y^{14}Y^{15}$, $Y^1Y^2Y^3Y^4Y^5Y^6Y^7Y^8Y^9Y^{10}Y^{11}Y^{12}Y^{13}Y^{14}Y^{15}Y^{16}$, $Y^1Y^2Y^3Y^4Y^5Y^6Y^7Y^8Y^9Y^{10}Y^{11}Y^{12}Y^{13}Y^{14}Y^{15}Y^{16}Y^{17}$, $Y^1Y^2Y^3Y^4Y^5Y^6Y^7Y^8Y^9Y^{10}Y^{11}Y^{12}Y^{13}Y^{14}Y^{15}Y^{16}Y^{17}Y^{18}$, $Y^1Y^2Y^3Y^4Y^5Y^6Y^7Y^8Y^9Y^{10}Y^{11}Y^{12}Y^{13}Y^{14}Y^{15}Y^{16}Y^{17}Y^{18}Y^{19}$, $Y^1Y^2Y^3Y^4Y^5Y^6Y^7Y^8Y^9Y^{10}Y^{11}Y^{12}Y^{13}Y^{14}Y^{15}Y^{16}Y^{17}Y^{18}Y^{19}Y^{20}$, $Y^1Y^2Y^3Y^4Y^5Y^6Y^7Y^8Y^9Y^{10}Y^{11}Y^{12}Y^{13}Y^{14}Y^{15}Y^{16}Y^{17}Y^{18}Y^{19}Y^{20}Y^{21}$, $Y^1Y^2Y^3Y^4Y^5Y^6Y^7Y^8Y^9Y^{10}Y^{11}Y^{12}Y^{13}Y^{14}Y^{15}Y^{16}Y^{17}Y^{18}Y^{19}Y^{20}Y^{21}Y^{22}$, $Y^1Y^2Y^3Y^4Y^5Y^6Y^7Y^8Y^9Y^{10}Y^{11}Y^{12}Y^{13}Y^{14}Y^{15}Y^{16}Y^{17}Y^{18}Y^{19}Y^{20}Y^{21}Y^{22}Y^{23}$, and $Y^1Y^2Y^3Y^4Y^5Y^6Y^7Y^8Y^9Y^{10}Y^{11}Y^{12}Y^{13}Y^{14}Y^{15}Y^{16}Y^{17}Y^{18}Y^{19}Y^{20}Y^{21}Y^{22}Y^{23}Y^{24}$, etc., wherein Y^9-Y^{24}, if present, are each independently D-proline or D-valine.

[0389] In some embodiments, the C-terminus of the non-naturally occurring melanocortin analog is modified by a functional group selected from the group consisting of an amide group, an ester group, and an aldehyde group.

[0390] In some embodiments, the C-terminus of the non-naturally occurring melanocortin analog is modified by an amide group (e.g., ). In the sequence of Formula (I), a non-naturally occurring melanocortin analog with a C-terminus modified by an amide may be represented by a terminal -NH_2, such as, for example, in the sequence Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Val-Pro-NH_2 (SEQ ID NO: 126). In some embodiments, the amide group is an N-alkyl amide group (e.g.,  , ) or an N-aryl amide group. In some embodiments, the N-aryl amide group is p-nitroanilide group (pNA) (e.g., ) or 7-amino-4-methylcoumarin (AMC) (e.g., ).

[0391] In some embodiments, the C-terminus of the non-naturally occurring melanocortin analog is modified by an ester group (e.g.,  , ).

[0392] In some embodiments, the C-terminus of the non-naturally occurring melanocortin analog is modified by an aldehyde (e.g., ).

[0393] In some embodiments, the C-terminus of the non-naturally occurring melanocortin analog is not modified. In the sequence of Formula (I), a non-naturally occurring melanocortin analog with an unmodified C-terminus may be represented by -OH, such as, for example, in the sequence Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-OH (SEQ ID NO: 127) or by the absence of a C-terminal group, such as, for example, in the sequence Ac-Nle-$_c$(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro (SEQ ID NO: 2; B07a). In some embodiments, the C-terminus of the non-naturally occurring melanocortin analog is not modified, and the sequence of Formula (I) is Ac-Nle-$_c$(Asp-Pro-dNal2'-Arg-Trp-Lys)-dVal-dPro (SEQ ID NO: 2).

[0394] In some embodiments, R^1 is absent, and R^2 is D-aspartic acid. In some embodiments, R^1 is acetylated norleucine, and R^2 is D-aspartic acid.

[0395] In some embodiments, X^1, X^2, and X^3 are absent. In some embodiments, X^1 is present and X^2 and X^3 are absent.

[0396] In some embodiments, R^4 is not D-phenylalanine. In some embodiments, R^4 is D-Nal(2'). When R^4 is D-Nal(2'), the non-naturally occurring melanocortin analog described herein may act as a melanocortin receptor antagonist.

[0397] In some embodiments, the non-naturally occurring melanocortin analog described herein is cyclized. For example, the non-naturally occurring melanocortin analog may be cyclized through a moiety selected from the group consisting of: a disulfide bond between R^1 or R^2 and R^7 or X^1 when R^1 or R^2 is cysteine and R^7 or X^1 is cysteine; a disulfide bond between R^2 and any one of R^5-R^{20} when R^2 and the any one of R^5-R^{20} are selected from the group consisting of cysteine, Pen, and dPen; a lactam bridge between R^1 and R^7 when R^1 is norleucine and R^7 is glutamic acid; a side-chain lactam bridge between R^1 and any of R^{5-8} when R^1 is aspartic acid and any of R^{5-8} are lysine; a side-chain lactam bridge between R^2 and R^7 when R^2 is lysine and R^7 is aspartic acid; a side-chain lactam bridge between R^2 and R^7 when R^2 is glutamic acid, aspartic acid, or CO-cis-CH=CH—CO, and R^7 is lysine, Dap, or ornithine; a side-chain lactam bridge between R^2 and R^8 when R^2 is glutamic acid or aspartic acid, R^8 is lysine, and R^7 is glycine, proline, or tryptophan; a side-chain lactam bridge between R^2 or R^4 and R^{10} when R^2 or R^4 is glutamic acid or aspartic acid and R^{10} is lysine; a lactam closure between R^1 and R^7 when R^1 is succinic acid or o-phthalic acid and R^7 is lysine; and/or a lactam closure between R^2 and R^7 when R^2 is succinic acid and R^7 is 2,3-

diamino-propionic acid. Cyclization may also occur from any of the X residues (optional stabilizing N-terminus residues). For example, X^2 may be an aspartic acid that may be used for cyclization.

[0398] In some embodiments, R^1, R^2, and R^7 are present and R^8-R^{20} are absent, and the sequence of Formula (I) is cyclized through R^2 and R^7 via a lactam bond. In some embodiments, R^1 is acetylated norleucine, R^2 is aspartic acid, R^3 is selected from the group consisting of proline, hydroxyproline, and D-hydroxyproline, R^4 is D-Nal(2′), R^5 is arginine, R^6 is D-tryptophan or L-tryptophan, R^7 is lysine, Y^1 is D-valine, and/or Y^2 is D-proline.

[0399] In some embodiments, the sequence of Formula (I) is: Ac-Nle-$_c$(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3; B07) or Ac-Nle-$_c$(Asp-Hyp-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 4; D3), wherein c represents cyclization through R^2 and R^7 via a lactam bond.

[0400] In some embodiments, R^1, R^2, R^7, and R^8 are present and R^9-R^{20} are absent, and the sequence of Formula (I) is cyclized through R^2 and R^8 via a lactam bond. In some embodiments, R^1 is acetylated norleucine, R^2 is aspartic acid, R^3 is selected from the group consisting of proline, hydroxyproline, D-hydroxyproline, phenylalanine, and histidine, R^4 is histidine or dNal(2′), R^5 is dNal(2′) or arginine, R^6 is selected from the group consisting of arginine, D-tryptophan, and L-tryptophan, R^7 is tryptophan or proline, R^8 is lysine, Y^1 is selected from the group consisting of D-valine, D-leucine, and D-isoleucine, and/or Y^2 is D-proline.

[0401] In some embodiments, the sequence of Formula (I) is selected from the group consisting of:

Ac-Nle-$_c$(Asp-Pro-His-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 5; D1);

Ac-Nle-$_c$(Asp-Phe-His-dNal(2')-Arg-Trp-Lys)-dLeu-dPro-NH_2 (SEQ ID NO: 6; D1γ);

Ac-Nle-$_c$(Asp-Phe-His-dNal(2')-Arg-Trp-Lys)-dTle-dPro-NH_2 (SEQ ID NO: 7; D1δ);

Ac-Nle-$_c$(Asp-His-dNal(2')-Arg-Trp-Pro-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 8; D2);

Ac-Nle-$_c$(Asp-Hyp-dNal(2')-Arg-Trp-Pro-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 9; D4); and

Ac-Nle-$_c$(Asp-Pro-His-dNal(2')-Arg-Trp-Lys)-dPro-dVal-NH_2 (SEQ ID NO: 10; D5),

wherein c represents cyclization through R^2 and R^8 via a lactam bond.

[0402] In some embodiments, R^1-R^2 and R^7-R^{10} are present and R^{11}-R^{20} are absent, and the sequence of Formula (I) is cyclized through R^2 and R^{10} via a lactam bond. In some embodiments, the sequence of Formula (I) is Ac-Nle-$_c$(Asp-Phe-Phe-Pro-His-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 11; D1α), wherein c represents cyclization through R^2 and R^{10} via a lactam bond.

[0403] In some embodiments, R^1-R^2 and R^7-R^{10} are present and R^{11}-R^{20} are absent, and the sequence of Formula (I) is cyclized through R^4 and R^{10} via a lactam bond. In some embodiments, the sequence of Formula (I) is Ac-Nle-Phe-Phe-$_c$(Asp-Phe-His-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 12; D1β), wherein c represents cyclization through R^4 and R^{10} via a lactam bond.

[0404] In some embodiments, the sequence of Formula (I) is linear. In some embodiments, the sequence of Formula (I) is Ac-Nle-Asp-Pro-dNal(2')-Arg-Trp-Lys-dVal-dPro-NH_2 (SEQ ID NO: 13; A1). In some embodiments, the sequence of Formula (I) is Ac-Nle-Pro-DNal(2')-Arg-Trp-dVal-dPro-NH_2 (SEQ ID NO: 14; A2).

[0405] In some embodiments of the sequence of Formula (I), R^1 is acetylated norleucine. Alternatively, in some embodiments, R^1 is an acetylated amino acid other than acetylated norleucine. In some embodiments, R^1 is a non-acetylated amino acid. In some embodiments, the sequence of Formula (I) is selected from the group consisting of:

Ac-dArg-$_c$(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 15);

Ac-dMet-$_c$(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 16);

Ac-dIle-$_c$(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 17);

Ac-dLeu-$_c$(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 18);

Ac-dVal-$_c$(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 19);

Ac-dAla-$_c$(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 20);

Ac-Ala-$_c$(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 21);

Ac-Tle-$_c$(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 22);

Ac-dTle-$_c$(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 23);

Ac-dNle-$_c$(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 24);

Ac-Nva-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 25);

Ac-Gly-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 26);

Ac-dPro-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 27);

Ac-dCys-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 28);

Ac-dPhe-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 29);

Ac-dTyr-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 30);

Ac-dGln-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 31);

Ac-dAsn-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 32);

Ac-*trans*Pro(guan)-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 33);

Ac-*cis*Pro(guan)-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 34);

dTyr-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 35);

Tyr-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 36);

Dmt-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 37);

Ac-Glu-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 38); and

Ac-Asn-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 39),

wherein c represents cyclization through R^2 and R^7 via a lactam bond.

[0406] In some embodiments, when the sequence of Formula (I) is cyclized through R^2 and R^7, then R^2 is Asp and R^7 is Lys. Alternatively, in some embodiments, when the sequence of Formula (I) is cyclized through R^2 and R^7, then R^2 is an amino acid capable of forming a linkage to the residue at R^7 other than Asp and R^7 is an amino acid capable of forming a linkage to the residue at R^2 other than Lys. For example, when R^2 is an amino acid other than Arg and R^7 is an amino acid other than Lys, the residue at R^2 may be capable of forming a linkage such as a lactam bond or a disulfide bond with the residue at R^7. In some embodiments, the sequence of Formula (I) is selected from the group consisting of:

Ac-Nle-c(dAsp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 40);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-dLys)-dVal-dPro-NH_2 (SEQ ID NO: 41);

Ac-Nle-c(Cys-Pro-dNal(2')-Arg-Trp-Cys)-dVal-dPro-NH_2 (SEQ ID NO: 42);

Ac-Nle-c(dCys-Pro-dNal(2')-Arg-Trp-Cys)-dVal-dPro-NH_2 (SEQ ID NO: 43);

Ac-Nle-c(Cys-Pro-dNal(2')-Arg-Trp-dCys)-dVal-dPro-NH_2 (SEQ ID NO: 44);

Ac-Nle-c(dCys-Pro-dNal(2')-Arg-Trp-dCys)-dVal-dPro-NH_2 (SEQ ID NO: 45);

Ac-Nle-c(Cys-dNal(2')-Arg-Trp-Cys)-dVal-dPro-NH_2 (SEQ ID NO: 46);

Ac-Nle-c(dCys-dNal(2')-Arg-Trp-Cys)-dVal-dPro-NH_2 (SEQ ID NO: 47);

Ac-Nle-c(Cys-dNal(2')-Arg-Trp-dCys)-dVal-dPro-NH_2 (SEQ ID NO: 48);

Ac-Nle-c(dCys-dNal(2')-Arg-Trp-dCys)-dVal-dPro-NH_2 (SEQ ID NO: 49);

Ac-Nle-c(Cys-Pro-dNal(2')-Arg-Trp-Pen)-dVal-dPro-NH_2 (SEQ ID NO: 50);

Ac-Nle-c(dCys-Pro-dNal(2')-Arg-Trp-Pen)-dVal-dPro-NH_2 (SEQ ID NO: 51);

Ac-Nle-c(Pen-Pro-dNal(2')-Arg-Trp-Cys)-dVal-dPro-NH_2 (SEQ ID NO: 52);

Ac-Nle-c(Pen-Pro-dNal(2')-Arg-Trp-dCys)-dVal-dPro-NH_2 (SEQ ID NO: 53);

Ac-Nle-c(Pen-Pro-dNal(2')-Arg-Trp-Pen)-dVal-dPro-NH_2 (SEQ ID NO: 54);

Ac-Nle-c(dPen-Pro-dNal(2')-Arg-Trp-Pen)-dVal-dPro-NH_2 (SEQ ID NO: 55);

Ac-Nle-c(dPen-Pro-dNal(2')-Arg-Trp-dPen)-dVal-dPro-NH_2 (SEQ ID NO: 56);

Ac-Nle-c(Pen-Pro-dNal(2')-Arg-Trp-dPen)-dVal-dPro-NH_2 (SEQ ID NO: 57);

Ac-Nle-c(Cys-dNal(2')-Arg-Trp-Pen)-dVal-dPro-NH_2 (SEQ ID NO: 58);

Ac-Nle-c(dCys-dNal(2')-Arg-Trp-Pen)-dVal-dPro-NH_2 (SEQ ID NO: 59);

Ac-Nle-c(Pen-dNal(2')-Arg-Trp-Cys)-dVal-dPro-NH_2 (SEQ ID NO: 60);

Ac-Nle-c(Pen-dNal(2')-Arg-Trp-dCys)-dVal-dPro-NH_2 (SEQ ID NO: 61);

Ac-Nle-c(Pen-dNal(2')-Arg-Trp-Pen)-dVal-dPro-NH_2 (SEQ ID NO: 62);

Ac-Nle-c(dPen-dNal(2')-Arg-Trp-Pen)-dVal-dPro-NH_2 (SEQ ID NO: 63);

Ac-Nle-c(dPen-dNal(2')-Arg-Trp-dPen)-dVal-dPro-NH_2 (SEQ ID NO: 64);

Ac-Nle-c(Pen-dNal(2')-Arg-Trp-dPen)-dVal-dPro-NH_2 (SEQ ID NO: 65);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Orn)-dVal-dPro-NH_2 (SEQ ID NO: 66);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-dOrn)-dVal-dPro-NH_2 (SEQ ID NO: 67);

Ac-Nle-c(Glu-Pro-dNal(2')-Arg-Trp-Orn)-dVal-dPro-NH_2 (SEQ ID NO: 68);

Ac-Nle-c(Glu-Pro-dNal(2')-Arg-Trp-dOrn)-dVal-dPro-NH_2 (SEQ ID NO: 69); and

Ac-Nle-c(Asp-Pro-dPhe-Arg-Trp-Dap)-dVal-dPro-NH_2 (SEQ ID NO: 70),

wherein c represents cyclization through R^2 and R^6 or R^7 via a lactam bond or a disulfide bond.

[0407] In some embodiments of the sequence of Formula (I), R^3 is Pro. Alternatively, in some embodiments, R^3 is absent or an amino acid other than Pro. In some embodiments, the sequence of Formula (I) is selected from the group consisting of:

Ac-Nle-c(Asp-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 71);

Ac-Nle-c(Asp-Ala-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 72);

Ac-Nle-c(Asp-dPro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 73);

Ac-Nle-c(Asp-dAla-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 74);

Ac-Nle-c(Asp-dMet-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 75);

Ac-Nle-c(Asp-Pro-Gly-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 76);

Ac-Nle-c(Asp-Gly-Gly-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 77);

Ac-Nle-c(Asp-Gly-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 78);

Ac-Nle-c(Asp-Leu-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 79);

Ac-Nle-c(Asp-Ile-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 80);

Ac-Nle-c(Asp-Val-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 81);

Ac-Nle-c(Asp-dLeu-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 82);

Ac-Nle-c(Asp-dIle-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 83);

Ac-Nle-c(Asp-dVal-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 84);

Ac-Nle-c(Asp-Trp-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 85);

Ac-Nle-c(Asp-dTrp-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 86);

Ac-Nle-c(Asp-*trans*Pro(guan)-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 87);

Ac-Nle-c(Asp-*cis*Pro(guan)-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 88);

Ac-Nle-c(Asp-Val-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 89);

Ac-Nle-c(Asp-Ile-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 90);

Ac-Nle-c(Asp-Gly-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 91);

Ac-Nle-c(Asp-Glu-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 92);

Ac-Nle-c(Asp-Arg-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 93);

Ac-Nle-c(Asp-dLeu-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 94);

Ac-Nle-c(Asp-dAla-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 95); and

Ac-Nle-c(Asp-dMet-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 96),

wherein c represents cyclization through R^2 and R^7 via a lactam bond.

[0408] In some embodiments of the sequence of Formula (I), R^5 is Arg. Alternatively, in some embodiments, R^5 is absent or an amino acid other than Arg. In some embodiments, the sequence of Formula (I) is selected from the group consisting of:

Ac-Nle-c(Asp-Pro-dNal(2')-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 97);

Ac-Nle-c(Asp-Pro-dNal(2')-Lys-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 98);

Ac-Nle-c(Asp-Pro-dNal(2')-dLys-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 99);

Ac-Nle-c(Asp-Pro-dNal(2')-dArg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 100);

Ac-Nle-c(Asp-Pro-dNal(2')-Orn-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 101);

Ac-Nle-c(Asp-Pro-dNal(2')-dOrn-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 102);

Ac-Nle-c(Asp-Pro-dNal(2')-His-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 103);

Ac-Nle-c(Asp-Pro-dNal(2')-Ala-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 104);

Ac-Nle-c(Asp-Pro-dNal(2')-Gly-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 105);

Ac-Nle-c(Asp-Pro-dNal(2')-Asp-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 106);

Ac-Nle-c(Asp-Pro-dNal(2')-Glu-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 107);

Ac-Nle-c(Asp-Pro-dNal(2')-dHis-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 108);

Ac-Nle-c(Asp-Pro-dNal(2')-dAla-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 109);

Ac-Nle-c(Asp-Pro-dNal(2')-dAsp-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 110); and

Ac-Nle-c(Asp-Pro-dNal(2')-dGlu-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 111),

wherein c represents cyclization through R^2 and R^7 via a lactam bond.

[0409] In some embodiments of the sequence of Formula (I), R^6 is Trp. Alternatively, in some embodiments, R^6 is absent or an amino acid other than Trp. In some embodiments, the sequence of Formula (I) is selected from the group consisting of:

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 112);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Nal(1')-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 113);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Aia-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 114);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Phe-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 115);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Tyr-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 116);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-His-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 117);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Ala-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 118);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-dNal(1')-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 119);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-dPhe-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 120);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-dNal(2')-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 121);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-dTyr-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 122);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-dHis-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 123); and

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-dAla-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 124),

wherein c represents cyclization through R^2 and R^7 via a lactam bond.

[0410] In some embodiments of the sequence of Formula (I), R^4 is dNal(2'). Alternatively, in some embodiments, R^4 is an amino acid other than dNal(2'). For example, in some embodiments, when R^4 is an amino acid other than dNal(2'), R^4 is Bip. In some embodiments, the sequence of Formula (I) is Ac-Nle-c(Asp-Pro-Bip-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 125), wherein c represents cyclization through R^2 and R^7 via a lactam bond.

[0411] In some embodiments of the sequence of Formula (I), Y^1 is dVal and Y^2 is dPro. Alternatively, in some embodiments, Y^1 is an amino acid other than dVal and Y^2 is an amino acid other than dPro. In some embodiments, Y^1 is dVal and Y^2 is an amino

acid other than dPro. In some embodiments, Y^1 is an amino acid other than dVal and Y^2 is dPro.

[0412] In some embodiments, Y^1 is dVal, Y^2 is dPro, and the C-terminus is modified by NH_2. In some embodiments, Y^1 is an amino acid other than dVal, Y^2 is an amino acid other than dPro, and the C-terminus is modified by NH_2. In some embodiments, Y^1 is dVal, Y^2 is an amino acid other than dPro, and the C-terminus is modified by NH_2. In some embodiments, Y^1 is an amino acid other than dVal, Y^2 is dPro, and the C-terminus is modified by NH_2. In some embodiments, Y^1 is dVal, Y^2 is dPro, and the C-terminus is unmodified.

[0413] In embodiments of Formula (I) when Y^1 is an amino acid other than dVal, then Y^1 is selected from dPro, Val, Hyp, dHyp, Pro, Ala, dAla, Gly, Asp, Arg, Asn, dAsp, dArg, dAsn, Lys, dLys, and dTle. In embodiments of Formula (I) when Y^2 is an amino acid other than dPro, then Y^2 or selected from dVal, Val, Hyp, dHyp, Pro, Ala, dAla, Gly, Asp, Arg, Asn, dAsp, dArg, dAsn, and dTle. In some embodiments, the sequence of Formula (I) is selected from the group consisting of:

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Val-Pro-NH_2 (SEQ ID NO: 126);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-OH (SEQ ID NO: 127);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dPro-dVal-OH (SEQ ID NO: 128);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-Hyp-NH_2 (SEQ ID NO: 129);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dHyp-NH_2 (SEQ ID NO: 130);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Val-Hyp-NH_2 (SEQ ID NO: 131);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Val-dHyp-NH_2 (SEQ ID NO: 132);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Hyp-dVal-NH_2 (SEQ ID NO: 133);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dHyp-dVal-NH_2 (SEQ ID NO: 134);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Hyp-Val-NH_2 (SEQ ID NO: 135);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dHyp-Val-NH_2 (SEQ ID NO: 136);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dVal-NH_2 (SEQ ID NO: 137);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dPro-dPro-NH_2 (SEQ ID NO: 138);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-NH_2 (SEQ ID NO: 139);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dPro-NH_2 (SEQ ID NO: 140);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Val-NH_2 (SEQ ID NO: 141);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Pro-NH_2 (SEQ ID NO: 142);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Ala-NH_2 (SEQ ID NO: 143);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dAla-NH_2 (SEQ ID NO: 144);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dHyp-NH_2 (SEQ ID NO: 145);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Hyp-NH_2 (SEQ ID NO: 146);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dAla-dAla-NH_2 (SEQ ID NO: 147);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Ala-Ala-NH_2 (SEQ ID NO: 148);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Gly-Gly-NH_2 (SEQ ID NO: 149);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-Asp-NH_2 (SEQ ID NO: 150);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-Arg-NH_2 (SEQ ID NO: 151);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-Asn-NH_2 (SEQ ID NO: 152);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dAsp-NH_2 (SEQ ID NO: 153);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dArg-NH_2 (SEQ ID NO: 154);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dAsn-NH_2 (SEQ ID NO: 155);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Asp-dPro-NH_2 (SEQ ID NO: 156);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Arg-dPro-NH_2 (SEQ ID NO: 157);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Asn-dPro-NH_2 (SEQ ID NO: 158);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dAsp-dPro-NH_2 (SEQ ID NO: 159);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dArg-dPro-NH_2 (SEQ ID NO: 160);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dAsn-dPro-NH_2 (SEQ ID NO: 161);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Asp-NH_2 (SEQ ID NO: 162);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Arg-NH_2 (SEQ ID NO: 163);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Asn-NH_2 (SEQ ID NO: 164);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dAsp-NH_2 (SEQ ID NO: 165);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dArg-NH_2 (SEQ ID NO: 166);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dAsn-NH_2 (SEQ ID NO: 167);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Lys-Pro-Val-NH_2 (SEQ ID NO: 168);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Lys-dPro-dVal-NH_2 (SEQ ID NO: 169);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dLys-dPro-dVal-NH_2 (SEQ ID NO: 170);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Lys-dPro-NH_2 (SEQ ID NO: 171);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dLys-dPro-NH_2 (SEQ ID NO: 172);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Lys-Val-Pro-NH_2 (SEQ ID NO: 173);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Lys-dVal-dPro-NH_2 (SEQ ID NO: 174);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dLys-dVal-dPro-NH_2 (SEQ ID NO: 175);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Arg-Pro-Val-NH_2 (SEQ ID NO: 176);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Arg-dPro-dVal-NH_2 (SEQ ID NO: 177);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dArg-dPro-dVal-NH_2 (SEQ ID NO: 178);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Arg-Val-Pro-NH_2 (SEQ ID NO: 179);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Arg-dVal-dPro-NH_2 (SEQ ID NO: 180);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dArg-dVal-dPro-NH_2 (SEQ ID NO: 181);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dTle-dVal-dPro-NH_2 (SEQ ID NO: 182);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dTle-dPro-NH_2 (SEQ ID NO: 183);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dTle-dVal-NH_2 (SEQ ID NO: 184);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dTle-dTle-NH_2 (SEQ ID NO: 185);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dTle-dTle-dPro-NH_2 (SEQ ID NO: 186);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dTle-dTle-dVal-NH_2 (SEQ ID NO: 187);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dPro-dTle-NH_2 (SEQ ID NO: 188); and

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dTle-NH_2 (SEQ ID NO: 189),

wherein c represents cyclization through R^2 and R^7 via a lactam bond.

[0414] In some embodiments of the sequence of Formula (I) when Y^3 is present and Y^{4-8} are absent, then each of Y^1, Y^2, and Y^3 are independently selected form dVal and dPro. In some embodiments of the sequence of Formula (I) when Y^3 and Y^4 are present and Y^{5-8} are absent, then each of Y^1, Y^2, Y^3, and Y^4 are independently selected from dVal and dPro. In some embodiments of the sequence of Formula (I) when Y^3-Y^5 are present and Y^{6-8} are absent, then each of Y^1-Y^5 are independently selected form dVal and dPro. In some embodiments of the sequence of Formula (I) when Y^3-Y^6 are present and Y^{7-8} are absent, then each of Y^1-Y^6 are independently selected form dVal and dPro. In some embodiments of the sequence of Formula (I) when Y^3-Y^7 are present and Y^8 is absent, then each of Y^1-Y^7 are independently selected form dVal and dPro. In some embodiments of the sequence of Formula (I) when Y^3-Y^8 are present, then each of Y^1-Y^8 are independently selected from dVal and dPro. In some embodiments, the sequence of Formula (I) is selected from the group consisting of:

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dVal-dPro-NH_2 (SEQ ID NO: 190);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dPro-dVal-dPro-NH_2 (SEQ ID NO: 191);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dVal-dVal-dPro-NH_2 (SEQ ID NO: 192);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-dVal-dPro-NH_2 (SEQ ID NO: 193); and

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dVal-dVal-dVal-dVal-dVal-dPro-NH_2 (SEQ ID NO: 194),

wherein c represents cyclization through R^2 and R^7 via a lactam bond.

[0415] In some embodiments of the sequence of Formula (I), X^1 is present and is acetylated norleucine, and R^1 is present and is norleucine. In some embodiments, X^2 is present and is norleucine. In some embodiments, X^3 is present and is norleucine. In some embodiments, the sequence of Formula (I) is selected from the group consisting of:

Ac-Nle-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 195);

Ac-Nle-Nle-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 196); and

Ac-Nle-Nle-Nle-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 197),

wherein c represents cyclization through R^2 and R^7 via a lactam bond.

[0416] As described above, some of the non-naturally occurring melanocortin analogs comprising the sequence of Formula (I) may bind the melanocortin 3 receptor and the melanocortin 4 receptor with the same or generally similar affinity. Other non-naturally occurring melanocortin analogs comprising the sequence of Formula (I) may bind the melanocortin 3 receptor with greater affinity than the melanocortin 4 receptor. In some embodiments, when the melanocortin antagonist of the present technology binds the melanocortin 3 receptor with greater affinity than the melanocortin 4 receptor, then the sequence of Formula (I) is selected from the group consisting of:

Ac-Nle-c(Asp-Pro-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 198);

Ac-Nle-c(Asp-Trp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 199);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-dTrp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 200);

c(CO-cis-CH=CH-CO-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 201);

Ac-Nle-c(Asp-β-Ala-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 202);

Ac-Nle-c(Asp-Mamb-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 203);

Ac-Nle-c(Asp-Acpc-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 204);

Ac-c(Cys-Arg-dPhe-Cys)-Trp-dVal-dPro-NH_2 (SEQ ID NO: 205);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Trp-NH_2 (SEQ ID NO: 206);

Ac-Nle-c(Asp-Aba-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 207);

Ac-Nle-c(Asp-Aia-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 208); and

Ac-Nle-c(Asp-Ata-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 209),

wherein c represents cyclization through R^1 or R^2 and R^7 or R^8 via a lactam bond or through R^2 and R^5 via a disulfide bond.

[0417] Some non-naturally occurring melanocortin analogs comprising the sequence of Formula (I) may bind the melanocortin 4 receptor with greater affinity than the melanocortin 3 receptor. In some embodiments, when the melanocortin antagonist

binds the melanocortin 4 receptor with greater affinity than the melanocortin 3 receptor, then the sequence of Formula (I) is selected from the group consisting of:

Ac-Nle-c(Asp-Aic-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 210);

Ac-Nle-c(Asp-Cpe-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 211);

Ac-Nle-c(Asp-Che-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 212);

Ac-Nle-c(Asp-Oic-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 213);

Ac-Nle-c(Asp-Ioc-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 214);

Ac-Nle-c(Asp-Tic-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 215);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Pro-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 216);

Ac-Nle-c(Asp-His-dNal(2')-Pro-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 217);

Ac-Nle-c(Asp-His-dNal(2')-*trans*Pro(guan)-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 218);

Ac-Nle-c(Asp-His-dNal(2')-*cis*Pro(guan)-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 219);

Ac-Nle-c(Asp-Pro-dNal(2')-Pro-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 220);

Ac-Nle-c(Asp-Pro-dNal(2')-*trans*Pro(guan)-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 221);

Ac-Nle-c(Asp-Pro-dNal(2')-*cis*Pro(guan)-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 222);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Aba-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 223);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Ata-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 224);

Ac-Nle-c(Asp-Glu-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 225);

Ac-Nle-c(Asp-Glu-dNal(2')-Arg-Trp-Gly-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 226);

Ac-Nle-c(Asp-Pro-Glu-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 227);

Ac-Nle-c(Asp-Pro-Glu-dNal(2')-Arg-Trp-Gly-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 228);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Gly-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 229);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Gly-Lys)-dPro-dPro-Lys-Asp-NH_2 (SEQ ID NO: 230);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Gly-Lys)-dPro-dPro-dLys-dAsp-NH_2 (SEQ ID NO: 231);

Ac-Glu-c(Asp-Pro-dNal(2')-Arg-Trp-Gly-Lys)-dPro-dPro-Lys-Asp-NH_2 (SEQ ID NO: 232); and

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dPro-dPro-dLys-dAsp-NH_2 (SEQ ID NO: 233),

wherein c represents cyclization through R^1 or R^2 and R^7 or R^8 via a lactam bond.

[0418] In some embodiments of the sequence of Formula (I), when X^1 is present and X^2 and X^3 are absent, the sequence of Formula (I) is cyclized through a lactam bond or a disulfide bond between R^1 and any one of R^{5-8}. In some embodiments, when X^1 is present and X^2 and X^3 are absent, the sequence of Formula (I) is cyclized through a lactam bond between R^1 and R^6. In some embodiments, when X^1 is present and X^2 and X^3 are absent, the sequence of Formula (I) is cyclized through a lactam bond between R^1 and R^7. In some embodiments, Y^1 and Y^2 are present and are dVal and dPro, respectively, and Y^3-Y^8 are absent. In some embodiments, Y^1-Y^8 are absent. In some embodiments, the sequence of Formula (I) is selected from the group consisting of:

Ac-Nle-c(Asp-Glu-His-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 234);

Ac-Nle-c(Asp-Glu-His-dNal(2')-Arg-Trp-Gly-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 235);

Ac-Nle-c(Asp-dAla-His-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 236);

Ac-Arg-c(Asp-dAla-His-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 237);

Ac-Arg-c(Asp-dAla-His-dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 238);

Ac-Arg-c(Cys-dAla-His-dNal(2')-Arg-Trp-Cys)-dVal-dPro-NH_2 (SEQ ID NO: 239);

Ac-dArg-c(Asp-dAla-His-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 240);

Ac-Arg-c(Asp-dAla-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 241);

Ac-dArg-c(Asp-dAla-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 242);

Ac-Nle-c(Asp-Ala-His-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 243);

Ac-Arg-c(Asp-Ala-His-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 244);

Ac-dArg-c(Asp-Ala-His-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 245);

Ac-Nle-c(Asp-Trp-Arg-dNal(2')-Pro-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 246);

Ac-Nle-c(Asp-Pro-Trp-dNal(2')-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 247);

Ac-Nle-c(Asp-Pro-Trp-Arg-dNal(2')-Pro-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 248);

Ac-Nle-c(Asp-Pro-Trp-Arg-dNal(2')-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 249);

Ac-Nle-c(Lys-Trp-Arg-dNal(2')-Pro-Asp)-dVal-dPro-NH_2 (SEQ ID NO: 250);

Ac-Arg-c(Cys-dAla-His-dNal(2')-Arg-Trp-Cys)-NH_2 (SEQ ID NO: 251);

Ac-Arg-c(Asp-dAla-His-dNal(2')-Arg-Trp-Lys)-NH_2 (SEQ ID NO: 252);

Ac-Arg-c(Asp-His-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 253); and

Ac-Arg-c(Asp-Glu-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 254),

wherein c represents cyclization through R^1 or R^2 and any one of R^{5-8} via a lactam bond or a disulfide bond.

[0419] In some embodiments of the sequence of Formula (I), when X^1 and X^2 are present and X^3 is absent, the sequence of Formula (I) is cyclized through a lactam bond between R^2 and R^7. In such embodiments, X^1 and X^2 are each independently selected from dVal and dPro. In some embodiments, the sequence of Formula (I) is selected from the group consisting of:

Ac-dVal-dPro-c(Asp-Trp-Arg-dNal(2')-Pro-Lys)-Nle-NH_2 (SEQ ID NO: 255);

Ac-dVal-dPro-c(Lys-Trp-Arg-dNal(2')-Pro-Asp)-Nle-NH_2 (SEQ ID NO: 256);

Ac-dVal-dPro-c(Asp-Trp-Arg-dNal(2')-Pro-Lys)-Nle-Nle-NH_2 (SEQ ID NO: 257);

Ac-dVal-dPro-c(Lys-Trp-Arg-dNal(2')-Pro-Asp)-Nle-Nle-NH_2 (SEQ ID NO: 258);

Ac-dVal-dPro-c(Asp-Trp-Arg-dNal(2')-Pro-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 259); and

Ac-dVal-dPro-c(Lys-Trp-Arg-dNal(2')-Pro-Asp)-dVal-dPro-NH_2 (SEQ ID NO: 260),

wherein c represents cyclization through R^2 and R^7 via a lactam bond.

[0420] In some embodiments of the sequence of Formula (I), R^1 is Nle and one or more of X^1 and X^2 are present. In some embodiments, R^1 is Nle X^1 is present, and X^2 is absent. In some embodiments, R^1 is Nle, and X^1 and X^2 are present. In some embodiments, the sequence of Formula (I) is:

Ac-dVal-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 261); or

Tyr-Val-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 262),

wherein c represents cyclization through R^2 and R^7 via a lactam bond.

[0421] In some embodiments of the sequence of Formula (I), R^1 is Ac-Glu. In some embodiments, R^1 is Ac-Glu, R^2 is Asp, R^3 is Glu, His, or Arg, R^4 is dNal(2'), R^5 is Arg, R^6 is Trp, and R^7 is Lys. In some embodiments, the sequence of Formula (I) is selected from the group consisting of:

Ac-Glu-c(Asp-Glu-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 263);

Ac-Glu-c(Asp-His-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 264); and

Ac-Glu-c(Asp-Arg-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 265),

wherein c represents cyclization through R^2 and R^7 via a lactam bond.

[0422] In some embodiments of the sequence of Formula (I), R^5 is His. In some embodiments, when R^5 is His, then R^3 is His and the sequence of Formula (I) is cyclized via a lactam bond through R^1 or R^2 and R^7. In some embodiments, X^1 is Ac-Arg or absent, R^1 is Ac-Nle, Asp or absent, R^2 is Asp or Pro, R^3 is His, R^4 is dNal(2'), R^5 is His, R^6 is Trp, and R^7 is Lys or Dap. In some embodiments, the sequence of Formula (I) is selected from the group consisting of:

Ac-Nle-c(Asp-Pro-His-dNal(2')-His-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 266);

Ac-Nle-c(Asp-His-dNal(2')-His-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 267);

Ac-Arg-c(Asp-Pro-His-dNal(2')-His-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 268);

Ac-Arg-c(Asp-His-dNal(2')-His-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 269);

Ac-Nle-c(Asp-Pro-His-dNal(2')-His-Trp-Orn)-dVal-dPro-NH_2 (SEQ ID NO: 270);

Ac-Nle-c(Asp-His-dNal(2')-His-Trp-Orn)-dVal-dPro-NH_2 (SEQ ID NO: 271);

Ac-Nle-c(Asp-Pro-His-dNal(2')-His-Trp-Lys)-dVal-Hyp-NH_2 (SEQ ID NO: 272);

Ac-Nle-c(Asp-His-dNal(2')-His-Trp-Lys)-dVal-Hyp-NH_2 (SEQ ID NO: 273);

Ac-Arg-c(Asp-Pro-His-dNal(2')-His-Trp-Orn)-dVal-dPro-NH_2 (SEQ ID NO: 274);

Ac-Arg-c(Asp-His-dNal(2')-His-Trp-Orn)-dVal-dPro-NH_2 (SEQ ID NO: 275);

Ac-Arg-c(Asp-Pro-His-dNal(2')-His-Trp-Lys)-dVal-Hyp-NH_2 (SEQ ID NO: 276);

Ac-Arg-c(Asp-His-dNal(2')-His-Trp-Lys)-dVal-Hyp-NH_2 (SEQ ID NO: 277);

Ac-Nle-c(Asp-Pro-His-dNal(2')-His-Trp-Dap)-dVal-dPro-NH_2 (SEQ ID NO: 278);

Ac-Nle-c(Asp-His-dNal(2')-His-Trp-Dap)-dVal-dPro-NH_2 (SEQ ID NO: 279);

Ac-Arg-c(Asp-Pro-His-dNal(2')-His-Trp-Dap)-dVal-dPro-NH_2 (SEQ ID NO: 280);

Ac-Arg-c(Asp-His-dNal(2')-His-Trp-Dap)-dVal-dPro-NH_2 (SEQ ID NO: 281);

wherein c represents cyclization through R^1 or R^2 and R^7 via a lactam bond.

[0423] In some embodiments of the sequence of Formula (I), R^1 is Ac-Nle, R^2 is Asp and dAsp, R^3 is Pro or His, R^4 is dNal(2'), R^5 is Arg, R^6 is Trp, and R^7 is Lys and dLys. In such embodiments, Y^1, Y^2, and Y^3 are varied. In some embodiments, the sequence of Formula (I) is selected from the group consisting of:

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dThr-dPro-dThr-NH_2 (SEQ ID NO: 282);

Ac-Nle-c(Asp-His-dNal(2')-Arg-Trp-Lys)-dThr-dPro-dThr (SEQ ID NO: 283);

Ac-Nle-c(dAsp-Pro-dNal(2')-Arg-Trp-dLys)-dThr-dPro-dThr (SEQ ID NO: 284);

Ac-Nle-c(dAsp-His-dNal(2')-Arg-Trp-dLys)-dThr-dPro-dThr (SEQ ID NO: 285);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dPro-dVal-NH_2 (SEQ ID NO: 286);

Ac-Nle-c(Asp-His-dNal(2')-Arg-Trp-Lys)-dPro-dVal-NH_2 (SEQ ID NO: 287);

Ac-Nle-c(dAsp-Pro-dNal(2')-Arg-Trp-dLys)-dPro-dVal-NH_2 (SEQ ID NO: 288);

Ac-Nle-c(dAsp-His-dNal(2')-Arg-Trp-dLys)-dPro-dVal-NH_2 (SEQ ID NO: 289);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 290);

Ac-Nle-c(Asp-His-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 291);

Ac-Nle-c(dAsp-Pro-dNal(2')-Arg-Trp-dLys)-dVal-dPro-NH_2 (SEQ ID NO: 292);

Ac-Nle-c(dAsp-His-dNal(2')-Arg-Trp-dLys)-dVal-dPro-NH_2 (SEQ ID NO: 293);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-β-Pro-β-Val-NH_2 (SEQ ID NO: 294);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-β^3Pro-β^2Val-NH_2 (SEQ ID NO: 295);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-β^3Pro-β^3Val-NH_2 (SEQ ID NO: 296);

Ac-Nle-c(Asp-His-dNal(2')-Arg-Trp-Lys)-β-Pro-β-Val-NH_2 (SEQ ID NO: 297);

Ac-Nle-c(dAsp-Pro-dNal(2')-Arg-Trp-dLys)-β-Pro-β-Val-NH_2 (SEQ ID NO: 298);

Ac-Nle-c(dAsp-His-dNal(2')-Arg-Trp-dLys)-β-Pro-β-Val-NH_2 (SEQ ID NO: 299);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-β-Val-β-Pro-NH_2 (SEQ ID NO: 300);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-β²Val-β³Pro-NH_2 (SEQ ID NO: 301);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-β³Val-β³Pro-NH_2 (SEQ ID NO: 302);

Ac-Nle-c(Asp-His-dNal(2')-Arg-Trp-Lys)-β-Val-β-Pro-NH_2 (SEQ ID NO: 303);

Ac-Nle-c(dAsp-Pro-dNal(2')-Arg-Trp-dLys)-β-Val-β-Pro-NH_2 (SEQ ID NO: 304);

Ac-Nle-c(dAsp-His-dNal(2')-Arg-Trp-dLys)-β-Val-β-Pro-NH_2 (SEQ ID NO: 305);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-β-Pro-β-Pro-NH_2 (SEQ ID NO: 306);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-β³Pro-β³Pro-NH_2 (SEQ ID NO: 307);

Ac-Nle-c(Asp-His-dNal(2')-Arg-Trp-Lys)-β-Pro-β-Pro-NH_2 (SEQ ID NO: 308);

Ac-Nle-c(dAsp-Pro-dNal(2')-Arg-Trp-dLys)-β-Pro-β-Pro-NH_2 (SEQ ID NO: 309);

Ac-Nle-c(dAsp-His-dNal(2')-Arg-Trp-dLys)-β-Pro-β-Pro-NH_2 (SEQ ID NO: 310);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-β-Val-β-Val-NH_2 (SEQ ID NO: 311);

Ac-Nle-c(Asp-His-dNal(2')-Arg-Trp-Lys)-β-Val-β-Val-NH_2 (SEQ ID NO: 312);

Ac-Nle-c(dAsp-Pro-dNal(2')-Arg-Trp-dLys)-β-Val-β-Val-NH_2 (SEQ ID NO: 313);

Ac-Nle-c(dAsp-His-dNal(2')-Arg-Trp-dLys)-β-Val-β-Val-NH_2 (SEQ ID NO: 314);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-(3-methyl)-β-Val-β-Val-NH_2 (SEQ ID NO: 315);

Ac-Nle-c(Asp-His-dNal(2')-Arg-Trp-Lys)-(3-methyl)-β-Val-β-Val-NH_2 (SEQ ID NO: 316);

Ac-Nle-c(dAsp-Pro-dNal(2')-Arg-Trp-dLys)-(3-methyl)-β-Val-β-Val-NH_2 (SEQ ID NO: 317);

Ac-Nle-c(dAsp-His-dNal(2')-Arg-Trp-dLys)-(3-methyl)-β-Val-β-Val-NH_2 (SEQ ID NO: 318);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-(3-methyl)-β-Val-β-Pro-NH_2 (SEQ ID NO: 319);

Ac-Nle-c(Asp-His-dNal(2')-Arg-Trp-Lys)-(3-methyl)-β-Val-β-Pro-NH_2 (SEQ ID NO: 320);

Ac-Nle-c(dAsp-Pro-dNal(2')-Arg-Trp-dLys)-(3-methyl)-β-Val-β-Pro-NH_2 (SEQ ID NO: 321);

Ac-Nle-c(dAsp-His-dNal(2′)-Arg-Trp-dLys)-(3-methyl)-β-Val-β-Pro-NH_2 (SEQ ID NO: 322);

Ac-Nle-c(Asp-Pro-dNal(2′)-Arg-Trp-Lys)-β-Thr-β-Pro-β-Thr (SEQ ID NO: 323);

Ac-Nle-c(Asp-His-dNal(2′)-Arg-Trp-Lys)-β-Thr-β-Pro-β-Thr (SEQ ID NO: 324);

Ac-Nle-c(dAsp-Pro-dNal(2′)-Arg-Trp-dLys)-β-Thr-β-Pro-β-Thr (SEQ ID NO: 325);

Ac-Nle-c(dAsp-His-dNal(2′)-Arg-Trp-dLys)-β-Thr-β-Pro-β-Thr (SEQ ID NO: 326);

Ac-Nle-c(Asp-Pro-dNal(2′)-Arg-Trp-Lys)-dPro-dAla-NH_2 (SEQ ID NO: 327);

Ac-Nle-c(Asp-His-dNal(2′)-Arg-Trp-Lys)-dPro-dAla-NH_2 (SEQ ID NO: 328);

Ac-Nle-c(dAsp-Pro-dNal(2′)-Arg-Trp-dLys)-dPro-dAla-NH_2 (SEQ ID NO: 329);

Ac-Nle-c(Asp-His-dNal(2′)-Arg-Trp-Lys)-dPro-dAla-NH_2 (SEQ ID NO: 330);

Ac-Nle-c(Asp-Pro-dNal(2′)-Arg-Trp-Lys)-dAla-dPro-NH_2 (SEQ ID NO: 331);

Ac-Nle-c(Asp-His-dNal(2′)-Arg-Trp-Lys)-dAla-dPro-NH_2 (SEQ ID NO: 332);

Ac-Nle-c(dAsp-Pro-dNal(2′)-Arg-Trp-dLys)-dAla-dPro-NH_2 (SEQ ID NO: 333);

Ac-Nle-c(dAsp-His-dNal(2′)-Arg-Trp-dLys)-dAla-dPro-NH_2 (SEQ ID NO: 334);

Ac-Nle-c(Asp-Pro-dNal(2′)-Arg-Trp-Lys)-β-Pro-β-Ala-NH_2 (SEQ ID NO: 335);

Ac-Nle-c(Asp-His-dNal(2′)-Arg-Trp-Lys)-β-Pro-β-Ala-NH_2 (SEQ ID NO: 336);

Ac-Nle-c(dAsp-Pro-dNal(2′)-Arg-Trp-dLys)-β-Pro-β-Ala-NH_2 (SEQ ID NO: 337);

Ac-Nle-c(dAsp-His-dNal(2′)-Arg-Trp-dLys)-β-Pro-β-Ala-NH_2 (SEQ ID NO: 338);

Ac-Nle-c(Asp-Pro-dNal(2′)-Arg-Trp-Lys)-β-Ala-β-Pro-NH_2 (SEQ ID NO: 339);

Ac-Nle-c(Asp-His-dNal(2′)-Arg-Trp-Lys)-β-Ala-β-Pro-NH_2 (SEQ ID NO: 340);

Ac-Nle-c(dAsp-Pro-dNal(2′)-Arg-Trp-dLys)-β-Ala-β-Pro-NH_2 (SEQ ID NO: 341);

Ac-Nle-c(dAsp-His-dNal(2′)-Arg-Trp-dLys)-β-Ala-β-Pro-NH_2 (SEQ ID NO: 342);

Ac-Nle-c(Asp-Pro-dNal(2′)-Arg-Trp-Lys)-β-Val-β-Ala-NH_2 (SEQ ID NO: 343);

Ac-Nle-c(Asp-His-dNal(2′)-Arg-Trp-Lys)-β-Val-β-Ala-NH_2 (SEQ ID NO: 344);

Ac-Nle-c(dAsp-Pro-dNal(2′)-Arg-Trp-dLys)-β-Val-β-Ala-NH_2 (SEQ ID NO: 345);

Ac-Nle-c(dAsp-His-dNal(2′)-Arg-Trp-dLys)-β-Val-β-Ala-NH_2 (SEQ ID NO: 346);

Ac-Nle-c(Asp-Pro-dNal(2′)-Arg-Trp-Lys)-(3-methyl)-β-Val-β-Ala-NH_2 (SEQ ID NO: 347);

Ac-Nle-c(Asp-His-dNal(2′)-Arg-Trp-Lys)-(3-methyl)-β-Val-β-Ala-NH_2 (SEQ ID NO: 348);

Ac-Nle-c(dAsp-Pro-dNal(2′)-Arg-Trp-dLys)-(3-methyl)-β-Val-β-Ala-NH_2 (SEQ ID NO: 349);

Ac-Nle-c(dAsp-His-dNal(2′)-Arg-Trp-dLys)-(3-methyl)-β-Val-β-Ala-NH_2 (SEQ ID NO: 350)

Ac-Nle-c(Asp-Pro-dNal(2′)-Arg-Trp-Lys)-dPro-dLeu-NH_2 (SEQ ID NO: 351);

Ac-Nle-c(Asp-His-dNal(2′)-Arg-Trp-Lys)-dPro-dLeu-NH_2 (SEQ ID NO: 352);

Ac-Nle-c(dAsp-Pro-dNal(2′)-Arg-Trp-Lys)-dPro-dLeu-NH_2 (SEQ ID NO: 353);

Ac-Nle-c(Asp-His-dNal(2′)-Arg-Trp-Lys)-dPro-dLeu-NH_2 (SEQ ID NO: 354);

Ac-Nle-c(Asp-Pro-dNal(2′)-Arg-Trp-Lys)-dLeu-dPro-NH_2 (SEQ ID NO: 355);

Ac-Nle-c(Asp-His-dNal(2′)-Arg-Trp-Lys)-dLeu-dPro-NH_2 (SEQ ID NO: 356);

Ac-Nle-c(dAsp-Pro-dNal(2′)-Arg-Trp-dLys)-dLeu-dPro-NH_2 (SEQ ID NO: 357);

Ac-Nle-c(dAsp-His-dNal(2′)-Arg-Trp-dLys)-dLeu-dPro-NH_2 (SEQ ID NO: 358);

Ac-Nle-c(Asp-Pro-dNal(2′)-Arg-Trp-Lys)-β-Pro-β-Leu-NH_2 (SEQ ID NO: 359);

Ac-Nle-c(Asp-His-dNal(2′)-Arg-Trp-Lys)-β-Pro-β-Leu-NH_2 (SEQ ID NO: 360);

Ac-Nle-c(dAsp-Pro-dNal(2′)-Arg-Trp-dLys)-β-Pro-β-Leu-NH_2 (SEQ ID NO: 361);

Ac-Nle-c(dAsp-His-dNal(2′)-Arg-Trp-dLys)-β-Pro-β-Leu-NH_2 (SEQ ID NO: 362);

Ac-Nle-c(Asp-Pro-dNal(2′)-Arg-Trp-Lys)-β-Leu-β-Pro-NH_2 (SEQ ID NO: 363);

Ac-Nle-c(Asp-His-dNal(2′)-Arg-Trp-Lys)-β-Leu-β-Pro-NH_2 (SEQ ID NO: 364);

Ac-Nle-c(dAsp-Pro-dNal(2′)-Arg-Trp-dLys)-β-Leu-β-Pro-NH_2 (SEQ ID NO: 365);

Ac-Nle-c(dAsp-His-dNal(2′)-Arg-Trp-dLys)-β-Leu-β-Pro-NH_2 (SEQ ID NO: 366);

Ac-Nle-c(Asp-Pro-dNal(2′)-Arg-Trp-Lys)-β-Val-β-Leu-NH_2 (SEQ ID NO: 367);

Ac-Nle-c(Asp-His-dNal(2′)-Arg-Trp-Lys)-β-Val-β-Leu-NH_2 (SEQ ID NO: 368);

Ac-Nle-c(dAsp-Pro-dNal(2′)-Arg-Trp-dLys)-β-Val-β-Leu-NH_2 (SEQ ID NO: 369);

Ac-Nle-c(dAsp-His-dNal(2′)-Arg-Trp-dLys)-β-Val-β-Leu-NH_2 (SEQ ID NO: 370);

Ac-Nle-c(Asp-Pro-dNal(2′)-Arg-Trp-Lys)-(3-methyl)-β-Val-β-Leu-NH_2 (SEQ ID NO: 371);

Ac-Nle-c(Asp-His-dNal(2′)-Arg-Trp-Lys)-(3-methyl)-β-Val-β-Leu-NH_2 (SEQ ID NO: 372);

Ac-Nle-c(dAsp-Pro-dNal(2′)-Arg-Trp-dLys)-(3-methyl)-β-Val-β-Leu-NH_2 (SEQ ID NO: 373); and

Ac-Nle-c(dAsp-His-dNal(2′)-Arg-Trp-dLys)-(3-methyl)-β-Val-β-Leu-NH_2 (SEQ ID NO: 374),

wherein c represents cyclization through R^1 and R^7 via a lactam bond.

[0424] Alternatively, in some embodiments, the non-naturally occurring melanocortin analog comprises a sequence selected from the group consisting of:

Ac-Nle-c(Asp-Pro-dPhe-Arg-dTrp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 375);

Ac-Nle-c(Asp-His-Arg-p(I)dPhe-Arg-Tic-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 376);

Ac-Nle-c(Asp-His-Arg-dBip-Arg-Tic-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 377);

Ac-Nle-c(Asp-Pro-Arg-p(I)dPhe-Arg-Tic-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 378);

Ac-Nle-c(Asp-Pro-Arg-dBip-Arg-Tic-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 379);

Ac-Nle-c(Asp-Arg-Pro-p(I)dPhe-Arg-Tic-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 380);

Ac-Nle-c(Asp-Arg-Pro-dBip-Arg-Tic-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 381);

Ac-Nle-c(Asp-Aba-dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 382);

Ac-Nle-c(Asp-Aia-dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 383);

Ac-Nle-c(Asp-Ata-dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 384);

Ac-Nle-c(Asp-Aba-p(Cl)dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 385);

Ac-Nle-c(Asp-Aia-p(Cl)dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 386);

Ac-Nle-c(Asp-Ata-p(Cl)dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 387);

Ac-Nle-c(Asp-Atc-dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 388);

Ac-Nle-c(Asp-APC-dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 389);

Ac-Nle-c(Asp-APPC-dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 390);

Ac-Nle-c(Asp-Pro-p(Cl)dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 391);

Ac-Nle-c(Asp-Pro-p(I)dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 392);

Ac-Nle-c(Asp-Pro-p(Br)dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 393);

Ac-Nle-c(Asp-Pro-p(F)dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 394);

Ac-Nle-c(Asp-Pro-p(CF_3)dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 395);

Ac-Nle-c(Asp-His-p(Cl)dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 396);

Ac-Nle-c(Asp-His-p(I)dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 397);

Ac-Nle-c(Asp-His-p(Br)dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 398);

Ac-Nle-c(Asp-His-p(F)dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 399);

Ac-Nle-c(Asp-His-p(CF_3)dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 400);

Ac-Nle-c(Asp-Pro-Pro-dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 401);

Ac-Nle-c(Asp-Trp-Pro-dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 402);

Ac-Nle-c(Asp-His-dPhe-Pro-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 403);

Ac-Nle-c(Asp-His-dPhe-*trans*Pro(guan)-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 404);

Ac-Nle-c(Asp-His-dPhe-*cis*Pro(guan)-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 405);

Ac-Nle-c(Asp-Pro-dPhe-Pro-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 406);

Ac-Nle-c(Asp-Pro-dPhe-*trans*Pro(guan)-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 407);

Ac-Nle-c(Asp-Pro-dPhe-*cis*Pro(guan)-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 408);

Ac-Nle-c(Asp-Pro-dPhe-Arg-Aia-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 409);

Ac-Nle-c(Asp-Pro-dPhe-Arg-Aba-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 410);

Ac-Nle-c(Asp-Pro-dPhe-Arg-Ata-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 411);

Ac-Nle-c(Asp-Pro-p(CF_3)dPhe-Arg-Aia-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 412);

Ac-Nle-c(Asp-Pro-p(CF_3)dPhe-Arg-Aba-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 413);

Ac-Nle-c(Asp-Pro-p(CF_3)dPhe-Arg-Ata-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 414); and

Ac-Arg-c(Asp-dAla-His-dPhe-Arg-Trp-Lys)-NH_2 (SEQ ID NO: 415),

wherein c represents cyclization through R^1 and R^7 or R^8 via a lactam bond.

[0425] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence selected from the group consisting of:

Ac-Nle-c(Asp-Pro-dPhe-Arg-Trp-Lys)-dThr-dPro-dThr (SEQ ID NO: 416);

Ac-Nle-c(Asp-His-dPhe-Arg-Trp-Lys)-dThr-dPro-dThr (SEQ ID NO: 417);

Ac-Nle-c(dAsp-Pro-dPhe-Arg-Trp-dLys)-dThr-dPro-dThr (SEQ ID NO: 418);

Ac-Nle-c(dAsp-His-dPhe-Arg-Trp-dlys)-dThr-dPro-dThr (SEQ ID NO: 419);

Ac-Nle-c(Asp-Pro-dPhe-Arg-Trp-Lys)-dPro-dVal-NH_2 (SEQ ID NO: 420);

Ac-Nle-c(dAsp-His-dPhe-Arg-Trp-dLys)-dPro-dVal-NH_2 (SEQ ID NO: 421);

Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dPro-dVal-NH_2 (SEQ ID NO: 422);

Ac-Nle-c(Asp-His-dNal(2')-Arg-Trp-Lys)-dPro-dVal-NH_2 (SEQ ID NO: 423);

Ac-Nle-c(Asp-Pro-dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 424);

Ac-Nle-c(Asp-His-dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 425);

Ac-Nle-c(dAsp-Pro-dPhe-Arg-Trp-dLys)-dVal-dPro-NH_2 (SEQ ID NO: 426);

Ac-Nle-c(dAsp-His-dNal(2')-Arg-Trp-dLys)-dVal-dPro-NH_2 (SEQ ID NO: 427);

Ac-Nle-c(Asp-Pro-dPhe-Arg-Trp-Lys)-βPro-βVal-NH_2 (SEQ ID NO: 428);

Ac-Nle-c(Asp-His-dPhe-Arg-Trp-Lys)-βPro-βVal-NH_2 (SEQ ID NO: 429);

Ac-Nle-c(dAsp-Pro-dPhe-Arg-Trp-dLys)-βPro-βVal-NH_2 (SEQ ID NO: 430);

Ac-Nle-c(dAsp-His-dPhe-Arg-Trp-dLys)-βPro-βVal-NH_2 (SEQ ID NO: 431);

Ac-Nle-c(Asp-Pro-dPhe-Arg-Trp-Lys)-βVal-βPro-NH_2 (SEQ ID NO: 432);

Ac-Nle-c(Asp-His-dPhe-Arg-Trp-Lys)-βVal-βPro-NH_2 (SEQ ID NO: 433);

Ac-Nle-c(dAsp-Pro-dPhe-Arg-Trp-dLys)-βVal-βPro-NH_2 (SEQ ID NO: 434);

Ac-Nle-c(dAsp-His-dNal(2')-Arg-Trp-dLys)-βVal-βPro-NH_2 (SEQ ID NO: 435);

Ac-Nle-c(Asp-Pro-dPhe-Arg-Trp-Lys)-βPro-βPro-NH_2 (SEQ ID NO: 436);

Ac-Nle-c(Asp-His-dPhe-Arg-Trp-Lys)-βPro-βPro-NH_2 (SEQ ID NO: 437);

Ac-Nle-c(dAsp-Pro-dNal(2')-Arg-Trp-dLys)-βPro-βPro-NH_2 (SEQ ID NO: 438);

Ac-Nle-c(dAsp-His-dNal(2')-Arg-Trp-dLys)-βPro-βPro-NH_2 (SEQ ID NO: 439);

Ac-Nle-c(Asp-Pro-dPhe-Arg-Trp-Lys)-βVal-βVal-NH_2 (SEQ ID NO: 440);

Ac-Nle-c(Asp-His-dPhe-Arg-Trp-Lys)-βVal-βVal-NH_2 (SEQ ID NO: 441);

Ac-Nle-c(dAsp-Pro-Phe-Arg-Trp-dLys)-βVal-βVal-NH_2 (SEQ ID NO: 442);

Ac-Nle-c(dAsp-His-dPhe-Arg-Trp-dLys)-βVal-βVal-NH_2 (SEQ ID NO: 443);

Ac-Nle-c(Asp-Pro-dPhe-Arg-Trp-Lys)-(3-methyl)-βVal-βVal-NH_2 (SEQ ID NO: 444);

Ac-Nle-c(Asp-His-dPhe-Arg-Trp-Lys)-(3-methyl)-βVal-βVal-NH_2 (SEQ ID NO: 445);

Ac-Nle-c(dAsp-Pro-dPhe-Arg-Trp-dLys)-(3-methyl)-βVal-βVal-NH_2 (SEQ ID NO: 446);

Ac-Nle-c(dAsp-His-dPhe-Arg-Trp-dLys)-(3-methyl)-βVal-βVal-NH_2 (SEQ ID NO: 447);

Ac-Nle-c(Asp-Pro-dPhe-Arg-Trp-Lys)-(3-methyl)-βVal-βPro-NH_2 (SEQ ID NO: 448);

Ac-Nle-c(Asp-His-dPhe-Arg-Trp-Lys)-(3-methyl)-βVal-βPro-NH_2 (SEQ ID NO: 449);

Ac-Nle-c(dAsp-Pro-dPhe-Arg-Trp-dLys)-(3-methyl)-βVal-βPro-NH_2 (SEQ ID NO: 450);

Ac-Nle-c(dAsp-His-dPhe-Arg-Trp-dLys)-(3-methyl)-βVal-βPro-NH_2 (SEQ ID NO: 451);

Ac-Nle-c(Asp-Pro-dPhe-Arg-Trp-Lys)-βThr-βPro-βThr (SEQ ID NO: 452);

Ac-Nle-c(Asp-His-dPhe-Arg-Trp-Lys)-βThr-βPro-βThr (SEQ ID NO: 453);

Ac-Nle-c(dAsp-Pro-dPhe-Arg-Trp-dLys)-βThr-βPro-βThr (SEQ ID NO: 454);

Ac-Nle-c(dAsp-His-dPhe-Arg-Trp-dLys)-βThr-βPro-βThr (SEQ ID NO: 455);

Ac-Nle-c(Asp-Pro-dPhe-Arg-Trp-Lys)-dPro-dAla-NH_2 (SEQ ID NO: 456);

Ac-Nle-c(Asp-His-dPhe-Arg-Trp-Lys)-dPro-dAla-NH_2 (SEQ ID NO: 457);

Ac-Nle-c(dAsp-Pro-dPhe-Arg-Trp-dLys)-dPro-dAla-NH_2 (SEQ ID NO: 458);

Ac-Nle-c(dAsp-His-dPhe-Arg-Trp-dLys)-dPro-dAla-NH_2 (SEQ ID NO: 459);

Ac-Nle-c(Asp-Pro-dPhe-Arg-Trp-Lys)-dAla-dPro-NH_2 (SEQ ID NO: 460);

Ac-Nle-c(Asp-His-dPhe-Arg-Trp-Lys)-dAla-dPro-NH_2 (SEQ ID NO: 461);

Ac-Nle-c(dAsp-Pro-dPhe-Arg-Trp-dLys)-dAla-dPro-NH_2 (SEQ ID NO: 462);

Ac-Nle-c(dAsp-His-dPhe-Arg-Trp-dLys)-dAla-dPro-NH_2 (SEQ ID NO: 463);

Ac-Nle-c(Asp-Pro-dPhe-Arg-Trp-Lys)-βPro-βAla-NH_2 (SEQ ID NO: 464);

Ac-Nle-c(Asp-His-dPhe-Arg-Trp-Lys)-βPro-βAla-NH_2 (SEQ ID NO: 465);

Ac-Nle-c(dAsp-Pro-dPhe-Arg-Trp-dLys)-βPro-βAla-NH_2 (SEQ ID NO: 466);

Ac-Nle-c(dAsp-His-dPhe-Arg-Trp-dLys)-βPro-βAla-NH_2 (SEQ ID NO: 467);

Ac-Nle-c(Asp-Pro-dPhe-Arg-Trp-Lys)-βAla-βPro-NH_2 (SEQ ID NO: 468);

Ac-Nle-c(Asp-His-dPhe-Arg-Trp-Lys)-βAla-βPro-NH_2 (SEQ ID NO: 469);

Ac-Nle-c(dAsp-Pro-dPhe-Arg-Trp-dLys)-βAla-βPro-NH_2 (SEQ ID NO: 470);

Ac-Nle-c(dAsp-His-dPhe-Arg-Trp-dLys)-βAla-βPro-NH_2 (SEQ ID NO: 471);

Ac-Nle-c(Asp-Pro-dPhe-Arg-Trp-Lys)-βVal-βAla-NH_2 (SEQ ID NO: 472);

Ac-Nle-c(Asp-His-dPhe-Arg-Trp-Lys)-βVal-βAla-NH_2 (SEQ ID NO: 473);

Ac-Nle-c(dAsp-Pro-dPhe-Arg-Trp-dLys)-βVal-βAla-NH_2 (SEQ ID NO: 474);

Ac-Nle-c(dAsp-His-dPhe-Arg-Trp-dLys)-βVal-βAla-NH_2 (SEQ ID NO: 475);

Ac-Nle-c(Asp-Pro-dPhe-Arg-Trp-Lys)-(3-methyl)-βVal-βAla-NH_2 (SEQ ID NO: 476);

Ac-Nle-c(Asp-His-dPhe-Arg-Trp-Lys)-(3-methyl)-βVal-βAla-NH_2 (SEQ ID NO: 477);

Ac-Nle-c(dAsp-Pro-dPhe-Arg-Trp-dLys)-(3-methyl)-βVal-βAla-NH_2 (SEQ ID NO: 478);

Ac-Nle-c(dAsp-His-dPhe-Arg-Trp-dLys)-(3-methyl)-β-Val-β-Ala-NH_2 (SEQ ID NO: 479);

Ac-Nle-c(Asp-Pro-dPhe-Arg-Trp-Lys)-dPro-dLeu-NH_2 (SEQ ID NO: 480);

Ac-Nle-c(Asp-His-dPhe-Arg-Trp-Lys)-dPro-dLeu-NH_2 (SEQ ID NO: 481);

Ac-Nle-c(dAsp-Pro-dPhe-Arg-Trp-dLys)-dPro-dLeu-NH_2 (SEQ ID NO: 482);

Ac-Nle-c(Asp-His-dPhe-Arg-Trp-Lys)-dPro-dLeu-NH_2 (SEQ ID NO: 483);

Ac-Nle-c(Asp-Pro-dPhe-Arg-Trp-Lys)-dLeu-dPro-NH_2 (SEQ ID NO: 484);

Ac-Nle-c(Asp-His-dPhe-Arg-Trp-Lys)-dLeu-dPro-NH_2 (SEQ ID NO: 485);

Ac-Nle-c(dAsp-Pro-dPhe-Arg-Trp-dLys)-dLeu-dPro-NH_2 (SEQ ID NO: 486);

Ac-Nle-c(dAsp-His-dPhe-Arg-Trp-dLys)-dLeu-dPro-NH_2 (SEQ ID NO: 487);

Ac-Nle-c(Asp-Pro-dPhe-Arg-Trp-Lys)-β-Pro-β-Leu-NH_2 (SEQ ID NO: 488);

Ac-Nle-c(Asp-His-dPhe-Arg-Trp-Lys)-β-Pro-β-Leu-NH_2 (SEQ ID NO: 489);

Ac-Nle-c(dAsp-Pro-dPhe-Arg-Trp-dLys)-β-Pro-β-Leu-NH_2 (SEQ ID NO: 490);

Ac-Nle-c(dAsp-His-dNal(2')-Arg-Trp-dLys)-β-Pro-β-Leu-NH_2 (SEQ ID NO: 491);

Ac-Nle-c(Asp-Pro-dPhe-Arg-Trp-Lys)-β-Leu-β-Pro-NH_2 (SEQ ID NO: 492);

Ac-Nle-c(Asp-His-dPhe-Arg-Trp-Lys)-β-Leu-β-Pro-NH_2 (SEQ ID NO: 493);

Ac-Nle-c(dAsp-Pro-dPhe-Arg-Trp-dLys)-β-Leu-β-Pro-NH_2 (SEQ ID NO: 494);

Ac-Nle-c(dAsp-His-dPhe-Arg-Trp-dLys)-β-Leu-β-Pro-NH_2 (SEQ ID NO: 495);

Ac-Nle-c(Asp-Pro-dPhe-Arg-Trp-Lys)-β-Val-β-Leu-NH_2 (SEQ ID NO: 496);

Ac-Nle-c(Asp-His-dPhe-Arg-Trp-Lys)-β-Val-β-Leu-NH_2 (SEQ ID NO: 497);

Ac-Nle-c(dAsp-Pro-dPhe-Arg-Trp-dLys)-β-Val-β-Leu-NH_2 (SEQ ID NO: 498);

Ac-Nle-c(dAsp-His-dPhe-Arg-Trp-dLys)-β-Val-β-Leu-NH_2 (SEQ ID NO: 499);

Ac-Nle-c(Asp-Pro-dPhe-Arg-Trp-Lys)-(3-methyl)-β-Val-β-Leu-NH_2 (SEQ ID NO: 500);

Ac-Nle-c(Asp-His-dPhe-Arg-Trp-Lys)-(3-methyl)-β-Val-β-Leu-NH_2 (SEQ ID NO: 501);

Ac-Nle-c(dAsp-His-dPhe-Arg-Trp-dLys)-(3-methyl)-β-Val-β-Leu-NH_2 (SEQ ID NO: 502); and

Ac-Nle-c(dAsp-His-dPhe-Arg-Trp-dLys)-(3-methyl)-β-Val-β-Leu-NH_2 (SEQ ID NO: 503),

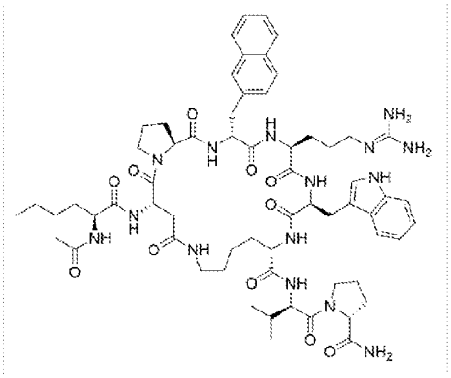
wherein c represents cyclization through R^1 and R^7 via a lactam bond.

[0426] In some embodiments, the non-naturally occurring melanocortin analog is a melanocortin receptor antagonist, such as a melanocortin 3 receptor and/or a melanocortin 4 receptor antagonist. In some embodiments, the non-naturally occurring melanocortin analog is a melanocortin receptor agonist, such as a melanocortin 1 receptor, melanocortin 3 receptor, melanocortin 4 receptor, and/or melanocortin 5 receptor agonist. For example, in some embodiments, the melanocortin analog has agonist activity at the melanocortin 3 receptor and/or the melanocortin 4 receptor, as well as the melanocortin 1 and melanocortin 5 receptors. In other embodiments, the melanocortin analog has antagonist activity at the melanocortin 3 receptor and/or the melanocortin 4 receptor, as well as agonist activity at the melanocortin 1 and melanocortin 5 receptors.

[0427] In some embodiments, the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 2-374. In some embodiments, the non-naturally occurring melanocortin antagonist analog comprises any one of the

sequences of SEQ ID NOs: 2-281. In some embodiments, the non-naturally occurring melanocortin antagonist analog comprises any one of the sequences of SEQ ID NOs: 3, 20, 29-32, 67-70, 99-102, 127-130, 159, 163-166, 187-190, 387, 391, 394, 396, 398 and 399. In some embodiments, the non-naturally occurring melanocortin antagonist analog comprises any one of the sequences of SEQ ID NOs: 10, 14, 33-39, 82-96, 108-111, 119-124, 128, 182-189, 212-281, 394 and 399.

[0428] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of SEQ ID NO: 3 (TCMCB07). The structure of TCMCB07 ("B07"), which comprises Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2, is shown below:



TCMCB07.

Anti-cancer Agents

[0429] The anti-cancer agent described herein is a therapeutic agent useful for the treatment or prevention of neoplasm, of tumor or cancer cell division, growth, proliferation and/or metastasis in a subject; induction of death or apoptosis of tumor and/or cancer cells; and/or any other forms of proliferative disorder. In some embodiments, such anti-cancer agents may be effective to treat, reduce, prevent, or otherwise be useful for a subject having a disease or condition that is not cancer, or besides cancer. The present technology is expected to be useful for subjects that may receive, have received, or are receiving one or more doses of an anti-cancer agent regardless of the underlying disease or condition that the subject has or develops.

[0430] Conventional anti-cancer agents include chemotherapeutic agents such as platinum-based chemotherapeutic agents and non-platinum-based chemotherapeutic agents. Conventional cancer therapies may include more than one anti-cancer agent, for example, a combination of two or more chemotherapeutic agents (e.g., 5-FU plus leucovorin (FOLFOX), sunitinib plus oxaliplatin), a combination of chemotherapeutic agent and immunotherapy, as well as a combination of two or more immunotherapies. In contrast, the methods of the present technology are directed to administration of a non-naturally occurring melanocortin analog prior to, during, and/or after administration of an anti-cancer agent.

[0431] Exemplary chemotherapeutic agents include, but are not limited to, (i) alkylating antineoplastic agents such as cyclophosphamide (CYTOXAN), thiotepa, busulfan, carmustine, chlorambucil, cyclophosphamide, dacarbazine, ifosfamide, lomustine, mechlorethamine, melphalan, mercaptopurine, and procarbazine; (ii) anti-metabolites such as 5-fluorouracil (5-FU), cladribine, cytarabine, fludarabine, gemcitabine (GEMZAR), tegafur (UFTORAL), pentostatin, clofarabine, capecitabine (XELODA), methotrexate, pemetrexed, and thioguanine; (iii) cytotoxic antibiotics such as doxorubicin (including ADRIAMYCIN, morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin, a doxorubicin salt (e.g., hydrochloride salt), doxorubicin HCl liposome injection (DOXIL), and deoxydoxorubicin), daunorubicin, idarubicin, mitomycins such as mitomycin C, actinomycin, epirubicin, calicheamicin, dynemicin, including dynemicin A, aclacinomysins, authramycin, azaserine, bleomycins, cactinomycin, carabicin, carminomycin, carzinophilin, chromomycinis, dactinomycin, detorubicin, 6-diazo-5-oxo-L-norleucine, esorubicin, idarubicin, marcellomycin, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, and zorubicin; (iv) tubulin binding agents such as vincristine (ONCOVIN), paclitaxel, epothilone, docetaxel, discodermolide, etoposide, vinblastine, teniposide, vinorelbine, and vindesine; and (v) platinum-coordination complexes such as cisplatin, oxaliplatin, carboplatin, and nedaplatin.

[0432] Additional examples of chemotherapeutic agents include, but are not limited to, tyrosine-kinase inhibitors such as imatinib, nilotinib, dasatinib, bosutinib, ponatinib, bafetinib, and sunitinib; topoisomerase inhibitors such as CPT-11 (irinotecan, CAMPTOSAR), mitoxantrone, and topotecan (HYCAMTIN); thymidine phosphorylase

(TPase) inhibitors such as tipiracil, and trifluridine; mitotic inhibitors; cell cycle inhibitors; enzymes; biological response modifiers; antiangiogenic agents such as MMP-2, MMP-9, and COX-2 inhibitor; anti-androgens such as fiutamide, nilutamide and bicalutamide; a substituted urea such as hydroxyurea; adrenocortical suppressants such as mitotane, aminoglutethimide, and trilostane; anti-hormonal agents such as antiestrogens and selective estrogen receptor modulators (SERMs), e.g., tamoxifen (including NOLVADEX tamoxifen), raloxifene (EVISTA), droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY 11 7018, onapristone, and toremifene (FARESTON®); hormone and/or hormone antagonists such as the adrenocorticosteriods (e.g., prednisone), progestins (e.g., hydroxyprogesterone caproate), and estrogens (e.g., diethylstilbestrol); androgens, such as testosterone propionate; and aromatase inhibitors, such as anastrozole (ARIMIDEX), exemestane (AROMASIN), 4(5)-imidazoles, aminoglutethimide, megestrol acetate (MEGASE), formestanie, fadrozole, vorozole (RJVISOR), and letrozole (FEMARA).

[0433] In some embodiments, the anti-cancer agent comprises a chemotherapy and the chemotherapy comprises at least one chemotherapeutic agent. In some embodiments, the at least one chemotherapeutic agent comprises one or more chemotherapeutic agents selected from the group consisting of a platinum-coordination complex, an antimetabolite, a tubulin binding agent or a plant alkaloid, an alkylating antineoplastic agent, and a cytotoxic antibiotic. In some embodiments, the chemotherapeutic agent is an antimetabolite, a pyrimidine antagonist, an alkylating agent, a topoisomerase inhibitor, a mitotic inhibitor, an antitumor antibiotic, a protein kinase inhibitor, a proteosome inhibitor, a poly(ADP-ribose) polymerase inhibitor, a plant alkaloid, an antimicrotubule agent, an antineoplastic agent, or an enzyme.

[0434] In some embodiments, the chemotherapeutic agent is an antimetabolite. Nonlimiting examples of antimetabolites include fluorouracil, 5-fluorouracil, 6-mercaptopurine, azacytidine, capecitabine, cladribine, clofarabine, cytarabine, floxuridine, fludarabine, gemcitabine, methotrexate, pemetrexed, pentostatin, pralatrexate, trifluridine, and tipiracil. In some embodiments, the chemotherapeutic agent comprises an antimetabolite selected from the group consisting of 5-fluorouracil (5-FU), 6-mercaptopurine, azacitidine, capecitabine, clofarabine, cytarabine, floxuridine, fludarabine, gemcitabine, methotrexate, pemetrexed, pentostatin, pralatrexate, trifluridine, and tipiracil.

[0435] In some embodiments, the chemotherapeutic agent is a pyrimidine antagonist. Nonlimiting examples of pyrimidine antagonists include vincristine, vinblastine, vinorelbine, paclitaxel, docetaxel, etoposide, teniposide, irinotecan, and topotecan.

[0436] In some embodiments, the chemotherapeutic agent is an alkylating agent. Nonlimiting examples of alkylating agents include altretamine, bendamustine, busulfan, carboplatin, carmustine, cisplatin, chlorambucil, cyclophosphamide, dacarbazine, ifosfamide, lomustine, melphalan, temozolomide, and trabectedin.

[0437] In some embodiments, the chemotherapeutic agent is a topoisomerase inhibitor. Nonlimiting examples of topoisomerase inhibitors include irinotecan, camptothecin, etoposide, doxorubicin, topotecan, mitoxantrone, teniposide, daunorubicin, idarubicin, epirubicin, SN-38, dexrazoxane, belotecan, levofloxacin, anthracycline, rubitecan, sacituzumab govitecan, moxifloxacin, gatifloxacin, rubitecan, nalidixic acid, nalidixic acid, novobiocin, enoxacin, flumequine, clinafloxacin.

[0438] In some embodiments, the chemotherapeutic agent is a mitotic inhibitor. Nonlimiting examples of mitotic inhibitors include paclitaxel, docetaxel, vinblastine, vincristine, vinorelbine, ixabepilone, colchicine, demecolcine, etoposide, teniposide, alisertib, barasertib, volasertib, paclitaxel protein-bound particles, albumin-bound paclitaxel, ispinesib, and eribulin.

[0439] In some embodiments, the chemotherapeutic agent is an antitumor antibiotic. Nonlimiting examples of antitumor antibiotics include daunorubicin, doxorubicin, liposomal doxorubicin, epirubicin, idarubicin, mitomycin, and valrubicin.

[0440] In some embodiments, the chemotherapeutic agent is a protein kinase inhibitor. Nonlimiting examples of protein kinase inhibitors include imatinib, dasatinib, nilotinib, bosutinib, ponatinib, sorafenib, sunitinib, pazopanib, cabozantinib, vandetanib, crizotinib, ceritinib, alectinib, brigatinib, osimertinib, larotrectinib, entrectinib, dabrafenib, trametinib, and cobimetinib.

[0441] In some embodiments, the chemotherapeutic agent is a proteosome inhibitor. Nonlimiting examples of proteosome inhibitors include bortezomib, carfilzomib, ixazomib, marizomib, delanzomib, oprozomib, delanzomib, belinostat,

panobinostat, romidepsin, vorinostat, belinostat, pracinostat, resminostat, givinostat, quisinostat, mocetinostat, chidamide, rocilinostat, and tucidinostat.

[0442] In some embodiments, the chemotherapeutic agent is a poly(ADP-ribose) polymerase inhibitor. Nonlimiting examples of poly(ADP-ribose) polymerase inhibitors include olaparib, rucaparib, niraparib, talazoparib, veliparib, pamiparib, ceralasertib, talazoparib, iniparib, niraparib, olaparib, rucaparib, veliparib, talazoparib, pamiparib, iniparib, veliparib, olaparib, talazoparib, and rucaparib.

[0443] In some embodiments, the chemotherapeutic agent is a plant alkaloid. Nonlimiting examples of plant alkaloids include vincristine, vinblastine, vinorelbine, paclitaxel, docetaxel, etoposide, teniposide, irinotecan, and topotecan.

[0444] In some embodiments, the chemotherapeutic agent is an antimicrotubule agent. Nonlimiting examples of antimicrotubule agents include docetaxel, paclitaxel, vinblastine, vincristine, vinorelbine, eribulin, ixabepilone, and cabazitaxel.

[0445] In some embodiments, the chemotherapeutic agent is an antineoplastic agent. Nonlimiting examples of antineoplastic agents include estramustine, mitomycin, hydroxydaunorubicin, chlorambucil, cisplatin, carboplatin, oxaliplatin, methotrexate, 5-fluorouracil, capecitabine, doxorubicin, epirubicin, idarubicin, daunorubicin, bleomycin, etoposide, teniposide, mitoxantrone, irinotecan, topotecan, gemcitabine, pemetrexed, paclitaxel, and docetaxel.

[0446] In some embodiments, the chemotherapeutic agent is an enzyme. Nonlimiting examples of enzymes include L-asparaginase, pegaspargase, glucarpidase, carboxypeptidase G2, methioninase, arginine deiminase, ADI-PEG 20, protease-activated receptor 1 (PAR-1) inhibitors, thymidylate synthase inhibitors, topoisomerase I inhibitors, topoisomerase II inhibitors, dihydrofolate reductase inhibitors, ribonucleotide reductase inhibitors, hypoxanthine-guanine phosphoribosyltransferase inhibitors, DNA polymerase inhibitors, telomerase inhibitors, histone deacetylase inhibitors, protein kinase C inhibitors, sirtuin inhibitors, and matrix metalloproteinase inhibitors.

[0447] In some embodiments, the at least one chemotherapeutic agent comprises a platinum-coordination complex. In some embodiments, the platinum-coordination complex is carboplatin and/or cisplatin.

[0448] In some embodiments, the at least one chemotherapeutic agent comprises a tubulin binding agent or a plant alkaloid. In some embodiments, the tubulin binding agent or the plant alkaloid is at least one selected from the group consisting of vincristine, vinblastine, vinorelbine, paclitaxel, docetaxel, etoposide, teniposide, irinotecan, and Topotecan.

[0449] In some embodiments, the at least one chemotherapeutic agent comprises an alkylating antineoplastic agent. In some embodiments, the alkylating antineoplastic agent is at least one selected from the group consisting of altretamine, busulfan, carmustine, cyclophosphamide, dacarbazine, ifosfamide, lomustine, melphalan, temozolomide, and trabectedin.

[0450] In some embodiments, the at least one chemotherapeutic agent comprises a cytotoxic antibiotic. In some embodiments, the cytotoxic antibiotic is at least one selected from the group consisting of daunorubicin, doxorubicin, doxorubicin liposomal, epirubicin, idarubicin, and valrubicin.

[0451] In some embodiments, the platinum-coordination complex is cisplatin. In some embodiments, the chemotherapy comprises cisplatin, and the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3).

[0452] In some embodiments, the antimetabolite is 5-fluorouracil (5-FU). In some embodiments, the chemotherapy comprises 5-FU, and the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3).

[0453] In some embodiments, the tubulin binding agent or the plant alkaloid is vincristine. In some embodiments, the chemotherapy comprises vincristine, and the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3).

[0454] In some embodiments, the alkylating antineoplastic agent is cyclophosphamide. In some embodiments, the chemotherapy comprises cyclophosphamide, and the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3).

[0455] In some embodiments, the cytotoxic antibiotic is doxorubicin. In some embodiments, the chemotherapy comprises doxorubicin, and the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3).

[0456] The present technology further encompasses combinations of two or more anti-cancer agents, including the above chemotherapeutic agents, as the anti-cancer agent of the combination therapy. Non-limiting examples include gemcitabine in combination with cisplatin; carboplatin in combination with pemetrexed; CHOP, an abbreviation for a combined therapy of cyclophosphamide, doxorubicin, vincristine, and prednisolone; and FOLFOX, an abbreviation for a treatment regimen with oxaliplatin combined with 5-FU and leucovovin.

[0457] In some embodiments, the method further comprises administering an antibody, or antigen binding fragment thereof, that specifically binds to human growth differentiation factor 15 (GDF15) such as, but not limited to, ponsegromab. See U.S. Patent No. 11,566,066 (or U.S. Patent Application No. 16/541,817, incorporated herein by reference). In some embodiments, the non-naturally occurring melanocortin analog treats, prevents, and/or reduces one or more side effects that an antibody, or antigen binding fragment thereof, that specifically binds to GDF15 may also treat, prevent, and/or reduce.

Formulations

[0458] The compositions comprising the carriers and/or excipients described in the present technology facilitate delivery of the non-naturally occurring melanocortin analog and/or one or more anti-cancer agents described herein in any of its embodiments to a subject.

[0459] In some embodiments, the one or more anti-cancer agents is present in a composition.

[0460] In some embodiments, the non-naturally occurring melanocortin analog is present in a composition.

[0461] In some embodiments, the non-naturally occurring melanocortin analog is present in the composition in a concentration of 0.1 mg/mL to 500 mg/mL, relative to a total volume of the composition. For example, the non-naturally occurring melanocortin

analog is present in the composition in a concentration of 0.1 mg/mL to 500 mg/mL, 0.5 mg/mL to 250 mg/mL, 1 mg/mL to 100 mg/mL, 2.5 mg/mL to 50 mg/mL, or 5 mg/mL to 25 mg/mL, relative to a total volume of the composition. In some embodiments, the non-naturally occurring melanocortin analog is present in the composition in a concentration of about 50 mg/mL, relative to a total volume of the composition.

[0462] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3), and the non-naturally occurring melanocortin analog is present in the composition in a concentration of 5 mg/mL to 100 mg/mL, relative to a total volume of the composition. For example, the non-naturally occurring melanocortin analog comprising a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3) is present in the composition in a concentration of 5 mg/mL to 100 mg/mL, 10 mg/mL to 75 mg/mL, 15 mg/mL to 50 mg/mL, 20 mg/mL to 40 mg/mL, or 25 mg/mL to 30 mg/mL, relative to a total volume of the composition. In some embodiments, the non-naturally occurring melanocortin analog comprising a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3) is present in the composition in a concentration of about 50 mg/mL, relative to a total volume of the composition.

[0463] In some embodiments, the composition comprising the non-naturally occurring melanocortin analog is administered to the subject parenterally. In some embodiments, the composition comprising the non-naturally occurring melanocortin analog is administered to the subject subcutaneously.

[0464] In some embodiments, the composition formulated for parenteral administration (e.g., subcutaneous administration) comprises the non-naturally occurring melanocortin analog of formula (I) at a concentration at about 0.001 nmol, 0.005 nmol, 0.01 nmol, 0.02 nmol, 0.05 nmol, 0.1 nmol, 0.25 nmol, 0.5 nmol, 1 nmol, 2.5 nmol, 5 nmol, 10 nmol, 20 nmol, 25 nmol, 50 nmol, 100 nmol, 250 nmol, 500 nmol, or 1000 nmol, or even more, depending on the specific peptide selected, the desired response, the route of administration, the formulation and other factors known to those of skill in the art. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3).

[0465] In some embodiments, the non-naturally occurring melanocortin analog crosses blood-brain-barrier (BBB) of the subject.

[0466] In some embodiments, the subject is a mammal, including but not limited to a human, a non-human primate such as a chimpanzee, a domestic livestock or a farm animal such as a cow, a bison, sheep, a pig, a goat, a horse, a chicken, and a rooster, a domestic pet animal such as a dog, a cat, a rat, a mouse, and a rabbit, and a laboratory subject such as a rodent, including a rat, a mouse, and a guinea pig. In some embodiments, the subject is a human. In some embodiments, the subject is an animal such as a rat or a dog.

[0467] In some embodiments, the subject has a body mass index (BMI) of 18.5 kg/m^2 to 35 kg/m^2. In some embodiments, the subject has a BMI of less than 35 kg/m^2. In some embodiments, the subject has a BMI of less than 18.5 kg/m^2.

[0468] In some embodiments, the subject is an underweight subject. Underweight subjects include those having a body weight about 3%, 5% or less, 10% or less, 20% or less, or 30% or less, than the lower end of "normal" BMI (e.g., 18.5 kg/m^2).

[0469] In some embodiments, the compositions of the present technology are administered to the subject at a dose that is based on the subject's BMI. In some embodiments, two or more doses of the compositions of the present technology are administered to the subject, wherein the two or more doses are titrated (e.g., inversely titrated) based on the subject's BMI at the time of each administration.

[0470] The compositions comprising the carriers and/or excipients described in the present technology facilitate delivery (e.g., parenteral administration, in particular subcutaneous injection) of the non-naturally occurring melanocortin analog described herein in any of its embodiments to a subject. Other purposes of the compositions comprising the carriers and/or excipients are to enhance dispersion, solubility, and stability of the non-naturally occurring melanocortin analog, and to reduce adverse injection site reactions.

[0471] The carriers and/or excipients of the composition may generally include one or more of the following components: a pH buffered aqueous solution comprising (a) sodium acetate, (b) Tris, and (c) water. In some embodiments, all components are compatible with the non-naturally occurring melanocortin analog (i.e., do not react or

cause the non-naturally occurring melanocortin analog to react) and are homogeneously dispersed or dissolved uniformly in the composition.

[0472] In some embodiments, the carrier and/or excipient is isotonic.

[0473] In order to achieve a desirable tonicity, the composition of the present technology may further include a salt such as sodium chloride, sodium succinate, sodium sulfate, potassium chloride, magnesium chloride, magnesium sulfate, and calcium chloride. In some embodiments, the salt is present in the composition in a concentration of 0.1 mg/mL to 50 mg/mL, 1 mg/mL to 25 mg/mL, or 5 mg/mL to 10 mg/mL, relative to a total volume of the composition.

[0474] The carriers and/or excipients of the composition also includes a pH buffered aqueous solution which comprises (a) sodium acetate, (b) Tris, and (c) water.

[0475] The water used herein may act as a diluent and include, without limitation, water for injection (WFI), sterile water, bacteriostatic water for injection (BWFI), distilled water, bidistilled water, deionized water, deionized distilled water, and reverse osmosis water. In some embodiments, the water present in the pH buffered aqueous solution is water for injection.

[0476] In some embodiments, the composition includes water in an amount of about 1 wt% to about 90 wt%, about 10 wt% to about 75 wt%, or about 25 wt% to about 50 wt%, relative to a total weight of the composition.

[0477] In some embodiments, sodium acetate is present in the composition in a concentration of 0.5 mg/mL to 50 mg/mL, relative to a total volume of the composition. For example, sodium acetate is present in the composition in a concentration of 0.5 mg/mL to 50 mg/mL, 1 mg/mL to 40 mg/mL, 2 mg/mL to 30 mg/mL, 4 mg/mL to 20 mg/mL, 5 mg/mL to 15 mg/mL, 6 mg/mL to 12 mg/mL, or 8 mg/mL to 10 mg/mL, relative to a total volume of the composition.

[0478] In some embodiments, sodium acetate is present in the composition in a concentration of about 6 mg/mL to about 8 mg/mL, relative to a total volume of the composition. For example, sodium acetate is present in the composition in a concentration of 6 mg/mL, 6.5 mg/mL, 7 mg/mL, 7.1 mg/mL, 7.5 mg/mL, or 8 mg/mL, relative to a total volume of the composition.

[0479] In some embodiments, sodium acetate is present in the composition in a molar concentration of 5 mM to 700 mM, relative to a total volume of the composition. For example, sodium acetate is present in the composition in a molar concentration of 5 mM to 700 mM, 10 mM to 600 mM, 20 mM to 500 mM, 30 mM to 400 mM, 40 mM to 300 mM, 50 mM to 200 mM, 60 mM to 100 mM, or 70 mM to 80 mM, relative to a total volume of the composition.

[0480] In some embodiments, sodium acetate is present in the composition in a molar concentration of about 80 mM to about 100 mM, relative to a total volume of the composition. For example, sodium acetate is present in the composition in a molar concentration of 80 mM, 85 mM, 87 mM, 90 mM, 95 mM, or 100 mM, relative to a total volume of the composition.

[0481] The term "Tris" represents tris(hydroxymethyl)aminomethane also known as Tris buffer, Tris base, TRIS, tromethamine, tromethamine buffer, Trizma®, Trisamine, Trometamol, Tromethane, Trisaminol, or THAM. In some embodiments, Tris is present in the composition in a concentration of 0.5 mg/mL to 50 mg/mL, relative to a total volume of the composition. For example, Tris is present in the composition in a concentration of 0.5 mg/mL to 50 mg/mL, 1 mg/mL to 40 mg/mL, 2 mg/mL to 30 mg/mL, 4 mg/mL to 20 mg/mL, 5 mg/mL to 15 mg/mL, 6 mg/mL to 12 mg/mL, or 8 mg/mL to 10 mg/mL, relative to a total volume of the composition.

[0482] In some embodiments, Tris is present in the composition in a concentration of about 6 mg/mL to about 8 mg/mL, relative to a total volume of the composition. For example, Tris is present in the composition in a concentration of 6 mg/mL, 6.5 mg/mL, 7 mg/mL, 7.3 mg/mL, 7.6 mg/mL, or 8 mg/mL, relative to a total volume of the composition.

[0483] In some embodiments, Tris is present in the composition in a molar concentration of 2 mM to 500 mM, relative to a total volume of the composition. For example, Tris is present in the composition in a molar concentration of 2 mM to 500 mM, 5 mM to 400 mM, 10 mM to 300 mM, 20 mM to 200 mM, 30 mM to 150 mM, 40 mM to 100 mM, 50 mM to 80 mM, or 60 mM to 70 mM, relative to a total volume of the composition.

[0484] In some embodiments, Tris is present in the composition in a molar concentration of about 50 mM to about 70 mM, relative to a total volume of the

composition. For example, Tris is present in the composition in a molar concentration of 50 mM, 55 mM, 60 mM, 65 mM, or 70 mM, relative to a total volume of the composition.

[0485] In some embodiments, the pH buffered aqueous solution provides the composition with a pH equivalent or close to the physiological pH levels. This may reduce adverse injection site reactions and also provide the non-naturally occurring melanocortin analog with enhanced stability and resistance to aggregation and degradation.

[0486] In addition to sodium acetate and Tris, the composition may include other buffering agents. Non-limiting examples of additional buffering agents include saline, phosphate, phosphoric acid, citrate, succinate, gluconate, histidine, acetic acid, ascorbate, tartartic acid, maleic acid, glycine, lactate, lactic acid, ascorbic acid, imidazole, bicarbonate, carbonic acid, succinic acid, sodium benzoate, benzoic acid, gluconate, edetate, malate, imidazole, and mixtures thereof. In some embodiments, the composition comprises acetic acid as an additional buffering agent.

[0487] In some embodiments, a weight ratio of sodium acetate to Tris is 1:4 to 4:1, 2:7 to 7:2, 1:3 to 3:1, 2:5 to 5:2, 1:2 to 2:1, 2:3 to 3:2, or about 1:1. In some embodiments, the weight ratio of sodium acetate to Tris is about 1:1.

[0488] In some embodiments, a weight ratio of the non-naturally occurring melanocortin analog to sodium acetate is 1:1 to 20:1, 3:2 to 15:1, 2:1 to 12:1, 3:1 to 10:1, 4:1 to 9:1, 5:1 to 8:1, or 6:1 to 7:1. In some embodiments, the weight ratio of the non-naturally occurring melanocortin analog to sodium acetate is about 7:1.

[0489] In some embodiments, a weight ratio of the non-naturally occurring melanocortin analog to Tris is 1:1 to 20:1, 3:2 to 15:1, 2:1 to 12:1, 3:1 to 10:1, 4:1 to 9:1, 5:1 to 8:1, or 6:1 to 7:1. In some embodiments, the weight ratio of the non-naturally occurring melanocortin analog to Tris is about 7:1.

[0490] The composition may also comprise a preservative agent. Exemplary preservative agents include, but are not limited to, ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite, ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, phenol, m-cresol, benzyl alcohol, alpha-tocopherol, citric acid, ethylenediamine tetraacetic acid

(EDTA), sorbitol, tartaric acid, phosphoric acid, benzalkonium chloride, phenoxyethanol, and methyl paraben.

[0491] If present, the concentration of the preservative agent may range from 0.001 mg/mL to 50 mg/mL, 0.01 mg/mL to 25 mg/mL, 0.1 mg/mL to 10 mg/mL, or 1 mg/mL to 5 mg/mL, relative to a total volume of the composition.

[0492] In some embodiments, the composition is in the form of an aqueous solution or a suspension. In some embodiments, the composition is in the form of an emulsion. In some embodiments, the composition is in the form of an aqueous solution. In some embodiments, the composition is in the form of an aqueous solution which is clear, colorless, and/or free of visible foreign matter.

[0493] In some embodiments, the composition has a pH ranging from 6.5 to 8.5. In some embodiments, the composition has a pH of about 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, or 8.5.

[0494] In some embodiments, the composition is basic and has a pH of about 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, or 8.5. In some embodiments, the composition has a pH ranging from about 7.3 to about 7.4. In some embodiments, the composition has a pH of 7.3 or 7.4.

[0495] In some embodiments, the composition has an osmolality ranging from 250 mOsm/kg to 350 mOsm/kg. For example, the composition has an osmolality ranging from 250 mOsm/kg to 360 mOsm/kg, 260 mOsm/kg to 340 mOsm/kg, 270 mOsm/kg to 330 mOsm/kg, 280 mOsm/kg to 320 mOsm/kg, 290 mOsm/kg to 310 mOsm/kg, or about 300 mOsm/kg. In some embodiments, the composition has an osmolarity of about 250 mOsm/kg, about 260 mOsm/kg, about 270 mOsm/kg, about 280 mOsm/kg, about 290 mOsm/kg, about 300 mOsm/kg, about 310 mOsm/kg, about 320 mOsm/kg, about 330 mOsm/kg, about 340 mOsm/kg, about 350 mOsm/kg, or about 360 mOsm/kg. In some embodiments, the composition has an osmolality ranging from about 275 mOsm/kg to about 330 mOsm/kg. In some embodiments, the composition has an osmolality of about 279 mOsm/kg, about 314 mOsm/kg, or about 329 mOsm/kg.

[0496] In some embodiments, the composition has a viscosity ranging from 0.5 cP to 5 cP. For example, the composition has a viscosity ranging from 0.5 cP to 5 cP, 0.75 cP to 4.5 cP, 1.0 cP to 4 cP, 1.2 cP to 3.5 cP, 1.3 cP to 3 cP, 1.4 cP to 2.5 cP, 1.5 cP

to 2 cP, or 1.6 cP to 1.8 cP. In some embodiments, the composition has a viscosity of about 0.5 cP, 0.6 cP, 0.7 cP, 0.8 cP, 0.9 cP, 1.0 cP, 1.1 cP, 1.2 cP, 1.3 cP, 1.4 cP, 1.5 cP, 1.6 cP, 1.7 cP, 1.8 cP, 1.9 cP, or 2.0 cP. In some embodiments, the composition has a viscosity of about 1.4 cP or 1.6 cP.

[0497] The composition described herein in any of its embodiments may be formulated for parenteral administration, such as, for example, in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. The term "parenteral", as used herein, includes subcutaneous, intravenous, intraperitoneal, intramuscular, and intralesional, or infusion techniques.

[0498] The active ingredient(s) (e.g., the non-naturally occurring melanocortin analog) may be dissolved or suspended in the aforementioned carrier and/or excipient. Additional aqueous or non-aqueous carriers that may facilitate dissolution of the active ingredient include, but are not limited to, ethanol, benzyl alcohol, DMSO, polyethylene glycol, propylene glycol, corn oil, cottonseed oil, peanut oil, sesame oil, and/or various buffers.

[0499] In some embodiments, the composition formulated for parenteral administration (e.g., subcutaneous administration) comprises a non-naturally occurring melanocortin analog at a concentration at about 0.001 nmol, 0.005 nmol, 0.01 nmol, 0.02 nmol, 0.05 nmol, 0.1 nmol, 0.25 nmol, 0.5 nmol, 1 nmol, 2.5 nmol, 5 nmol, 10 nmol, 20 nmol, 25 nmol, 50 nmol, 100 nmol, 250 nmol, 500 nmol, or 1000 nmol, or even more, depending on the specific peptide selected, the desired therapeutic response, the route of administration, the formulation and other factors known to those of skill in the art.

[0500] In some embodiments, the composition formulated for parenteral administration (e.g., subcutaneous administration) comprises sodium acetate at a concentration at about 5 mM, 10 mM, 15 mM, 20 mM, 25 mM, 30 mM, 35 mM, 40 mM, 45 mM, 50 mM, 55 mM, 60 mM, 65 mM, 70 mM, 75 mM, 76 mM, 77 mM, 78 mM, 79 mM, 80 mM, 81 mM, 82 mM, 83 mM, 84 mM, 85 mM, 86 mM, 87 mM, 88 mM, 89 mM, 90 mM, 91 mM, 92 mM, 93 mM, 94 mM, 95 mM, 96 mM, 97 mM, 98 mM, 99 mM, 100 mM, 105 mM, 110 mM, 120 mM, 130 mM, 140 mM, 150 mM, 160 mM, 170 mM, 180 mM, 190 mM, or 200 mM.

[0501] In some embodiments, the composition formulated for parenteral administration (e.g., subcutaneous administration) comprises Tris at a concentration at

about 5 mM, 10 mM, 15 mM, 20 mM, 25 mM, 30 mM, 3 5mM, 40 mM, 45 mM, 50 mM, 55 mM, 60 mM, 65 mM, 70 mM, 75 mM, 80 mM, 85 mM, 90 mM, 95 mM, 100 mM, 105 mM, 110 mM, or 120 mM.

[0502] The compositions of the present technology may be formulated for intranasal delivery. In some embodiments, the intranasal composition comprises a non-naturally occurring melanocortin analog of the present technology and a carrier and/or excipient.

[0503] The carriers and/or excipients of the composition may generally include one or more of the following components: (i) one or more antioxidants, (ii) one or more preservatives, (iii) one or more buffers, (iv) one or more tonicity adjustors, (v) one or more surfactants, (vi) flavor, (vii) propellants, and/or (viii) a vehicle or solvent. In some embodiments, all components are compatible with the non-naturally occurring melanocortin analog (i.e., do not react or cause the non-naturally occurring melanocortin analog to react) and are homogeneously dispersed or dissolved uniformly in the composition.

[0504] In some embodiments, the carrier and/or excipient is isotonic to nasal fluids.

[0505] In order to achieve a desirable tonicity, the composition of the present technology may further include a salt such as sodium chloride, sodium succinate, sodium sulfate, potassium chloride, magnesium chloride, magnesium sulfate, and calcium chloride. In some embodiments, the salt is present in the composition in a concentration of 0.1 mg/mL to 50 mg/mL, 1 mg/mL to 25 mg/mL, or 5 mg/mL to 10 mg/mL, relative to a total volume of the composition. In some aspects, the salt is sodium chloride at a concentration of 0.9% wt.

[0506] The carriers and/or excipients of the composition also includes a pH buffered aqueous solution which comprises sodium acetate, Tris, and/or a phosphate buffer.

[0507] The water used herein may act as a diluent and include, without limitation, water for injection (WFI), sterile water, bacteriostatic water for injection (BWFI), distilled water, bidistilled water, deionized water, deionized distilled water, and reverse osmosis water. In some embodiments, the water present in the pH buffered aqueous solution is water for injection.

[0508] In some embodiments, the composition includes water (e.g., water for injection) in an amount of about 1 wt% to about 90 wt%, about 10 wt% to about 75 wt%, or about 25 wt% to about 50 wt%, relative to a total weight of the composition.

[0509] In some embodiments, sodium acetate is present in the composition in a concentration of 0.5 mg/mL to 50 mg/mL, relative to a total volume of the composition. For example, sodium acetate is present in the composition in a concentration of 0.5 mg/mL to 50 mg/mL, 1 mg/mL to 40 mg/mL, 2 mg/mL to 30 mg/mL, 4 mg/mL to 20 mg/mL, 5 mg/mL to 15 mg/mL, 6 mg/mL to 12 mg/mL, or 8 mg/mL to 10 mg/mL, relative to a total volume of the composition.

[0510] In some embodiments, sodium acetate is present in the composition in a molar concentration of about 80 mM to about 100 mM, relative to a total volume of the composition. For example, sodium acetate is present in the composition in a molar concentration of 80 mM, 85 mM, 87 mM, 90 mM, 95 mM, or 100 mM, relative to a total volume of the composition.

[0511] The term "Tris" represents tris(hydroxymethyl)aminomethane also known as Tris buffer, Tris base, TRIS, tromethamine, tromethamine buffer, Trizma®, Trisamine, Trometamol, Tromethane, Trisaminol, or THAM. In some embodiments, Tris is present in the composition in a concentration of 0.5 mg/mL to 50 mg/mL, relative to a total volume of the composition. For example, Tris is present in the composition in a concentration of 0.5 mg/mL to 50 mg/mL, 1 mg/mL to 40 mg/mL, 2 mg/mL to 30 mg/mL, 4 mg/mL to 20 mg/mL, 5 mg/mL to 15 mg/mL, 6 mg/mL to 12 mg/mL, or 8 mg/mL to 10 mg/mL, relative to a total volume of the composition.

[0512] In some embodiments, the pH buffered aqueous solution provides the composition with a pH equivalent or close to the physiological pH levels. This may reduce adverse injection site reactions and also provide the non-naturally occurring melanocortin analog with enhanced stability and resistance to aggregation and degradation.

[0513] In addition to sodium acetate and Tris, the composition may include other buffering agents. Non-limiting examples of additional buffering agents include saline, phosphate, phosphoric acid, citrate, succinate, gluconate, histidine, acetic acid, ascorbate, tartartic acid, maleic acid, glycine, lactate, lactic acid, ascorbic acid, imidazole, bicarbonate, carbonic acid, succinic acid, sodium benzoate, benzoic acid,

gluconate, edetate, malate, imidazole, and mixtures thereof. In some embodiments, the composition comprises acetic acid as an additional buffering agent.

[0514] In some embodiments, sodium phosphate is present in the composition in a molar concentration of 5 mM to 700 mM, relative to a total volume of the composition. For example, sodium acetate is present in the composition in a molar concentration of 5 mM to 700 mM, 10 mM to 600 mM, 20 mM to 500 mM, 30 mM to 400 mM, 40 mM to 300 mM, 50 mM to 200 mM, 60 mM to 100 mM, or 70 mM to 80 mM, relative to a total volume of the composition.

[0515] The composition may also comprise a preservative agent. Exemplary preservative agents include, but are not limited to, ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite, ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, phenol, m-cresol, benzyl alcohol, benzalkonium chloride, alpha-tocopherol, citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, benzalkonium chloride, phenoxyethanol, and methyl paraben.

[0516] If present, the concentration of the preservative agent may range from 0.001 mg/mL to 50 mg/mL, 0.01 mg/mL to 25 mg/mL, 0.1 mg/mL to 10 mg/mL, or 1 mg/mL to 5 mg/mL, relative to a total volume of the composition.

[0517] In some embodiments, the composition is in the form of an aqueous solution or a suspension. In some embodiments, the composition is in the form of an emulsion. In some embodiments, the composition is in the form of an aqueous solution. In some embodiments, the composition is in the form of an aqueous solution which is clear, colorless, and/or free of visible foreign matter.

[0518] In some embodiments, the composition has a pH approximating the normal pH range of the nasal fluid. In some embodiments, the composition has a pH ranging from 5.5 to 6.5. In some embodiments, the composition has a pH of about 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, or 6.5.

[0519] In some embodiments, the composition has an osmolality ranging from 250 mOsm/kg to 350 mOsm/kg. For example, the composition has an osmolality ranging from 250 mOsm/kg to 360 mOsm/kg, 260 mOsm/kg to 340 mOsm/kg, 270 mOsm/kg to 330 mOsm/kg, 280 mOsm/kg to 320 mOsm/kg, 290 mOsm/kg to 310 mOsm/kg, or

about 300 mOsm/kg. In some embodiments, the composition has an osmolarity of about 250 mOsm/kg, about 260 mOsm/kg, about 270 mOsm/kg, about 280 mOsm/kg, about 290 mOsm/kg, about 300 mOsm/kg, about 310 mOsm/kg, about 320 mOsm/kg, about 330 mOsm/kg, about 340 mOsm/kg, about 350 mOsm/kg, or about 360 mOsm/kg. In some embodiments, the composition has an osmolality ranging from about 275 mOsm/kg to about 330 mOsm/kg. In some embodiments, the composition has an osmolality of about 279 mOsm/kg, about 314 mOsm/kg, or about 329 mOsm/kg.

[0520] In some embodiments, the composition has a viscosity ranging from 0.5 cP to 5 cP. For example, the composition has a viscosity ranging from 0.5 cP to 5 cP, 0.75 cP to 4.5 cP, 1.0 cP to 4 cP, 1.2 cP to 3.5 cP, 1.3 cP to 3 cP, 1.4 cP to 2.5 cP, 1.5 cP to 2 cP, or 1.6 cP to 1.8 cP. In some embodiments, the composition has a viscosity of about 0.5 cP, 0.6 cP, 0.7 cP, 0.8 cP, 0.9 cP, 1.0 cP, 1.1 cP, 1.2 cP, 1.3 cP, 1.4 cP, 1.5 cP, 1.6 cP, 1.7 cP, 1.8 cP, 1.9 cP, or 2.0 cP. In some embodiments, the composition has a viscosity of about 1.4 cP or 1.6 cP.

[0521] In some embodiments, the composition comprises one or more antioxidants. For example, the composition may comprise ascorbic acid, cysteine, sodium metabisulfite, propyl gallate, butylated hydroxytoluene, and/or butylated hydroxyanisole.

[0522] In some embodiments, the composition comprises a surfactant, such as a sorbitan ester.

[0523] In some embodiments, the composition comprises a flavoring or scent, such as an aromatic oil.

[0524] The active ingredient(s) (e.g., the non-naturally occurring melanocortin analog) may be dissolved or suspended in the aforementioned carrier and/or excipient. Additional aqueous or non-aqueous carriers that may facilitate dissolution of the active ingredient include, but are not limited to, ethanol, benzyl alcohol, DMSO, polyethylene glycol, propylene glycol, corn oil, cottonseed oil, peanut oil, sesame oil, and/or various buffers.

[0525] In some embodiments, the non-naturally occurring melanocortin analog is solubilized or suspended in a solvent or vehicle. In some aspects, the solvent or vehicle is purified water, ethyl alcohol, propylene glycol. The composition may comprise

between 0.03% wt and 1% wt melanocortin solubilized or suspended in a solvent or vehicle. The composition may comprise about 0.03% wt, 0.05% wt, 0.1% wt, 0.15% wt, 0.2% wt, 0.25% wt, 0.3% wt, 0.35% wt, 0.4% wt, 0.45% wt, 0.5% wt, 0.55% wt, 0.6% wt, 0.65% wt 0.7% wt, 0.75% wt, 0.8% wt, 0.85% wt, 0.9% wt, 0.95% wt, or 1% wt melanocortin.

[0526] In some embodiments, the composition formulated for intranasal administration comprises a non-naturally occurring melanocortin analog at a concentration at about 0.001 nmol, 0.005 nmol, 0.01 nmol, 0.02 nmol, 0.05 nmol, 0.1 nmol, 0.25 nmol, 0.5 nmol, 1 nmol, 2.5 nmol, 5 nmol, 10 nmol, 20 nmol, 25 nmol, 50 nmol, 100 nmol, 250 nmol, 500 nmol, or 1000 nmol, or even more, depending on the specific peptide selected, the desired therapeutic response, the route of administration, the formulation and other factors known to those of skill in the art.

[0527] The composition may be formulated to be delivered by nose drop, spray device, or topical solution. In some embodiments, the pharmaceutical composition may be formulated as an aerosol, atomizer, inhalation, insufflation, metered-dose inhaler, nebulizer, or hydrobromide. In some embodiments, the composition includes a propellant, such as hydrofluoroalkane.

[0528] In some embodiments, the composition may be configured to be administered using a spray device or nasal inhaler. The spray device or nasal inhaler may be configured to deliver 1ug to 100ug per spray. In some embodiments, the spray device or nasal inhaler may be configured to deliver 1ug to 100ug, 5ug to 90ug, 10ug to 80ug, 15ug to 70ug, 20ug to 60ug, 25ug, to 50ug, or 30ug to 40ug per spray.

Pharmacokinetics and Pharmacodynamics

[0529] The non-naturally occurring melanocortin analogs of the present technology exhibit pharmacokinetic (pK) and/or pharmacodynamic (pD) parameters. Such pK and/or pD may be expressed or otherwise determined relative to a control, which, in some instances, may be a non-naturally occurring melanocortin analog lacking one or more features of the non-naturally occurring melanocortin analogs of the present technology.

[0530] In some embodiments, the pK and/or pD of the non-naturally occurring melanocortin analogs may be assessed using concentration and/or temporal

measurements (e.g., T_{final}, C_{max}, T ½ (h)), AUC, or T_{max}. In some embodiments, the non-naturally occurring melanocortin analogs have reduced clearance and/or metabolism, increased uptake, absorption, and/or stability, relative to a control.

Clearance

[0531] "Clearance" may refer to the elimination, absorption, and/or metabolism of the non-naturally occurring melanocortin analogs in the subject's plasma. Clearance may be assessed as volume of plasma cleared of the non-naturally occurring melanocortin analogs over time (e.g., mL/min, L/hr, or L/day) and/or may be normalized to body weight of the subject (e.g., mL/min/kg). Reduced clearance may also be represented by an increase in half-life or volume of distribution (V_d). In some embodiments, measuring clearance comprises measuring a terminal elimination rate constant (λ_z) or an inter-compartmental clearance (Q).

[0532] In some embodiments, the reduction in clearance comprises a measurement about 10 minutes, 20 minutes, 30 minutes, 40 minutes, 50 minutes, 1 hour, 1.5 hours, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 12 hours, 1 day, 2 days, 3 days, 4 days, 5 day, 6 days, or 1 week after administration of the non-naturally occurring melanocortin analogs.

[0533] In some embodiments, the reduction in clearance comprises a measurement during administration of the non-naturally occurring melanocortin analogs. In some embodiments, the reduction in clearance comprises a measurement at the completion of administration of the non-naturally occurring melanocortin analogs.

Concentration

[0534] In some embodiments, the non-naturally occurring melanocortin analogs of the present technology comprise an increased tissue, plasma, and/or serum concentration relative to a control. "Concentration" may comprise a measurement reflecting one or more of the absolute amounts of the non-naturally occurring melanocortin analogs, the absorption of the non-naturally occurring melanocortin analogs, the metabolism of non-naturally occurring melanocortin analogs, or the elimination of non-naturally occurring melanocortin analogs.

[0535] The increased tissue, plasma, and/or serum concentration may be an increase in concentration of the non-naturally occurring melanocortin analogs at a given

time point relative to a control administered at the same dose and measured at the same time point. The concentration may be measured at an intermediate time point or a final time point and may be measured as a mean residence time (MRT), an average concentration (C_{avg}), a trough concentration (C_{trough}), or a concentration at the end of administration (e.g., infusion) time (C_T).

[0536] In some embodiments, the increased concentration is reflected by an increase in peak plasma concentration (C_{max}). An increase in C_{max} may suggest increased absorption, reduced metabolism, or slower elimination of the non-naturally occurring melanocortin analogs, relative to a control. In some embodiments, C_{max} comprises a dose normalized C_{max} (DNC_{max}).

[0537] In some embodiments, the increased concentration is reflected by an increase in minimum plasma concentration (C_{min}). An increase in C_{min} may suggest increased absorption, reduced metabolism, or slower elimination of the non-naturally occurring melanocortin analogs, relative to a control. In some embodiments, C_{min} comprises a dose normalized C_{min} (DNC_{min}).

[0538] In some embodiments, the increased concentration is reflected by a reduction in time to reach C_{max} (T_{max}). A reduced T_{max} may suggest increased absorption, reduced metabolism, or slower elimination of the non-naturally occurring melanocortin analogs, relative to a control.

[0539] In some embodiments, the increased concentration is reflected by a final measurable concentration (T_{final}). An increased T_{final} may suggest increased absorption, reduced metabolism, or slower elimination of the non-naturally occurring melanocortin analogs, relative to a control.

[0540] In some embodiments, the increased concentration is reflected by an increase in area under the curve (AUC). An increase in AUC may signify increased exposure to the non-naturally occurring melanocortin analogs and/or may suggest increased absorption, reduced metabolism, or slower elimination of the non-naturally occurring melanocortin analogs, relative to a control. The AUC measurement may comprise an Area Under the Curve for Concentration of Drug in Non-Compartmental Analysis (DNAUC).

[0541] In some embodiments, the increase in tissue, plasma, and/or serum concentration comprises a measurement about 10 minutes, 20 minutes, 30 minutes, 40 minutes, 50 minutes, 1 hour, 1.5 hours, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 12 hours, 1 day, 2 days, 3 days, 4 days, 5 day, 6 days, or 1 week after administration of the non-naturally occurring melanocortin analogs.

[0542] In some embodiments, the increase in tissue, plasma, and/or serum concentration comprises a measurement at least 10 minutes, 20 minutes, 30 minutes, 40 minutes, 50 minutes, 1 hour, 1.5 hours, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 12 hours, 1 day, 2 days, 3 days, 4 days, 5 day, 6 days, or 1 week after administration of the non-naturally occurring melanocortin analogs.

[0543] In some embodiments, the increase in tissue, plasma, and/or serum concentration comprises a measurement at least about 10 minutes, 20 minutes, 30 minutes, 40 minutes, 50 minutes, 1 hour, 1.5 hours, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 12 hours, 1 day, 2 days, 3 days, 4 days, 5 day, 6 days, or 1 week after administration of the non-naturally occurring melanocortin analogs.

[0544] In some embodiments, the increase in tissue, plasma, and/or serum concentration comprises a measurement during administration of the non-naturally occurring melanocortin analogs.

[0545] In some embodiments, the increase in tissue, plasma, and/or serum concentration comprises a measurement at the completion of administration of the non-naturally occurring melanocortin analogs.

Distribution

[0546] In some embodiments, the non-naturally occurring melanocortin analogs of the present technology comprise an increased distribution relative to a control. The increased distribution may be an increase in distribution of the non-naturally occurring melanocortin analogs at a given time point relative to a control administered at the same dose and measured at the same time point. The distribution may be measured at an intermediate time point or a final time point.

[0547] In some embodiments, the measurement of distribution comprises measuring a volume of distribution at the terminal phase (V_d or $V_{dß}$), a central volume of distribution (V), a peripheral volume of distribution (V2), an apparent volume of

distribution (V_z), or a measurement of distribution comprises measuring a volume of distribution at steady state (V_{ss}). A high or increased V_d, $V_{dß}$, V_z, and/or V_{ss} may suggest large distribution beyond the tissue, plasma, and/or serum compartment, relative to the control.

[0548] In some embodiments, the increase in distribution comprises a measurement about 10 minutes, 20 minutes, 30 minutes, 40 minutes, 50 minutes, 1 hour, 1.5 hours, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 12 hours, 1 day, 2 days, 3 days, 4 days, 5 day, 6 days, or 1 week after administration of the non-naturally occurring melanocortin analogs.

[0549] In some embodiments, the increase in distribution comprises a measurement at least 10 minutes, 20 minutes, 30 minutes, 40 minutes, 50 minutes, 1 hour, 1.5 hours, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 12 hours, 1 day, 2 days, 3 days, 4 days, 5 day, 6 days, or 1 week after administration of the non-naturally occurring melanocortin analogs.

[0550] In some embodiments, the increase in distribution comprises a measurement at least about 10 minutes, 20 minutes, 30 minutes, 40 minutes, 50 minutes, 1 hour, 1.5 hours, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 12 hours, 1 day, 2 days, 3 days, 4 days, 5 day, 6 days, or 1 week after administration of the non-naturally occurring melanocortin analogs.

[0551] In some embodiments, the increase in distribution comprises a measurement during administration of the non-naturally occurring melanocortin analogs.

[0552] In some embodiments, the increase in distribution comprises a measurement at the completion of administration of the non-naturally occurring melanocortin analogs.

Additional pD and pK Embodiments

[0553] In some embodiments, the non-naturally occurring melanocortin analog of the present technology exhibits one or more of the following:

(a) an increase in half-life relative to a control;

(b) a reduction in clearance relative to a control;

(c) an increase in tissue concentration relative to a control;

(d) an increase in plasma concentration relative to a control;

(e) an increase in serum concentration relative to a control;

(f) an increase in distribution relative to a control;

(g) an increase in an AUC measurement relative to a control;

(h) an increase in a DNAUC measurement relative to a control;

(i) an increase in T_{final} relative to a control;

(j) an increase in C_{max} relative to a control;

(k) an increase in C_{min} relative to a control;

(l) an increase in DNC_{min} relative to a control;

(m) an increase in MRT relative to a control;

(n) an increase in C_{avg} relative to a control;

(o) an increase in C_{trough} relative to a control;

(p) an increase in C_T relative to a control;

(q) an increase in V_d relative to a control;

(r) a reduction in T_{max} relative to a control; or

(s) a reduction in Q relative to a control.

[0554] In some embodiments, the non-naturally occurring melanocortin analog of the present technology exhibits one or more of the following, relative to a control:

(a) an increase in half-life by at least about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 150%, 200%, 250%, 300%, 350%, 400%, 450%, 500%, 600%, 700%, 800%, 900%, or 1000% relative to a control;

(b) a reduction in clearance by at least about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% relative to a control;

(c) an increase in tissue concentration by at least about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 150%, 200%, 250%, 300%, 350%, 400%, 450%, 500%, 600%, 700%, 800%, 900%, or 1000% relative to a control;

(d) an increase in plasma concentration by at least about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 150%, 200%, 250%, 300%, 350%, 400%, 450%, 500%, 600%, 700%, 800%, 900%, or 1000% relative to a control;

(e) an increase in serum concentration by at least about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 150%, 200%, 250%, 300%, 350%, 400%, 450%, 500%, 600%, 700%, 800%, 900%, or 1000% relative to a control;

(f) an increase in distribution by at least about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 150%, 200%, 250%, 300%, 350%, 400%, 450%, 500%, 600%, 700%, 800%, 900%, or 1000% relative to a control;

(g) an increase in an AUC by at least about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 150%, 200%, 250%, 300%, 350%, 400%, 450%, 500%, 600%, 700%, 800%, 900%, or 1000% measurement relative to a control;

(h) an increase in a DNAUC measurement by at least about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 150%, 200%, 250%, 300%, 350%, 400%, 450%, 500%, 600%, 700%, 800%, 900%, or 1000% relative to a control;

(i) an increase in T_{final} by at least about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 150%, 200%, 250%, 300%, 350%, 400%, 450%, 500%, 600%, 700%, 800%, 900%, or 1000% relative to a control;

(j) an increase in C_{max} by at least about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 150%, 200%, 250%, 300%, 350%, 400%, 450%, 500%, 600%, 700%, 800%, 900%, or 1000% relative to a control;

(k) an increase in C_{min} by at least about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 150%, 200%, 250%, 300%, 350%, 400%, 450%, 500%, 600%, 700%, 800%, 900%, or 1000% relative to a control;

(l) an increase in DNC_{min} by at least about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 150%, 200%, 250%, 300%, 350%, 400%, 450%, 500%, 600%, 700%, 800%, 900%, or 1000% relative to a control;

(m) an increase in MRT by at least about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 150%, 200%, 250%, 300%, 350%, 400%, 450%, 500%, 600%, 700%, 800%, 900%, or 1000% relative to a control;

(n) an increase in C_{avg} by at least about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 150%, 200%, 250%, 300%, 350%, 400%, 450%, 500%, 600%, 700%, 800%, 900%, or 1000% relative to a control;

(o) an increase in C_{trough} by at least about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 150%, 200%, 250%, 300%, 350%, 400%, 450%, 500%, 600%, 700%, 800%, 900%, or 1000% relative to a control;

(p) an increase in C_T by at least about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 150%, 200%, 250%, 300%, 350%, 400%, 450%, 500%, 600%, 700%, 800%, 900%, or 1000% relative to a control;

(q) an increase in V_d by at least about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 150%, 200%, 250%, 300%, 350%, 400%, 450%, 500%, 600%, 700%, 800%, 900%, or 1000% relative to a control;

(r) a reduction in T_{max} by at least about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% relative to a control; or

(s) a reduction in Q by at least about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% relative to a control.

Therapeutic Methods

[0555] The present technology provides methods of treating, preventing, or reducing one or more conditions and/or side effects induced by anti-cancer agents (e.g., chemotherapeutic agents) as well as symptoms or conditions associated with cancer via administration of a non-naturally occurring melanocortin analog to a subject in need thereof. The methods may promote appetite and food consumption, and increase or maintain body weight, muscle mass, and/or fat mass of the subject. The methods are also effective in treating anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, loss of appetite, nausea, emesis, and symptoms associated with hypermetabolic immunoinflammatory syndrome. In some embodiments, the methods are effective in improving quality of life and/or increasing life expectancy. The methods of the present technology include administration of a non-naturally occurring melanocortin analog to a subject in need thereof prior to onset, during, and/or after onset of such conditions and/or side effects. These methods also include administration of a non-naturally occurring melanocortin analog to a subject in need thereof prior to,

during, and/or after administration of an anti-cancer agent to the subject who may have cancer or may have another condition which is not cancer, but administration of the anti-cancer agent provides therapeutic benefit to the non-cancer condition.

[0556] The subject applicable to the methods of the present technology may be any subject who experiences involuntary loss of appetite, reduced appetite, decreased food consumption, and/or weight loss. For example, the subject may be a cancer patient, including those that have received, are receiving, or will receive anti-cancer treatment (e.g., chemotherapy) and a subject having another condition which is not cancer but administration of the anti-cancer agent provides therapeutic benefit to the non-cancer condition.

[0557] In some aspects, the present technology comprises a method of treating, preventing, or reducing one or more side effects associated with an anti-cancer agent in a subject, comprising administering a non-naturally occurring melanocortin analog to the subject prior to, during, and/or after administration of the anti-cancer agent, wherein the one or more side effects associated with the anti-cancer agent are selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite. In some embodiments, the method maintains or increases lean body mass, fat body mass, and/or weight of the subject. In some embodiments, the subject has a cancer. In some embodiments, administration of the non-naturally occurring melanocortin analog treats, prevents or reduces the one or more side effects associated with an anti-cancer agent in a subject.

[0558] In some aspects, the present technology comprises a method of maintaining or increasing weight in a subject prior to, during, and/or after administration of an anti-cancer agent, comprising administering a non-naturally occurring melanocortin analog to the subject, wherein the weight of the subject is maintained or increased by preventing or reducing anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and/or loss of appetite in the subject. In some embodiments, the subject has a cancer. In some embodiments, administration of the non-naturally occurring melanocortin analog maintains or increases weight in the subject by preventing or reducing anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and/or loss of appetite in the subject.

[0559] In some aspects, the present technology comprises a method of maintaining or increasing weight in a subject prior to, during, and/or after administration of an anti-cancer agent, comprising administering a non-naturally occurring melanocortin analog to the subject, wherein the weight of the subject is maintained or increased by preventing or reducing one or more side effects associated with the anti-cancer agent selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite. In some embodiments, the subject has a cancer. In some embodiments, administration of the non-naturally occurring melanocortin analog maintains or increases weight in the subject by preventing or reducing one or more side effects associated with the anti-cancer agent selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

[0560] In some aspects, the present technology comprises a method of stimulating appetite or reducing loss of appetite induced by an anti-cancer agent in a subject, comprising administering a non-naturally occurring melanocortin analog to the subject prior to, during, and/or after administration of the anti-cancer agent. In some embodiments, the method maintains or increases lean body mass, fat body mass, and/or body weight of the subject. In some embodiments, the subject has a cancer. In some embodiments, administration of the non-naturally occurring melanocortin analog stimulates appetite or reduces loss of appetite induced by an anti-cancer agent in the subject.

[0561] In some aspects, the present technology comprises a method of preventing, reducing, or restoring weight loss induced by an anti-cancer agent in a subject, comprising administering a non-naturally occurring melanocortin analog to the subject prior to, during, and/or after administration of the anti-cancer agent. In some embodiments, the subject has a cancer. In some embodiments, administration of the non-naturally occurring melanocortin analog prevents, reduces, or restores weight loss induced by an anti-cancer agent in the subject.

[0562] In some aspects, the present technology comprises a method of increasing, maintaining, reducing rate of loss, or otherwise ameliorating loss of body mass index (BMI) in a subject prior to, during, and/or after administration of an anti-cancer agent, comprising administering a non-naturally occurring melanocortin analog to the subject,

wherein the BMI of the subject is maintained or increased by preventing or reducing one or more side effects associated with the anti-cancer agent selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite. In some embodiments, the subject has a cancer. In some embodiments, administration of the non-naturally occurring melanocortin analog maintains or increases BMI in the subject by preventing or reducing one or more side effects associated with the anti-cancer agent selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

[0563] In some aspects, the present technology comprises a method of increasing, maintaining, reducing rate of loss, or otherwise ameliorating loss of BMI durability in a subject prior to, during, and/or after administration of an anti-cancer agent, comprising administering a non-naturally occurring melanocortin analog to the subject, wherein the BMI durability of the subject is maintained or increased by preventing or reducing one or more side effects associated with the anti-cancer agent selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite. In some embodiments, the subject has a cancer. In some embodiments, administration of the non-naturally occurring melanocortin analog maintains or increases BMI durability in the subject by preventing or reducing one or more side effects associated with the anti-cancer agent selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

[0564] In some aspects, the present technology comprises a method of preventing, reducing rate of loss, or otherwise ameliorating BMI reduction induced by an anti-cancer agent in a subject, comprising administering a non-naturally occurring melanocortin analog to the subject prior to, during, and/or after administration of the anti-cancer agent. In some embodiments, the subject has a cancer. In some embodiments, administration of the non-naturally occurring melanocortin analog prevents, reduces, or restores BMI reduction induced by an anti-cancer agent in the subject.

[0565] In some aspects, the present technology comprises a method of treating, preventing, reducing, or otherwise ameliorating one or more side effects associated with

an anti-cancer agent in a subject who failed to respond to an antiemetic treatment, comprising administering a non-naturally occurring melanocortin analog to the subject prior to, during, and/or after administration of the anti-cancer agent, wherein the one or more side effects associated with the anti-cancer agent are selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite. In some embodiments, the failure to respond to an antiemetic treatment further comprises clinically and/or therapeutically insufficient weight gain, muscle mass gain, fat mass gain, increased appetite, and/or increased food intake. In some embodiments, the subject has a cancer. In some embodiments, administration of the non-naturally occurring melanocortin analog treats, prevents, or reduces the one or more side effects associated with an anti-cancer agent in the subject who failed to respond to an antiemetic treatment.

[0566] In some aspects, the present technology comprises a method of treating, preventing, reducing, or otherwise ameliorating one or more side effects associated with an anti-cancer agent in a subject who failed to respond to nutritional intervention, comprising administering a non-naturally occurring melanocortin analog to the subject prior to, during, and/or after administration of the anti-cancer agent, wherein the one or more side effects associated with the anti-cancer agent are selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite. wherein the nutritional intervention further comprises nutritional supplementation. In some embodiments, the subject has a cancer. In some embodiments, administration of the non-naturally occurring melanocortin analog treats, prevents, or reduces the one or more side effects associated with an anti-cancer agent in the subject who failed to respond to nutritional intervention.

[0567] In some aspects, the present technology comprises a method of preventing, reducing, or otherwise ameliorating an anti-cancer agent induced side effect in a subject having cancer, comprising administering the anti-cancer agent and a non-naturally occurring melanocortin analog to the subject. In some embodiments, the side effect is selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite. In some embodiments, administration of the non-naturally occurring melanocortin analog prevents or reduces the anti-cancer agent induced side effect in the subject having cancer.

[0568] In some aspects, the present technology comprises a method of treating, preventing, reducing, or otherwise ameliorating iatrogenic injury caused by an anti-cancer agent in a subject having cancer, comprising administering the anti-cancer agent and a non-naturally occurring melanocortin analog to the subject. In some embodiments, the iatrogenic injury is selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite. In some embodiments, administration of the non-naturally occurring melanocortin analog treats, prevents, or reduces the iatrogenic injury caused by an anti-cancer agent in the subject having cancer.

[0569] In some aspects, the present technology comprises a method of reducing time to cancer treatment failure in a subject having cancer, comprising administering the anti-cancer agent and a non-naturally occurring melanocortin analog to the subject. In some embodiments, the time to cancer treatment failure is the interval from initiation of administration of the anti-cancer agent to its premature discontinuation. In some embodiments, the premature discontinuation is a discontinuation in anti-cancer administration due to cancer progression, adverse events associated with administration of the anti-cancer agent, or death of the subject. In some embodiments, the premature discontinuation is a change in a primary anti-cancer agent treatment.

[0570] In some aspects, the present technology comprises a method increasing, maintaining, reducing rate of loss, or otherwise ameliorating loss of Eastern Cooperative Oncology Group (ECOG) score, a Functional Assessment of Anorexia/Cachexia Therapy (FAACT) score, overall survival (OS), progression-free survival (PFS), and/or Karnofsky performance status (KPS) score of a subject having cancer, comprising administering an anti-cancer agent and a non-naturally occurring melanocortin analog to the subject. In some embodiments, the ECOG score, FAACT score, OS, PFS, and/or KPS is improved, maintained, and/or reduction of is prevented or otherwise ameliorated by inhibiting or reducing anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and/or loss of appetite in the subject. In some embodiments, administration of the non-naturally occurring melanocortin analog prevents reduction of, maintains, or improves ECOG score, FAACT score, OS, PFS, and/or KPS score of the subject having cancer.

[0571] In some embodiments, the subject is a mammal, including but not limited to a human, a non-human primate such as a chimpanzee, a domestic livestock or a farm animal such as a cow, a bison, sheep, a pig, a goat, a horse, a chicken, and a rooster, a domestic pet animal such as a dog, a cat, a rat, a mouse, and a rabbit, and a laboratory subject such as a rodent, including a rat, a mouse, and a guinea pig. In some embodiments, the subject is a human. In some embodiments, the subject is an animal such as a rat or a dog.

[0572] In some embodiments, the subject has a body mass index (BMI) of 18.5 kg/m^2 to 25 kg/m^2. In some embodiments, the subject has a BMI of less than 20 kg/m^2. In some embodiments, the subject has a BMI of less than 18.5 kg/m^2.

[0573] In some embodiments, the subject is an underweight subject. Underweight subjects include those having a body weight about 3%, 5% or less, 10% or less, 20% or less, or 30% or less, than the lower end of "normal" BMI (e.g., 18.5 kg/m^2). In some embodiments, the subject has a BMI of less than about 18.5 kg/m^2, less than about 17.0 kg/m^2, less than about 16.0 kg/m^2, less than about 15.0 kg/m^2, less than about 14.0 kg/m^2, less than about 13.0 kg/m^2, less than about 12.0 kg/m^2, less than about 11.0 kg/m^2, or less than about 10.0 kg/m^2.

[0574] In some embodiments, the subject is a patient who has experienced an involuntary weight loss prior to commencement of the administration. For example, the subject is a patient who has experienced a weight loss of 1% per month, 2% per month, 5% per month, or 10% per month for at least 2 months, at least 3 months, at least 6 months, at least 9 months, or at least 12 months, prior to commencement of the administration.

[0575] In some embodiments, the subject has a cancer. In other embodiments, the subject has another condition which is not cancer but administration of the anti-cancer agent provides therapeutic benefit to the non-cancer condition.

[0576] In any of the foregoing aspects, the subject experiences loss of appetite, reduced appetite, decreased food consumption, and/or weight loss prior to the administration of the non-naturally occurring melanocortin analog. In some embodiments, the loss of appetite, reduced appetite, decreased food consumption, and/or weight loss is caused by the cancer. In some embodiments, the loss of appetite, reduced appetite, decreased food consumption, and/or weight loss is caused by cancer

cachexia. In some embodiments, the loss of appetite, reduced appetite, decreased food consumption, and/or weight loss is caused by the anti-cancer agent.

[0577] In any of the foregoing aspects, the anti-cancer agent may comprise a chemotherapy. In some embodiments, the method reduces chemotherapy induced mass loss and/or wasting in the subject and increases lean body mass and body weight of the subject. In some embodiments, the method maintains or increases weight of the subject prior to, during, or after administration of the chemotherapy, and wherein the method reduces mass loss and/or wasting in the subject.

[0578] The methods described herein using anti-cancer agents (e.g., chemotherapy) may inhibit, remove, eradicate, reduce, regress, diminish, arrest or stabilize a cancerous tumor, including at least one of the tumor growth, tumor cell viability, tumor cell division and proliferation, tumor metabolism, blood flow to the tumor and metastasis of the tumor. In some embodiments, the size of a tumor, whether by volume, weight or diameter, is reduced after the treatment by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100%, relative to the tumor size before treatment. In some embodiments, the size of a tumor after treatment does not reduce but is maintained the same as the tumor size before treatment. Methods of assessing tumor size and/or presence include, but are not limited to, CT scan, MRI, DCE-MRI, PET scan, and assessing circulating tumor DNA (ctDNA) levels.

[0579] In some embodiments, the subject with a cancer has previously undergone a treatment with the anti-cancer agent. In related embodiments, the subject has previously experienced one or more adverse side effects when treated with the anti-cancer agent. In some embodiments, such adverse side effects are selected from the group consisting of nausea, emesis, anorexia, weight loss, fatigue, fat mass loss, and muscle mass loss.

[0580] The subject may be any subject already with the disease or condition (e.g., cancer). In some embodiments, the subject may be a subject which does not yet experience or exhibit symptoms of the disease or condition, or a subject predisposed to the disease or condition. In some embodiments, the subject is a person who is predisposed to cancer, e.g., a person with a family history of cancer.

[0581] In some embodiments, the method of the present technology in any of its aspects (i) stimulates appetite of the subject; (ii) increases food consumption of the subject; (iii) prevents or alleviates nausea, emesis, and/or anorexia in the subject; (iv) increases or maintains body weight of the subject; (v) prevents or reduces weight loss of the subject; (vi) increases or maintains muscle mass of the subject; (vii) prevents or reduces muscle mass loss of the subject; (viii) increases or maintains fat mass of the subject; and/or (ix) prevents or reduces fat mass loss of the subject.

[0582] In any of the foregoing aspects, the anorexia may be associated with weight loss.

[0583] In any of the foregoing aspects, the subject's mass and/or weight is not more than 5% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent.

[0584] In any of the foregoing aspects, the subject's mass and/or weight is not more than 10% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent.

[0585] In any of the foregoing aspects, the muscle mass loss may be cardiac muscle mass loss, skeletal muscle mass loss, or both. In some embodiments, the cardiac muscle mass loss is determined by measuring change in heart weight. In some embodiments, the cardiac muscle mass loss is determined by cardiac echocardiography. In some embodiments, the skeletal muscle mass loss is determined by measuring change in gastrocnemius tissue weight. In some embodiments, the skeletal muscle mass loss is determined by computed tomography scan. In some embodiments, the skeletal muscle mass loss is determined by dual-energy X-ray absorptiometry.

[0586] In some embodiments, muscle mass of the subject is increased by at least 1% to 100% after the administration of the non-naturally occurring melanocortin analog or the pharmaceutical composition thereof. For example, muscle mass of the subject is increased by at least 1% to 100%, at least 5% to 75%, at least 10% to 50%, or at least 20% to 35%, after the administration.

[0587] In some embodiments, muscle mass of the subject is increased by at least 5% to 15% after the administration. For example, muscle mass of the subject is

increased by at least 5% to 15%, at least 6% to 14%, at least 7% to 12%, or at least 8% to 9%, after the administration.

[0588] In some embodiments, muscle mass of the subject is increased by at least 25% to 50% after the administration. For example, muscle mass of the subject is increased by at least 25% to 50%, at least 28% to 48%, at least 25% to 45%, or at least 30% to 40%, after the administration.

[0589] In some embodiments, the increased muscle mass is maintained for at least 1 week, 2 weeks, 3 weeks, 1 month, 3 months, 6 months, 1 year, or 5 years, after the administration is stopped.

[0590] In some embodiments, the method prevents, reduces, or otherwise ameliorates muscle mass loss (e.g., involuntary muscle mass loss) in the subject.

[0591] In some embodiments, the muscle mass is cardiac muscle mass, skeletal muscle mass, or both. In some embodiments, the cardiac muscle mass is determined by measuring change in heart weight. In some embodiments, the skeletal muscle mass is determined by measuring change in gastrocnemius tissue weight. In related embodiments, the muscle mass change is cardiac muscle mass change, skeletal muscle mass change, or both. In some embodiments, cardiac muscle is determined by heart weight. In some embodiments, skeletal muscle mass is determined by gastrocnemius tissue weight. In some embodiments, the muscle mass changes may be assessed by using magnetic resonance imaging (MRI) and/or nuclear magnetic resonance (NMR).

[0592] In any of the foregoing aspects, anorexia may be determined by daily food intake, daily food consumption, and/or weekly food intake. In some embodiments, the daily food intake is determined by total calories (kcal) consumed in 1 day or mass of food (grams or kilograms) consumed in 1 day. In some embodiments, the daily food consumption is determined by the daily food intake normalized to daily body weight of the subject. In some embodiments, the weekly food intake is determined total calories (kcal) consumed in 1 day or mass of food (grams or kilograms) consumed in 1 week.

[0593] In any of the foregoing aspects, the weight loss may be determined by daily body weight, and/or daily body weight gain.

[0594] In any of the foregoing aspects, the fat mass of the subject treated with the method may be at least 10% to 100% greater than a baseline or control, wherein the baseline or control is the subject prior to the administration of the non-naturally occurring melanocortin analog and/or a subject who is receiving or has received the anti-cancer agent without the non-naturally occurring melanocortin analog.

[0595] In some embodiments, fat mass of the subject is increased by at least 1% to 100% after the administration (e.g., administration of the therapeutically effective amount of the non-naturally occurring melanocortin analog or the pharmaceutical composition thereof). For example, fat mass of the subject is increased by at least 1% to 100%, at least 5% to 75%, at least 10% to 50%, or at least 20% to 35%, after the administration.

[0596] In some embodiments, fat mass of the subject is increased by at least 5% to 15% after the administration. For example, fat mass of the subject is increased by at least 5% to 15%, at least 6% to 14%, at least 7% to 12%, or at least 8% to 9%, after the administration.

[0597] In some embodiments, fat mass of the subject is increased by at least 25% to 50% after the administration. For example, fat mass of the subject is increased by at least 25% to 50%, at least 28% to 48%, at least 25% to 45%, or at least 30% to 40%, after the administration.

[0598] In some embodiments, the increased fat mass is maintained for at least 1 week, 2 weeks, 3 weeks, 1 month, 3 months, 6 months, 1 year, or 5 years, after the administration is stopped.

[0599] In some embodiments, the method prevents or reduces fat mass loss (e.g., involuntary fat mass loss) in the subject.

[0600] In some embodiments, the fat mass may be determined by the fat fold technique. In some embodiments, the fat mass changes may be assessed by using magnetic resonance imaging (MRI) and/or nuclear magnetic resonance (NMR).

[0601] In any of the foregoing aspects, the heart weight of the subject treated with the method may be at least 0.1% to 10% greater than a baseline or control, wherein the baseline or control is the subject prior to the administration of the non-naturally occurring

melanocortin analog and/or a subject who is receiving or has received the anti-cancer agent without the non-naturally occurring melanocortin analog.

[0602] In any of the foregoing aspects, the daily food intake of the subject treated with the method may be at least 5% to 50% greater than a baseline or control, wherein the baseline or control is the subject prior to the administration of the non-naturally occurring melanocortin analog and/or a subject who is receiving or has received the anti-cancer agent without the non-naturally occurring melanocortin analog.

[0603] In any of the foregoing aspects, the daily body weight of the subject treated with the method may be at least 1% to 15% greater than a baseline or control, wherein the baseline or control is the subject prior to the administration of the non-naturally occurring melanocortin analog and/or a subject who is receiving or has received the anti-cancer agent without the non-naturally occurring melanocortin analog.

[0604] In some embodiments, body weight of the subject is increased by at least 5% to 200% after the administration of the non-naturally occurring melanocortin analog or the pharmaceutical composition thereof. For example, body weight of the subject is increased by at least 5% to 200%, at least 10% to 150%, at least 25% to 100%, or at least 50% to 75%, after the administration.

[0605] In some embodiments, body weight of the subject is increased by at least 5% to 25% after the administration. For example, body weight of the subject is increased by at least 5% to 25%, at least 10% to 20%, or at least 12% to 15%, after the administration.

[0606] In some embodiments, body weight of the subject is increased by at least 20% to 100% after the administration. For example, body weight of the subject is increased by at least 20% to 100%, at least 35% to 90%, at least 50% to 80%, or at least 60% to 70%, after the administration.

[0607] In some embodiments, the increased body weight is maintained for at least 1 week, 2 weeks, 3 weeks, 1 month, 3 months, 6 months, 1 year, or 5 years, after the administration is stopped.

[0608] In some embodiments, the method prevents or reduces weight loss (e.g., involuntary weight loss) in the subject.

[0609] In some embodiments, the body weight (or weight loss) is determined by monitoring daily body weight. In some embodiments, the body weight (or weight loss) is determined by monitoring daily body weight gain (or loss). In some embodiments, the body weight (or weight loss) is determined by monitoring cumulative body weight for at least 1 week, 2 weeks, 3 weeks, 4 weeks, 3 months, 6 months, 1 year, or 5 years.

[0610] In any of the foregoing aspects, appetite of the subject is increased by at least 10% to 200% after the administration of the non-naturally occurring melanocortin analog or a pharmaceutical composition thereof. For example, appetite of the subject is increased by at least 10% to 200%, at least 20% to 175%, at least 30 to 150%, at least 40% to 125%, at least 50% to 100%, or at least 60% to 75%, after the administration.

[0611] In some embodiments, appetite of the subject is increased by at least 25% to 100% after the administration of the non-naturally occurring melanocortin analog or a pharmaceutical composition thereof. For example, appetite of the subject is increased by at least 25% to 100%, at least 30% to 90%, at least 35 to 80%, at least 40% to 70%, at least 45% to 60%, or at least 50% to 55%, after the administration.

[0612] In some embodiments, appetite is increased for at least 1 day, 1 week, 1 month, 3 months, 6 months, 1 year, 2 years, 3 years, 4 years, or 5 years during the administration.

[0613] In some embodiments, appetite is increased for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 14 days, 21 days, 28 days, 35 days, 40 days, 45 days, 50 days, 60 days, 75 days, 90 days, 100 days, 110 days, or 120 days during the administration.

[0614] In some embodiments, the increased appetite is maintained for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks, 3 weeks, 1 month, 3 months, 6 months, 1 year, or 5 years, after the administration is stopped.

[0615] In some embodiments, the appetite is assessed by a scale for measuring desire to eat, feeling of hunger, and/or level of satiety. For example, the appetite may be assessed through a daily questionnaire given at specified or random times of the day. In the questionnaire, subjects rate their hunger and/or desire to eat greater varieties of food using scales ranging from 0 (not at all) to 100 (extremely). In some

embodiments, the appetite is assessed by the subject's rating of feeling of hunger using a scale ranging from 0 (not at all) to 100 (extremely). In some embodiments, the appetite is assessed by the subject's scaling of satiety (e.g., easy or hard to eat) from 0 (extremely easy to eat) to 100 (extremely hard to eat).

[0616] In some embodiments, the appetite is assessed between meals. In some embodiments, the appetite is assessed during a meal.

[0617] In some embodiments, the appetite is assessed after a meal, for example, 1 minute after a meal, 5 minutes, 10 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hour, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, or 24 hours after a meal.

[0618] In some embodiments, the subject comprises two or more subjects, and the appetite is an average appetite (e.g., average rating of feeling of hunger, average scaling of satiety) of the two or more subjects. In some embodiments, the subject comprises at least 3 subjects, and the appetite is an average appetite of the at least 3 subjects. In some embodiments, the subject comprises at least 4 subjects, and the appetite is an average appetite of the at least 4 subjects. In some embodiments, the subject comprises at least 5 subjects, and the appetite is an average appetite of the at least 5 subjects. In some embodiments, the subject comprises at least 6 subjects, and the appetite is an average appetite of the at least 6 subjects. In some embodiments, the subject comprises at least 7 subjects, and the appetite is an average appetite of the at least 7 subjects. In some embodiments, the subject comprises at least 8 subjects, and the appetite is an average appetite of the at least 8 subjects. In some embodiments, the subject comprises at least 9 subjects, and the appetite is an average appetite of the at least 9 subjects. In some embodiments, the subject comprises at least 10 subjects, and the appetite is an average appetite of the at least 10 subjects. The subject may comprise e.g., at least 10, 15, 20, 30, 40, 50, 75, 100, 200, 300, 400, 500, 750, 1,000, 2,500, or 5,000 subjects, and the appetite is an average appetite of the at least 10, 15, 20, 30, 40, 50, 75, 100, 200, 300, 400, 500, 750, 1,000, 2,500, or 5,000 subjects.

[0619] In some embodiments, food consumption of the subject is increased by at least 25% to 2,000% after the administration (e.g., administration of the therapeutically effective amount of the non-naturally occurring melanocortin analog or the pharmaceutical composition thereof). For example, food consumption of the subject

may be increased by at least at least 25% to 2,000%, at least 50% to 1,750%, at least 75% to 1,500%, at least 100% to 1,000%, at least 250% to 750%, or at least 400% to 500%, after the administration.

[0620] In some embodiments, food consumption of the subject is increased by at least 50% to 500% after the administration. For example, food consumption of the subject may be increased by at least at least 50% to 500%, at least 60% to 400%, at least 70% to 300%, at least 80% to 250%, at least 90% to 200%, at least 100% to 175%, or at least 125% to 150%, after the administration.

[0621] In some embodiments, food consumption is increased for at least 1 day, 1 week, 1 month, 3 months, 6 months, 1 year, or 5 years during the administration.

[0622] In some embodiments, food consumption is increased for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 14 days, 21 days, 28 days, 35 days, 40 days, 45 days, 50 days, 60 days, 75 days, 90 days, 100 days, 110 days, or 120 days during the administration.

[0623] In some embodiments, the increased food consumption is maintained for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks, 3 weeks, 1 month, 3 months, 6 months, 1 year, or 5 years, after the administration is stopped.

[0624] In some embodiments, the food consumption is determined by daily food consumption, which is total calories (kcal) consumed in 1 day or mass of food (grams or kilograms) consumed in 1 day. In some embodiments, the food consumption is determined by weekly food consumption, which is total calories (kcal) consumed in 1 week or mass of food (grams or kilograms) consumed in 1 week. In some embodiments, the daily food consumption is determined by the daily food consumed normalized to daily body weight of the subject.

[0625] In some embodiments, the subject comprises two or more subjects, and the food consumption is an average food consumption (e.g., average daily food consumption, average weekly food consumption) of the two or more subjects. In some embodiments, the subject comprises at least 3 subjects, and the food consumption is an average food consumption of the at least 3 subjects. In some embodiments, the subject comprises at least 4 subjects, and the food consumption is an average food consumption of the at least 4 subjects. In some embodiments, the subject comprises

at least 5 subjects, and the food consumption is an average food consumption of the at least 5 subjects. In some embodiments, the subject comprises at least 6 subjects, and the food consumption is an average food consumption of the at least 6 subjects. In some embodiments, the subject comprises at least 7 subjects, and the food consumption is an average food consumption of the at least 7 subjects. In some embodiments, the subject comprises at least 8 subjects, and the food consumption is an average food consumption of the at least 8 subjects. In some embodiments, the subject comprises at least 9 subjects, and the food consumption is an average food consumption of the at least 9 subjects. In some embodiments, the subject comprises at least 10 subjects, and the food consumption is an average food consumption of the at least 10 subjects. The subject may comprise e.g., at least 10, 15, 20, 30, 40, 50, 75, 100, 200, 300, 400, 500, 750, 1,000, 2,500, or 5,000 subjects, and the food consumption is an average food consumption of the at least 10, 15, 20, 30, 40, 50, 75, 100, 200, 300, 400, 500, 750, 1,000, 2,500, or 5,000 subjects.

[0626] In some embodiments, the method prevents, reduces, or otherwise ameliorates anorexia in the subject.

[0627] In any of the foregoing aspects, anorexia is determined by food consumption. In some embodiments, anorexia is determined by daily food consumption, and/or weekly food consumption. In some embodiments, anorexia is determined by cumulative food consumption for at least 2 days, at least 5 days, at least 7 days, at least 14 days, or at least 21 days, after the administration.

[0628] In some embodiments, the method prevents or alleviates nausea, emesis, or both, in the subject.

[0629] In any of the foregoing aspects, the subject has a performance status on the ECOG scale of 1 or higher prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent. In any of the foregoing aspects, the subject has a performance status on the ECOG scale of 2 or higher prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent. In some embodiments, the method lowers the ECOG scale of the subject. In some embodiments, the method lowers the ECOG scale of the subject by at least 10%, 25%, 50%, or 100%.

[0630] In any of the foregoing aspects, the subject's KPS score is not more than 70 prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent. In any of the foregoing aspects, the subject's KPS score is not more than 50 prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent. In some embodiments, the method increases the subject's KPS score. In some embodiments, the method increases the subject's KPS score by at least 10%, 25%, 50%, or 100%.

[0631] In some embodiments, a reduced or maintained ECOG score of the subject may result during or after administration of the non-naturally occurring melanocortin analog. In some embodiments, the ECOG score of the subject is about grade 0, 1, 2, 3 before, during, or after administration of the non-naturally occurring melanocortin analog. In some embodiments, the ECOG score reduces by a score of about 1, 2, or 3 during or after administration of the non-naturally occurring melanocortin analog. In some embodiments, the ECOG score reduces by a score of at least 1, 2, or 3 during or after administration of the non-naturally occurring melanocortin analog. In some embodiments, the ECOG score reduces by a score of at least about 1, 2, or 3 during or after administration of the non-naturally occurring melanocortin analog. In some embodiments, an increased or maintained KPS score of the subject may result during or after administration of the non-naturally occurring melanocortin analog. In some embodiments, the KPS score of the subject is about grade 100, 90, 80, 70, 60, 50, 40, or 30 before, during, or after administration of the non-naturally occurring melanocortin analog. In some embodiments, the KPS score increases by a score of about 10, 20, 30, 40, 50, 60, or 70 during or after administration of the non-naturally occurring melanocortin analog. In some embodiments, the KPS score increases by a score of at least 10, 20, 30, 40, 50, 60, or 70 during or after administration of the non-naturally occurring melanocortin analog. In some embodiments, the KPS score increases by a score of at least about 10, 20, 30, 40, 50, 60, or 70 during or after administration of the non-naturally occurring melanocortin analog.

[0632] In some embodiments, the non-naturally occurring melanocortin analog is administered before the anti-cancer agent. For example, the non-naturally occurring melanocortin analog may be administered to the subject having cancer before the subject is administered an anti-cancer agent. When administered to the subject having cancer prior to administration of an anti-cancer agent, the subject may be pretreated or

preloaded with a non-naturally occurring melanocortin analog for a duration of time, including 1 day, 1 week, 1 month, 3 months, 6 months, 9 months, 12 months, or more than 12 months. By pretreating or preloading the subject with the non-naturally occurring melanocortin analog, the subject experiences mass gain (e.g., fat mass, lean muscle mass, etc.), appetite increase, ECOG score increase, KPS score increase, reduction in risk of iatrogenic injury, or other beneficial outcomes due to the non-naturally occurring melanocortin analog prior to receiving the anti-cancer agent. In these embodiments, the preloaded subject may exhibit decreased and/or delayed side-effects of the anti-cancer agent or no side-effects of the anti-cancer agent compared to a subject not preloaded with the non-naturally occurring melanocortin analog.

[0633] In some embodiments, the non-naturally occurring melanocortin analog may be administered to the subject during an anti-cancer agent therapeutic regimen where the subject has or has not received at least a first dose of the anti-cancer agent prior to administration of the non-naturally occurring melanocortin analog. In embodiments where a non-naturally occurring melanocortin analog is administered during or after administration of the anti-cancer agent therapeutic regimen, the subject may or may not be preloaded with the non-naturally occurring melanocortin analog. In some embodiments, the non-naturally occurring melanocortin analog is co-administered with the anti-cancer agent. In some embodiments, the non-naturally occurring melanocortin analog is administered after the anti-cancer agent. In some embodiments, the non-naturally occurring melanocortin analog is present in a first pharmaceutical composition and the anti-cancer agent is present in a second pharmaceutical composition. In some embodiments, the non-naturally occurring melanocortin analog and the anti-cancer agent are present in a single pharmaceutical composition.

[0634] In some embodiments, the anti-cancer agent is administered to a subject for treating or preventing one of one or more cancers, including, but not limited to, bone cancer, testicular cancer, gastric cancer, sarcoma, lymphoma, Hodgkin's lymphoma, leukemia, head and neck cancer, squamous cell head and neck cancer, thymic cancer, epithelial cancer, salivary cancer, liver cancer, stomach cancer, thyroid cancer, lung cancer (e.g., non-small cell lung cancer, small cell lung cancer, mesothelioma, etc.), ovarian cancer, breast cancer, prostate cancer, esophageal cancer, pancreatic cancer, glioma, leukemia, multiple myeloma, renal cell carcinoma, bladder cancer, cervical

cancer, choriocarcinoma, colon cancer, oral cancer, skin cancer, and melanoma. In some embodiments, the subject has more than one cancer, is at risk for developing more than one cancers, or has symptoms of more than one cancer.

[0635] In some embodiments, the subject has one or more or a cancer, an autoimmune disease, a hematological disorder, an immune system disorder, a need for an organ transplant, a rheumatic disease, a dermatological condition, or a rare disease, including, but not limited to: Wegener's granulomatosis or eosinophilic granulomatosis with polyangiitis. In some embodiments, the chemotherapeutic agent is useful in treating any one of these diseases or conditions.

[0636] In some embodiments, the autoimmune disorder is rheumatoid arthritis, systemic lupus erythematosus, or multiple sclerosis. In some embodiments, the hematological disorder is an abnormal cell proliferation or dysfunction in the blood or bone marrow, immune thrombocytopenia, or autoimmune hemolytic anemia. In some embodiments, the need for an organ transplant includes a subject receiving a transplant or undergoing conditioning for a transplant.

[0637] In some embodiments, the cancer is at risk of metastasis, has metastasized, or is metastasizing. In some embodiments, the cancer is a Stage 0 cancer, a Stage I cancer, a Stage II cancer, a Stage III cancer, or a Stage IV cancer. In some embodiments, the subject has received or is receiving radiation therapy for at least one cancer. In some embodiments, the subject has received or is receiving a surgical intervention related to at least one cancer. In some embodiments, the subject is administered an anti-cancer agent or a non-naturally occurring melanocortin analog before, during, or after radiation therapy. In some embodiments, the subject is administered an anti-cancer agent or a non-naturally occurring melanocortin analog before, during, or after a surgical intervention. In some embodiments, the subject does not receive radiation therapy. In some embodiments, the subject does not receive surgical intervention.

[0638] In some embodiments, the subject has received or is receiving nutritive therapy or a nutrition supplement. In some embodiments, the subject has received or is receiving an antiemetic. In some embodiments, the antiemetic is ondansetron, granisetron, dolasetron, palonosetron, metoclopramide, prochlorperazine, promethazine, droperidol, dimenhydrinate, cyclizine, meclizine, scopolamine,

aprepitant, fosaprepitant, netupitant, olanzapine, dexamethasone, lorazepam, ginger, dronabinol, marijuana, and tetrahydrocannabinol. In some embodiments, the subject has received or is receiving a therapeutic for preventing cancer associated wasting. In some embodiments, the therapeutic for preventing cancer associated wasting is a corticosteroid, testosterone, testosterone cypionate, etanercept, formoterol, formoterol fumarate, dronabinol, Marinol, medroxyprogesterone, medroxyprogesterone acetate, Megace ES, megesterol, megesterol acetate suspension, oxandrolone, prednisone, ghrelin receptor agonists, a selective androgen receptor modulator (SARM), a selective androgen receptor degraders (SARD), anamorelin, omega-3 fatty acids, thalidomide, pentoxifylline, a nonsteroidal anti-inflammatory drug (NSAID), cyproheptadine, progestogens, metformin, branched-chain amino acids, eicosapentaenoic acid (EPA), coenzyme Q10, melatonin, dexamethasone, and creatine. In some embodiments, the subject has failed or is failing to response adequately to nutritive therapy, a nutrition supplement, an antiemetic, or a therapeutic for preventing cancer associated wasting.

[0639] In some embodiments, administration of the anti-cancer agent is associated with one or more side effects. In some embodiments, the administration of the anti-cancer agent and the non-naturally occurring melanocortin analog reduces one or more of these side effects. Nonlimiting examples of the one or more side effects may include nausea, emesis (i.e., vomiting), anorexia (e.g., decreasing food intake, decreasing appetite), cachexia, weight loss, reduced body mass index (BMI), fatigue, fat mass loss, and muscle mass loss. Other side effects include, but are not limited to, cytopenia (e.g., anemia (low red blood cell counts), myelosuppression, infection, mucositis, alopecia (hair loss), easy bruising and bleeding, cutaneous complications, such as pruritis, urticaria, and angioedema, constipation, diarrhea, neurological complications (e.g., chemo brain, mood changes), pulmonary and cardiac complications (e.g., cardiac toxicity) especially in patients receiving chemotherapy and/or radiation, and reproductive and endocrine complications. Cachexia may include, but is not limited to, one or more of the foregoing side effects and one or more of the foregoing side-effects may occur in the absence of cachexia.

[0640] In any of the foregoing aspects, the administration of the non-naturally occurring melanocortin analog enhances tolerability of the anti-cancer agent. In some embodiments, the enhanced tolerability results in a greater dosage, an increased frequency of administration, and/or an increased duration of administration of the anti-

cancer agent, compared to a baseline or control, wherein the baseline or control is the subject prior to the administration of the non-naturally occurring melanocortin analog and/or a subject who is receiving or has received the anti-cancer agent without the non-naturally occurring melanocortin analog. In some embodiments, the anti-cancer agent comprises a chemotherapy comprising at least two chemotherapeutic agents, and wherein the enhanced tolerability results in a second chemotherapeutic agent being administered to the subject during or after administration of a first chemotherapeutic agent.

[0641] In any of the foregoing aspects, the administration of the non-naturally occurring melanocortin analog prevents or reduces a downward titration in dosing regimen of the anti-cancer agent. In some embodiments, the downward titration comprises a decreased dosage, a decreased frequency of administration, and/or a decreased duration of administration, compared to a baseline or control, wherein the baseline or control is the subject prior to the administration of the non-naturally occurring melanocortin analog and/or a subject who is receiving or has received the anti-cancer agent without the non-naturally occurring melanocortin analog.

[0642] In any of the foregoing aspects, the subject may have been administered or is being administered an antiemetic. In other aspects, the subject has not received an antiemetic. In certain aspects, the subject received an antiemetic but failed to respond adequately. In some embodiments, the antiemetic is marijuana, megestrol, somatropin, or dronabinol.

[0643] In some embodiments, the baseline or control is the subject before receiving the non-naturally occurring melanocortin analog. In some embodiments, the baseline or control is a subject receiving an anti-cancer agent without administration of the non-naturally occurring melanocortin analog. In some embodiments, the baseline or control is a subject after receiving an anti-cancer agent without administration of the non-naturally occurring melanocortin analog. In some embodiments, the baseline or control is a second subject that has not received the non-naturally occurring melanocortin analog. In some embodiments, the second subject has received or is receiving an anti-cancer agent.

[0644] In some embodiments, the subject administered the non-naturally occurring melanocortin analog prior to, during administration of, and/or after administration of the anti-cancer agent exhibits one or more of

(a) an increase in body weight compared to baseline or control;

(b) an increase in muscle mass compared to baseline or control;

(c) an increase in fat mass compared to baseline or control;

(d) an increase in cardiac mass compared to baseline or control;

(e) an increase in bone density compared to baseline or control;

(f) an increase in appetite compared to baseline or control;

(g) a reduction in fatigue compared to baseline or control;

(h) a reduction in vomiting compared to baseline or control;

(i) a reduction in diarrhea compared to baseline or control;

(j) an increase in BMI compared to baseline or control;

(k) a reduction in an inflammatory transcript level (mRNA) compared to baseline or control;

(l) a reduction in an inflammatory protein level compared to baseline or control;

(m) an increase in a FAACT score compared to baseline or control;

(n) an increase in OS compared to baseline or control;

(o) an increase in PFS compared to baseline or control;

(p) an increase in BMI durability compared to baseline or control;

(q) a reduction in time to cancer treatment failure compared to baseline or control; or

(r) a reduction in ctDNA levels compared to baseline or control.

[0645] The reduction in an inflammatory transcript level may comprise a reduction in one or more inflammatory transcript levels. In some embodiments, the reduction in the inflammatory transcript level comprises a reduction in two or more transcript levels (e.g., two or more transcript levels comprising two or more transcripts, each transcribed from different genes). The inflammatory transcript may be a transcript selected from the group consisting of an interleukin (IL) transcript (e.g., IL1 (NCBI Gene ID: 3553; NCBI

Transcript Accession Number: NM_000576.3) IL6 (NCBI Gene ID: 3569; NCBI Transcript Accesion Numbers: NM_000600.5, NM_001318095.2, NM_001371096.1), IL1R1 (NCBI Gene ID: 3554; NCBI Transcript Accession Numbers: NM_000877.4, NM_001288706.2, NM_001320978.2, NM_001320980.2, NM_001320981.2, NM_001320982.2, NM_001320983.1, NM_001320984.1, NM_001320985.1, NM_001320986.2), a tumor necrosis factor (TNF) transcript (e.g., TNFα) (NCBI Gene ID: 7124; NCBI Transcript Accession Number: NM_000594.4), a selectin transcript (e.g., Selectin P) (NCBI Gene ID; 6403; NCBI Transcript Accession Number: NM_003005.4), a cytokine transcript, and a chemokine transcript.

[0646] The reduction in an inflammatory protein level may comprise a reduction in one or more inflammatory protein levels. In some embodiments, the reduction in the inflammatory protein level comprises a reduction in two or more protein levels (e.g., two or more proteins levels comprising two or more proteins, each translated from different transcripts). The inflammatory protein may be a protein selected from the group consisting of an interleukin (IL) protein (e.g., IL-1B (NCBI Accession Numbers: XP_047300131.1, XP_054197785.1), IL-6 (NCBI Accession Numbers: NP_000591.1, NP_001305024.1, NP_001358025.1, XP_005249802.1, XP_054214121.1) IL-1R1 (NCBI Accession Number: XP_011509420.1), a tumor necrosis factor (TNF) protein (e.g., TNF-α) (NCBI Accession Number: NP_000585.2), and a selectin protein (e.g., Selectin P) (NCBI Accession Numbers: XP_005245492.1, XP_005245495.1). In some embodiments, the subject administered the non-naturally occurring melanocortin analog and the anti-cancer agent exhibits one or more of

(a) an increase in body weight by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 225%, 250%, 275%, 300%, 350%, 400%, 450%, or 500% compared to baseline or control;

(b) an increase in muscle mass by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%

(c) an increase in fat mass by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% compared to baseline or control;

(d) an increase in cardiac mass by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% compared to baseline or control;

(e) an increase in bone density by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% compared to baseline or control;

(f) an increase in appetite as measured by an increased food intake (by about 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1200, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000, 2500, 3000, or more calories compared to baseline or control;

(g) a reduction in fatigue compared to baseline or control;

(h) a reduction in vomiting compared to baseline or control;

(i) a reduction in diarrhea compared to baseline or control;

(j) a decrease in tumor size by about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% compared to control;

(k) a decrease in cancer metastasis as measured by a decrease in cancer cell proliferation by about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% compared to control;

(l) a maintenance in ECOG performance score or a reduction in ECOG performance score by about 1, 2, or 3 compared to baseline or control;

(m) a maintenance in KPS score or an increase in KPS score by about 100, 90, 80, 70, 60, 50, 40, or 30 compared to baseline or control;

(n) an increase in cumulative mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(o) a reduction in rate of loss of cumulative mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(p) an increase in net weight gain compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(q) an increase in cumulative food intake compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(r) an increase in BMI compared to baseline or control by at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35 points;

(s) a reduction in an inflammatory transcript level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(t) a reduction in an inflammatory protein level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(u) an increase in FAACT score compared to baseline or control by at least 1, 2, 3, 4, or 5 points;

(v) an increase in OS compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(w) an increase in PFS compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(x) an increase in BMI durability compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(y) a reduction in time to cancer treatment failure compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%; and

(z) a reduction in ctDNA levels compared to baseline or control by at least about 10%, 20%, 30%m 40%, 50%, 60%, 70%, 80%, 90%, or 100%.

[0647] "Cumulative mass" refers to the total mass of a subject. A change (e.g., increase or decrease) in cumulative mass may refer to the change in cumulative mass between any two time points. In some embodiments, the change is cumulative mass is the change in cumulative mass between one or more timepoints. In some

embodiments, the change in cumulative mass is the change in cumulative mass between two or more timepoints. In some embodiments, the change in cumulative mass is the change in cumulative mass between baseline and end of treatment.

[0648] "Net weight gain" may refer to the change (e.g., increase or decrease) in weight of a subject between any two time points. In some embodiments, the change in net weight gain is the change in net weight gain between one or more timepoints. In some embodiments, the change in net weight gain is the change in net weight gain between two or more timepoints. In some embodiments, the change in net weight gain is the change in net weight gain between baseline and end of treatment.

[0649] "Cumulative food intake" refers to the total food intake between any two time points. In some embodiments, the change in cumulative food intake is the change in cumulative food intake between one or more timepoints. In some embodiments, the change in cumulative food intake is the change in cumulative food intake between two or more timepoints. In some embodiments, the change in cumulative food intake is the change in cumulative food intake between baseline and end of treatment.

[0650] In some embodiments, the cancer is at least one selected from the group consisting of bone cancer, testicular cancer, gastric cancer, sarcoma, lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, leukemia, head and neck cancer, squamous cell head and neck cancer, thymic cancer, epithelial cancer, salivary cancer, liver cancer, stomach cancer, thyroid cancer, lung cancer (e.g., non-small cell lung cancer, small cell lung cancer, mesothelioma, etc.), ovarian cancer, breast cancer, prostate cancer, esophageal cancer, pancreatic cancer, glioma, leukemia, multiple myeloma, renal cell carcinoma, bladder cancer, cervical cancer, choriocarcinoma, colorectal cancer, oral cancer, skin cancer, and melanoma.

[0651] In some embodiments, the cancer is at least one selected from the group consisting of bone cancer, lung cancer (e.g., non-small cell lung cancer, small cell lung cancer, mesothelioma, etc.), testicular cancer, breast cancer, prostate cancer, colorectal cancer, non-Hodgkin's lymphoma, ovarian cancer, cervical cancer, bladder cancer, and head and neck cancer.

[0652] In some embodiments, the cancer is breast cancer, and the chemotherapy is at least one selected from the group consisting of an anthracycline, cyclophosphamide, epirubicin, fluorouracil, methotrexate, a taxane, and docetaxel. In

some embodiments, the anthracycline is doxorubicin. In some embodiments, the taxane is paclitaxel.

[0653] In some embodiments, the cancer is lung cancer (e.g., non-small cell lung cancer, small cell lung cancer, mesothelioma, etc.), and the chemotherapy is at least one selected from the group consisting of cisplatin, carboplatin, paclitaxel, albumin-bound paclitaxel, docetaxel, gemcitabine, vinorelbine, etoposide, and pemetrexed.

[0654] In some embodiments, the cancer is prostate cancer, and the chemotherapy is at least one selected from the group consisting of docetaxel, cabazitaxel, mitoxantrone, and estramustine.

[0655] In some embodiments, the cancer is colorectal cancer, and the chemotherapy is at least one selected from the group consisting of 5-FU, capecitabine, irinotecan, oxaliplatin, trifluridine, and tipiracil.

[0656] In some embodiments, the cancer is colorectal cancer, the subject is receiving radiation therapy, and the chemotherapy is at least one selected from the group consisting of cisplatin, cisplatin plus 5-FU, and mitomycin plus 5-FU.

[0657] In some embodiments, the cancer is colorectal cancer, the subject is not receiving radiation therapy, and the chemotherapy is at least one selected from the group consisting of gemcitabine plus cisplatin, methotrexate, vinblastine, doxorubicin, plus cisplatin, cisplatin, methotrexate, plus vinblastine, and gemcitabine plus paclitaxel.

[0658] In some embodiments, the cancer is melanoma, and the chemotherapy is dacarbazine and/or temozolomide.

[0659] In some embodiments, the cancer is non-Hodgkin's lymphoma, and the chemotherapy is at least one selected from the group consisting of cyclophosphamide, chlorambucil, bendamustine, ifosfamide, prednisone, dexamethasone, cisplatin, carboplatin, oxaliplatin, fludarabine, pentostatin, cladribine (2-CdA), cytarabine (ara-C), gemcitabine, methotrexate, pralatrexate, doxorubicin, liposomal doxorubicin, hydroxydaunorubicin, vincristine, mitoxantrone, etoposide, and bleomycin.

Side Effects

[0660] In some embodiments, the subject administered the non-naturally occurring melanocortin analog prior to, during administration of, and/or after administration of the anti-cancer agent does not experience an unwanted side effect,

has a reduction in an unwanted side effect, or has an otherwise amelioration in an unwanted side effect associated with melanocortin analogs and/or melanocortin receptor antagonists, compared to baseline or control. Nonlimiting examples of unwanted side effects associated with melanocortin analogs and/or agonists include reduced potassium channel amplitude (e.g., hERG (human ether-a-go-go-related gene) potassium (K+) channel amplitude), increased skin discoloration, hyperpigmentation (e.g., skin or hair hyperpigmentation) of any grade, hypopigmentation (e.g., skin or hair hypopigmentation) of any grade, increased skin pigmentation/melanin production (e.g., epithelial black melanin), changes in echocardiogram (ECG) parameters (e.g., qualitative ECG changes or quantitative ECG changes), increased blood pressure, increased heart rate, hepatocellular vacuolation (e.g., periportal hepatocellular vacuolation), injection site reaction (e.g., injection site reaction grade 3 or 4), and change in hair and/or skin color relative to baseline or control.

[0661] In some embodiments, the subject administered the non-naturally occurring melanocortin analog prior to, during administration of, and/or after administration of the anti-cancer agent does not experience an immunogenic reaction to the non-naturally occurring melanocortin analog and/or does not develop antibodies against the non-naturally occurring melanocortin analog (e.g., antibodies that specifically bind the non-naturally occurring melanocortin analog).

[0662] In some embodiments, the subject administered the non-naturally occurring melanocortin analog prior to, during administration of, and/or after administration of the anti-cancer agent does not experience, has a reduced severity, or otherwise an amelioration of one or more of:

(a) a reduced potassium channel amplitude compared to baseline or control;

(b) an increased skin discoloration compared to baseline or control;

(c) increased hyperpigmentation compared to baseline or control;

(d) increased hypopigmentation compared to baseline or control;

(e) increased melanin production compared to baseline or control;

(f) changes in ECG parameters compared to baseline or control;

(g) increased blood pressure compared to baseline or control;

(h) increased heart rate compared to baseline or control;

(i) increased hepatocellular vacuolation compared to baseline or control;

(j) an increased injection site reaction compared to baseline or control;

(k) a change in hair color relative to baseline or control;

(l) a change in skin color relative to baseline or control;

(m) an increased immunogenic reaction to the non-naturally occurring melanocortin analog relative to baseline or control; and

(n) an increase in an antibody level that specifically binds the non-naturally occurring melanocortin analog.

Cisplatin

[0663] In some embodiments, the anti-cancer agent is an alkylating agent. In some embodiments, the alkylating agent is a platinum-based chemotherapy. In some embodiments, the platinum-based chemotherapy is cisplatin.

[0664] In some embodiments, cisplatin is administered hourly, daily, weekly, biweekly, monthly, or bimonthly. In some embodiments, cisplatin is administered through continuous infusion. In some embodiments, cisplatin is administered per cycle at a dose of about 5 mg/m IV to about 1000 mg/m IV. In some embodiments, cisplatin is administered per cycle at a dose of at least 5 mg/m IV to at least 1000 mg/m IV. In some embodiments, cisplatin is administered per cycle at a dose of at least about 5 mg/m IV to at least about 1000 mg/m IV. In some embodiments, cisplatin is administered at a dose of about 0.5 mg/m^2 per cycle to about 1000 mg/m^2 per cycle. In some embodiments, cisplatin is administered at a dose of at least 0.5 mg/m^2 per cycle to at least 1000 mg/m^2 per cycle. In some embodiments, cisplatin is administered at a dose of at least about 0.5 mg/m^2 per cycle to at least about 1000 mg/m^2 per cycle.

[0665] In some embodiments, cisplatin is administered a dose of about 20 mg/m IV daily for 5 days per cycle. In some embodiments, cisplatin is administered at a dose of 75 to 100 mg/m IV per cycle once every 4 weeks. In some embodiments, cisplatin is administered at a dose of 600 mg/m IV once every 4 weeks. In some embodiments, cisplatin is administered at a dose of 100 mg/m IV per cycle once every 4 weeks. In some embodiments, cisplatin is administered at a dose of 50 to 70 mg/m IV per cycle

once every 3 to 4 weeks. In some embodiments, cisplatin is administered at a dose of 50 mg/m per cycle repeated every 4 weeks.

[0666] In some embodiments, administration of cisplatin is associated with one or more symptoms selected from the group consisting of vomiting, nausea, anorexia, fatigue, diarrhea, weight loss, fat mass loss, muscle mass loss, cardiac muscle loss, and general weakness. In some embodiments, nausea or vomiting may begin within 1 minute to 24 hours after administration of cisplatin. In some embodiments, nausea or vomiting lasts up to 1 hour to one week after administration of cisplatin. In some embodiments, nausea or vomiting beings or persists 1 minute to one week after administration of cisplatin. In some embodiments, the administration of cisplatin and a non-naturally occurring melanocortin analog reduces or prevents one or more of these symptoms.

[0667] In some embodiments, nausea or vomiting may begin within 1 to 4 hours after administration of cisplatin. In some embodiments, nausea or vomiting lasts up to 24 to 28 hours after administration of cisplatin. In some embodiments, nausea or vomiting begins or persists 24 hours or more after administration of cisplatin. In some embodiments, various degrees of vomiting, nausea and/or anorexia may persist for a week after administration of cisplatin. In some embodiments, the administration of cisplatin and a non-naturally occurring melanocortin analog reduces or prevents one or more of these symptoms.

[0668] In some embodiments, cisplatin is administered before, during, or after administration of a non-naturally occurring melanocortin analog. In some embodiments, cisplatin is administered at a dose of about 0.5 mg/m^2 per cycle to about 1000 mg/m^2 per cycle before, during, or after administration of the non-naturally occurring melanocortin analog. In some embodiments, cisplatin is administered at a dose of at least 0.5 mg/m^2 per cycle to at least 1000 mg/m^2 per cycle before, during, or after administration of the non-naturally occurring melanocortin analog. In some embodiments, cisplatin is administered at a dose of at least about 0.5 mg/m^2 per cycle to at least about 1000 mg/m^2 per cycle before, during, or after administration of the non-naturally occurring melanocortin analog.

[0669] In some embodiments, cisplatin is administered at a dose of about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 200, 250, 300, 350, 400, 450, 500,

550, 600, 650, 700, 750, 800, 850, 900, or mg/m^2 per cycle before, during, or after administration of the non-naturally occurring melanocortin analog.

[0670] In some embodiments, cisplatin is administered at a dose of at least 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, or mg/m^2 per cycle before, during, or after administration of the non-naturally occurring melanocortin analog.

[0671] In some embodiments, cisplatin is administered at a dose of at least about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, or 1000 mg/m^2 per cycle before, during, or after administration of the non-naturally occurring melanocortin analog.

[0672] In some embodiments, the cisplatin is administered hourly, daily, every 2 days, every 3 days, every 4 days, every 5 days, once a week, once every 2 weeks, once every 3 weeks, or once every four weeks.

[0673] In some embodiments, the cisplatin is administered by continuous 1-hour, 2-hour, 3-hour, 4-hour, 5-hour, 6-hour, 7-hour, 8-hour, 9-hour, 10-hour, 12-hour, 14-hour, 16-hour, 18-hour, 20-hour, 22-hour, 24-hour, 36-hour, or 72-hour infusion.

[0674] In some embodiments, the subject has received one or more of a nutritive therapy, a nutritional supplement, an antiemetic, or a therapeutic for preventing cancer associated wasting before during, or after administration of cisplatin or the non-naturally occurring melanocortin analog.

[0675] In some embodiments, the subject administered the non-naturally occurring melanocortin analog before, during, or after administration of the cisplatin exhibits one or more of a reduction in vomiting or nausea compared to baseline or control, a reduction in gastrointestinal side effects that are not vomiting or nausea compared to baseline or control, a reduction in asthenia compared to baseline or control, a reduction in anorexia compared to baseline or control, an increase in appetite compared to baseline or control, a reduction in fatigue compared to baseline or control, a reduction in diarrhea compared to baseline or control, an increase in body weight compared to baseline or control, a reduced rate of weight loss compared to baseline or control, an increase in skeletal muscle mass compared to baseline or control, a reduced rate of loss of skeletal muscle mass compared to baseline or control, an increase in cardiac

muscle mass compared to baseline or control, a reduced rate of loss of cardiac muscle mass compared to baseline or control, an increase in fat mass compared to baseline or control, a reduced rate of loss of fat mass compared to baseline or control, an increase in bone density compared to baseline or control, a reduction in rate of loss of bone density compared to baseline or control, a reduction in general weakness compared to baseline or control, a reduction of ECOG performance score compared to baseline or control, a maintenance in ECOG performance score, an increase in KPS score compared to baseline or control, a maintenance in KPS score, no titration of cisplatin treatment, a reduced titration of cisplatin treatment compared to baseline or control, a reduction in iatrogenic injury, an increase in cumulative mass compared to baseline or control, a reduction in rate of loss of cumulative mass compared to baseline or control, an increase in net weight gain compared to baseline or control, an increase in cumulative food intake compared to baseline or control, an increase in BMI compared to baseline or control, a reduced BMI decline compared to baseline or control, or a reduced proinflammatory transcript/protein level compared to baseline or control.

[0676] In some embodiments, the subject administered the non-naturally occurring melanocortin analog before, during, or after administration of the cisplatin exhibits one or more of

(a) a reduction in the onset of vomiting or nausea compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after cisplatin administration;

(b) a reduction in the duration of vomiting or nausea compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 24 hours, 48 hours, 72 hours, 96 hours, 5 days, 6 days, or 7 days after cisplatin administration;

(c) a reduction in the onset of abdominal discomfort or pain compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after cisplatin administration;

(d) a reduction in the duration of abdominal discomfort or pain compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 24 hours, 48 hours, 72 hours, 96 hours, 5 days, 6 days, or 7 days after cisplatin administration;

(e) a reduction in the onset of hemorrhagic colitis compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after cisplatin administration;

(f) a reduction in the duration of hemorrhagic colitis compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after cisplatin administration;

(g) a reduction in asthenia compared to baseline or control compared to control within about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after cisplatin administration;

(h) a reduction in general physical deterioration to baseline or control compared to control measured by an increase in body mass index by about 0.25, 0.5, 1.0, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 5.75, 6, 6.26, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 9.25, 9.5, 9.75, or 10 or more;

(i) a reduction in the onset of influenza-like illness or chills about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after cisplatin administration;

(j) a reduction in the duration of influenza-like illness or chills about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12

hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after cisplatin administration;

(k) a reduction in anorexia compared to baseline or control measured by an increase in body mass index by about 0.25, 0.5, 1.0, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 5.75, 6, 6.26, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 9.25, 9.5, 9.75, or 10 or more;

(l) an increase in appetite compared to baseline or control, which may be measured by an increase in calorie consumption by about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 125%, 150%, 175%, 200%, 250%, 300%, 350%, 400%, 450%, or 500% or more;

(m) a reduction in fatigue compared to baseline or control, which may be measured by an increase in perceived energy or reduced energy expenditure about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after cisplatin administration;

(n) a reduction in diarrhea compared to baseline or control about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after cisplatin administration;

(o) an increase in body weight compared to baseline or control measured by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 225%, 250%, 275%, 300%, 350%, 400%, 450%, or 500%;

(p) a reduced rate of weight loss compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(q) an increase in skeletal mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(r) a reduction in rate of loss of skeletal mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(s) an increase in cardiac mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(t) a reduction in rate of loss of cardiac mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(u) an increase in fat mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(v) a reduction in rate of loss of fat mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(w) an increase in bone density compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(x) a reduction in rate of loss of bone density compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(y) a reduction in general weakness compared to baseline or control as measured by an increase perceived or exerted force without increased energy expenditure about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after administration of cisplatin;

(z) a maintenance in ECOG performance score or a reduction in ECOG performance score compared to baseline or control by about 1, 2, or 3;

(aa) a maintenance in KPS score or an increase in KPS score compared to baseline or control by about 100, 90, 80, 70, 60, 50, 40, or 30;

(bb) a reduction in titration of cisplatin treatment by about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% compared to baseline or control;

(cc) an increase in tolerance of administered dose of cisplatin treatment compared to baseline or control by about 1 mg/m^2, 2 mg/m^2, 5 mg/m^2, 10 mg/m^2, 25 mg/m^2, 50 mg/m^2, 75 mg/m^2, 100 mg/m^2, 150 mg/m^2, 200 mg/m^2, 250 mg/m^2, 300 mg/m^2, 350 mg/m^2, 400 mg/m^2, 450 mg/m^2, 500 mg/m^2, 600 mg/m^2, 700 mg/m^2, 800 mg/m^2, 900 mg/m^2, 1000 mg/m^2;

(dd) an increase in frequency of administration of cisplatin treatment compared to baseline or control by about 1 hour, 12 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 2 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, or 6 months;

(ee) a reduction iatrogenic injury by about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% compared to baseline or control;

(ff) an increase in cumulative mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(gg) a reduction in rate of loss of cumulative mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(hh) an increase in net weight gain compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(ii) an increase in cumulative food intake compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(jj) an increase in BMI compared to baseline or control by at least about 0.5 kg/m^2, 1.0 kg/m^2, 1.5 kg/m^2, 2.0 kg/m^2, 2.5 kg/m^2, 3.0 kg/m^2, 3.5 kg/m^2, 4.0 kg/m^2, 4.5 kg/m^2, 5.0 kg/m^2, 5.5 kg/m^2, 6.0 kg/m^2, 6.5 kg/m^2, 7.0 kg/m^2, 7.5 kg/m^2, 8.0 kg/m^2, 8.5 kg/m^2, 9.0 kg/m^2, 9.5 kg/m^2, 10.0 kg/m^2, 10.5 kg/m^2, 11.0 kg/m^2, 11.5 kg/m^2, or 12.0 kg/m^2;

(kk) a reduction in an inflammatory transcript level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(ll) a reduction in an inflammatory protein level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(mm) an increase in FAACT score compared to baseline or control by at least 1, 2, 3, 4, or 5 points;

(nn) an increase in OS compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(oo) an increase in PFS compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;(pp) an increase in BMI durability compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(pp) an increase in BMI durability compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(qq) a reduction in time to cancer treatment failure compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%; and

(rr) a reduction in ctDNA levels compared to baseline or control by at least about 10%, 20%, 30%m 40%, 50%, 60%, 70%, 80%, 90%, or 100%.

Carboplatin

[0677] In some embodiments, the anti-cancer agent is an alkylating agent. In some embodiments, the alkylating agent is a platinum-based chemotherapy. In some embodiments, the platinum-based chemotherapy is carboplatin.

[0678] In some embodiments, carboplatin is administered hourly, daily, weekly, biweekly, monthly, or bimonthly. In some embodiments, carboplatin is administered

through continuous infusion. In some embodiments, carboplatin is administered per cycle at a dose of about 5 mg/m IV to about 2000 mg/m IV.

[0679] In some embodiments, carboplatin is administered per cycle at a dose of at least 5 mg/m IV to at least 2000 mg/m IV.

[0680] In some embodiments, carboplatin is administered per cycle at a dose of at least about 5 mg/m IV to at least about 2000 mg/m IV.

[0681] In some embodiments, carboplatin is administered at a dose of about 0.5 mg/m^2 per cycle to about 2000 mg/m^2 per cycle.

[0682] In some embodiments, carboplatin is administered at a dose of at least 0.5 mg/m^2 per cycle to at least 2000 mg/m^2 per cycle.

[0683] In some embodiments, carboplatin is administered at a dose of at least about 0.5 mg/m^2 per cycle to at least about 2000 mg/m^2 per cycle.

[0684] In some embodiments, carboplatin is administered a dose of about 200 mg/m^2, 250 mg/m^2, 300 mg/m^2, 360 mg/m^2. In some embodiments, the carboplatin is administered every 4 weeks. In some embodiments, the carboplatin is administered every 4 weeks for 6 cycles. In some embodiments, carboplatin is administered more than once when the neutrophil count of the subject is at least about 2,000 or the platelet count is at least about 100,000. In some embodiments, the carboplatin is administered with carboplatin or cyclophosphamide.

[0685] In some embodiments, administration of carboplatin is associated with one or more symptoms selected from the group consisting of vomiting, nausea, gastrointestinal side effects that are not vomiting or nausea, electrolyte loss in one or more electrolytes, asthenia, anorexia, fatigue, diarrhea, weight loss, fat mass loss, muscle mass loss, cardiac muscle loss, and general weakness. In some embodiments, nausea or vomiting may begin within 1 minute to 24 hours after administration of carboplatin. In some embodiments, nausea or vomiting lasts up to 1 hour to one week after administration of carboplatin. In some embodiments, nausea or vomiting beings or persists 1 minute to one week after administration of carboplatin. In some embodiments, the administration of carboplatin and a non-naturally occurring melanocortin analog reduces or prevents one or more of these symptoms.

[0686] In some embodiments, nausea or vomiting may begin within 1 to 24 hours after administration of carboplatin. In some embodiments, nausea or vomiting lasts up to 1 hour to 24 hours after administration of carboplatin. In some embodiments, nausea or vomiting begins or persists 24 hours or more after administration of carboplatin. In some embodiments, the administration of carboplatin and a non-naturally occurring melanocortin analog reduces or prevents one or more of these symptoms.

[0687] In some embodiments, carboplatin is administered before, during, or after administration of a non-naturally occurring melanocortin analog. In some embodiments, carboplatin is administered at a dose of about 5 mg/m^2 per cycle to about 2000 mg/m^2 per cycle before, during, or after administration of the non-naturally occurring melanocortin analog.

[0688] In some embodiments, carboplatin is administered at a dose of at least 5 mg/m^2 per cycle to at least 2000 mg/m^2 per cycle before, during, or after administration of the non-naturally occurring melanocortin analog.

[0689] In some embodiments, carboplatin is administered at a dose of at least about 5 mg/m^2 per cycle to at least about 2000 mg/m^2 per cycle before, during, or after administration of the non-naturally occurring melanocortin analog.

[0690] In some embodiments, carboplatin is administered at a dose of about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, or mg/m^2 per cycle before, during, or after administration of the non-naturally occurring melanocortin analog.

[0691] In some embodiments, carboplatin is administered at a dose of at least 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, or mg/m^2 per cycle before, during, or after administration of the non-naturally occurring melanocortin analog.

[0692] In some embodiments, carboplatin is administered at a dose of at least about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, or 1000 mg/m^2 per cycle before, during, or after administration of the non-naturally occurring melanocortin analog

[0693] . In some embodiments, the carboplatin is administered hourly, daily, every 2 days, every 3 days, every 4 days, every 5 days, once a week, once every 2 weeks, once every 3 weeks, or once every four weeks.

[0694] In some embodiments, the carboplatin is administered by continuous 1-hour, 2-hour, 3-hour, 4-hour, 5-hour, 6-hour, 7-hour, 8-hour, 9-hour, 10-hour, 12-hour, 14-hour, 16-hour, 18-hour, 20-hour, 22-hour, 24-hour, 36-hour, or 72-hour infusion. In some embodiments, carboplatin is administered by daily pulse doses. In some embodiments, the subject has received one or more of a nutritive therapy, a nutritional supplement, an antiemetic, or a therapeutic for preventing cancer associated wasting before during, or after administration of carboplatin or the non-naturally occurring melanocortin analog.

[0695] In some embodiments, the subject administered the non-naturally occurring melanocortin analog before, during, or after administration of the carboplatin exhibits one or more of a reduction in vomiting or nausea compared to baseline or control, a reduction in gastrointestinal side effects that are not vomiting or nausea compared to baseline or control, a reduction in asthenia compared to baseline or control, a reduction in anorexia compared to baseline or control, an increase in appetite compared to baseline or control, a reduction in fatigue compared to baseline or control, a reduction in diarrhea compared to baseline or control, an increase in body weight compared to baseline or control, a reduced rate of weight loss compared to baseline or control, an increase in skeletal muscle mass compared to baseline or control, a reduced rate of loss of skeletal muscle mass compared to baseline or control, an increase in cardiac muscle mass compared to baseline or control, a reduced rate of loss of cardiac muscle mass compared to baseline or control, an increase in fat mass compared to baseline or control, a reduced rate of loss of fat mass compared to baseline or control, an increase in bone density compared to baseline or control, a reduction in rate of loss of bone density compared to baseline or control, a reduction in general weakness compared to baseline or control, a reduction of ECOG performance score compared to baseline or control, a maintenance in ECOG performance score, an increase in KPS score compared to baseline or control, a maintenance in KPS score, no titration of carboplatin treatment, a reduced titration of carboplatin treatment compared to baseline or control, a reduction in iatrogenic injury, an increase in cumulative mass compared to baseline or control, a reduction in rate of loss of cumulative mass compared to baseline or

control, an increase in net weight gain compared to baseline or control, an increase in cumulative food intake compared to baseline or control, an increase in BMI compared to baseline or control, a reduced BMI decline compared to baseline or control, or a reduced proinflammatory transcript/protein level compared to baseline or control.

[0696] In some embodiments, the subject administered the non-naturally occurring melanocortin analog before, during, or after administration of the carboplatin exhibits one or more of

(a) a reduction in the onset of vomiting or nausea compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after carboplatin administration;

(b) a reduction in the duration of vomiting or nausea compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 24 hours, 48 hours, 72 hours, 96 hours, 5 days, 6 days, or 7 days after carboplatin administration;

(c) a reduction in the onset of abdominal discomfort or pain compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after carboplatin administration;

(d) a reduction in the duration of abdominal discomfort or pain compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 24 hours, 48 hours, 72 hours, 96 hours, 5 days, 6 days, or 7 days after carboplatin administration;

(e) a reduction in the onset of hemorrhagic colitis compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19

hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after carboplatin administration;

(f) a reduction in the duration of hemorrhagic colitis compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after carboplatin administration;

(g) a reduction in asthenia compared to baseline or control compared to control within about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after carboplatin administration;

(h) a reduction in general physical deterioration to baseline or control compared to control measured by an increase in body mass index by about 0.25, 0.5, 1.0, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 5.75, 6, 6.26, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 9.25, 9.5, 9.75, or 10 or more;

(i) a reduction in the onset of influenza-like illness or chills about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after carboplatin administration;

(j) a reduction in the duration of influenza-like illness or chills about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after carboplatin administration;

(k) a reduction in anorexia compared to baseline or control measured by an increase in body mass index by about 0.25, 0.5, 1.0, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 5.75, 6, 6.26, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 9.25, 9.5, 9.75, or 10 or more;

(l) an increase in appetite compared to baseline or control, which may be measured by an increase in calorie consumption by about 5%, 10%, 15%, 20%, 25%, 30%, 35%,

40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 125%, 150%, 175%, 200%, 250%, 300%, 350%, 400%, 450%, or 500% or more;

(m) a reduction in fatigue compared to baseline or control, which may be measured by an increase in perceived energy or reduced energy expenditure about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after carboplatin administration;

(n) a reduction in diarrhea compared to baseline or control about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after carboplatin administration;

(o) an increase in body weight compared to baseline or control measured by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 225%, 250%, 275%, 300%, 350%, 400%, 450%, or 500%;

(p) a reduced rate of weight loss compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(q) an increase in skeletal mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(r) a reduction in rate of loss of skeletal mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(s) an increase in cardiac mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(t) a reduction in rate of loss of cardiac mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(u) an increase in fat mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(v) a reduction in rate of loss of fat mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(w) an increase in bone density compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(x) a reduction in rate of loss of bone density compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(y) a reduction in general weakness compared to baseline or control as measured by an increase perceived or exerted force without increased energy expenditure about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after administration of carboplatin;

(z) a maintenance in ECOG performance score or a reduction in ECOG performance score compared to baseline or control by about 1, 2, or 3;

(aa) a maintenance in KPS score or an increase in KPS score compared to baseline or control by about 100, 90, 80, 70, 60, 50, 40, or 30;

(bb) a reduction in titration of carboplatin treatment by about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% compared to baseline or control;

(cc) an increase in tolerance of administered dose of carboplatin treatment compared to baseline or control by about 1 mg/m^2, 2 mg/m^2, 5 mg/m^2, 10 mg/m^2, 25 mg/m^2, 50 mg/m^2, 75 mg/m^2, 100 mg/m^2, 150 mg/m^2, 200 mg/m^2, 250 mg/m^2, 300 mg/m^2, 350 mg/m^2, 400 mg/m^2, 450 mg/m^2, 500 mg/m^2, 600 mg/m^2, 700 mg/m^2, 800 mg/m^2, 900 mg/m^2, 1000 mg/m^2, 1250 mg/m^2, 1500 mg/m^2, 1750 mg/m^2, or 2000 mg/m^2 or more;

(dd) an increase in frequency of administration of carboplatin treatment compared to baseline or control by about 1 hour, 12 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 2 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, or 6 months;

(ee) a reduction iatrogenic injury by about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% compared to baseline or control;

(ff) an increase in cumulative mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(gg) a reduction in rate of loss of cumulative mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(hh) an increase in net weight gain compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(ii) an increase in cumulative food intake compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(jj) an increase in BMI compared to baseline or control by at least about 0.5 kg/m^2, 1.0 kg/m^2, 1.5 kg/m^2, 2.0 kg/m^2, 2.5 kg/m^2, 3.0 kg/m^2, 3.5 kg/m^2, 4.0 kg/m^2, 4.5 kg/m^2, 5.0 kg/m^2, 5.5 kg/m^2, 6.0 kg/m^2, 6.5 kg/m^2, 7.0 kg/m^2, 7.5 kg/m^2, 8.0 kg/m^2, 8.5 kg/m^2, 9.0 kg/m^2, 9.5 kg/m^2, 10.0 kg/m^2, 10.5 kg/m^2, 11.0 kg/m^2, 11.5 kg/m^2, or 12.0 kg/m^2;

(kk) a reduction in an inflammatory transcript level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(ll) a reduction in an inflammatory protein level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(mm) an increase in FAACT score compared to baseline or control by at least 1, 2, 3, 4, or 5 points;

(nn) an increase in OS compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(oo) an increase in PFS compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(pp) an increase in BMI durability compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(qq) a reduction in time to cancer treatment failure compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%; and

(rr) a reduction in ctDNA levels compared to baseline or control by at least about 10%, 20%, 30%m 40%, 50%, 60%, 70%, 80%, 90%, or 100%.

Cyclophosphamide

[0697] In some embodiments, the anti-cancer agent is an alkylating agent. In some embodiments, the alkylating agent is an antineoplastic. In some embodiments, the antineoplastic is cyclophosphamide.

[0698] In some embodiments, cyclophosphamide is administered hourly, daily, weekly, biweekly, monthly, or bimonthly. In some embodiments, cyclophosphamide is administered per cycle at a dose of about 0.5 mg/kg to about 20 mg/kg per day.

[0699] In some embodiments, cyclophosphamide is administered per cycle at a dose of at least 0.5 mg/kg to at least 20 mg/kg.

[0700] In some embodiments, cyclophosphamide is administered per cycle at a dose of at least about 0.5 mg/kg to at least about 20 mg/kg.

[0701] In some embodiments, cyclophosphamide is administered a dose of about 1 mg/kg per day. 1.5 mg/kg per day, 2 mg/kg per day, 2.5 mg/kg per day, 3 mg/kg per day, 3.5 mg/kg per day, 4 mg/kg per day, 4.5 mg/kg per day, 5 mg/kg per day, 10 mg/kg per day, 15 mg/kg per day, or 20 mg/kg per day or more. In some embodiments, the cyclophosphamide is administered once daily.

[0702] In some embodiments, the cyclophosphamide is administered once daily for 8 to 12 weeks. In some embodiments, cyclophosphamide is administered at a maximum cumulative dose of 168 mg/kg. In some embodiments, cyclophosphamide is administered to a subject having neutrophils ≤1,500/mm or platelets <50,000/mm prior to administration of cyclophosphamide.

[0703] In some embodiments, administration of cyclophosphamide is associated with one or more symptoms selected from the group consisting of vomiting, nausea, abdominal discomfort or pain, hemorrhagic colitis, asthenia, general physical deterioration, influenza-like illness, cardiac function, anorexia, fatigue, diarrhea, weight loss, fat mass loss, muscle mass loss, cardiac muscle loss, and general weakness. In some embodiments, nausea or vomiting may begin within 1 minute to 24 hours after administration of cyclophosphamide. In some embodiments, nausea or vomiting lasts up to 1 hour to one week after administration of cyclophosphamide. In some embodiments, nausea or vomiting beings or persists 1 minute to one week after administration of cyclophosphamide. In some embodiments, the administration of cyclophosphamide and a non-naturally occurring melanocortin analog reduces or prevents one or more of these symptoms.

[0704] In some embodiments, nausea or vomiting may begin within 1 to 24 hours after administration of cyclophosphamide. In some embodiments, nausea or vomiting lasts up to 1 hour to 24 hours after administration of cyclophosphamide. In some embodiments, nausea or vomiting begins or persists 24 hours or more after administration of cyclophosphamide. In some embodiments, the administration of cyclophosphamide and a non-naturally occurring melanocortin analog reduces or prevents one or more of these symptoms.

[0705] In some embodiments, cyclophosphamide is administered before, during, or after administration of a non-naturally occurring melanocortin analog. In some embodiments, cyclophosphamide is administered at a dose of about 0.5 mg/kg to about

30 mg/kg per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0706] In some embodiments, cyclophosphamide is administered at a dose of at least 0.5 mg/kg to at least 30 mg/kg per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0707] In some embodiments, cyclophosphamide is administered at a dose of at least about 0.5 mg/kg per day to at least about 30 mg/kg per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0708] In some embodiments, cyclophosphamide is administered at a dose of about 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 mg/kg per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0709] In some embodiments, cyclophosphamide is administered at a dose of at least 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 mg/kg per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0710] In some embodiments, cyclophosphamide is administered at a dose of at least about 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 mg/kg per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0711] In some embodiments, the cyclophosphamide is administered hourly, twice daily, once daily, once every 2 days, once every 3 days, once every 4 days, once every 5 days, or once a week.

[0712] In some embodiments, the cyclophosphamide is administered by continuous 1-hour, 2-hour, 3-hour, 4-hour, 5-hour, 6-hour, 7-hour, 8-hour, 9-hour, 10-hour, 12-hour, 14-hour, 16-hour, 18-hour, 20-hour, 22-hour, 24-hour, 36-hour, or 72-hour infusion.

[0713] In some embodiments, cyclophosphamide is administered by daily pulse doses. In some embodiments, the subject has received one or more of a nutritive therapy, a nutritional supplement, an antiemetic, or a therapeutic for preventing cancer associated wasting before during, or after administration of cyclophosphamide or the non-naturally occurring melanocortin analog.

[0714] In some embodiments, the subject administered the non-naturally occurring melanocortin analog before, during, or after administration of the cyclophosphamide exhibits one or more of a reduction in vomiting or nausea compared to baseline or control, a reduction in gastrointestinal side effects that are not vomiting or nausea compared to baseline or control, a reduction in asthenia compared to baseline or control, a reduction in anorexia compared to baseline or control, an increase in appetite compared to baseline or control, a reduction in fatigue compared to baseline or control, a reduction in diarrhea compared to baseline or control, an increase in body weight compared to baseline or control, a reduced rate of weight loss compared to baseline or control, an increase in skeletal muscle mass compared to baseline or control, a reduced rate of loss of skeletal muscle mass compared to baseline or control, an increase in cardiac muscle mass compared to baseline or control, a reduced rate of loss of cardiac muscle mass compared to baseline or control, an increase in fat mass compared to baseline or control, a reduced rate of loss of fat mass compared to baseline or control, an increase in bone density compared to baseline or control, a reduction in rate of loss of bone density compared to baseline or control, a reduction in general weakness compared to baseline or control, a reduction of ECOG performance score compared to baseline or control, a maintenance in ECOG performance score, an increase in KPS score compared to baseline or control, a maintenance in KPS score, no titration of cyclophosphamide treatment, a reduced titration of cyclophosphamide treatment compared to baseline or control, a reduction in iatrogenic injury, an increase in cumulative mass compared to baseline or control, a reduction in rate of loss of cumulative mass compared to baseline or control, an increase in net weight gain compared to baseline or control, an increase in cumulative food intake compared to baseline or control; an increase in BMI compared to baseline or control, or a reduced BMI decline compared to baseline or control.

[0715] In some embodiments, the subject administered the non-naturally occurring melanocortin analog before, during, or after administration of the cyclophosphamide exhibits one or more of

(a) a reduction in the onset of vomiting or nausea compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after cyclophosphamide administration;

(b) a reduction in the duration of vomiting or nausea compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 24 hours, 48 hours, 72 hours, 96 hours, 5 days, 6 days, or 7 days after cyclophosphamide administration;

(c) a reduction in the onset of abdominal discomfort or pain compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after cyclophosphamide administration;

(d) a reduction in the duration of abdominal discomfort or pain compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 24 hours, 48 hours, 72 hours, 96 hours, 5 days, 6 days, or 7 days after cyclophosphamide administration;

(e) a reduction in the onset of hemorrhagic colitis compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after cyclophosphamide administration;

(f) a reduction in the duration of hemorrhagic colitis compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours,

19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after cyclophosphamide administration;

(g) a reduction in asthenia compared to baseline or control compared to control within about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after cyclophosphamide administration;

(h) a reduction in general physical deterioration to baseline or control compared to control measured by an increase in body mass index by about 0.25, 0.5, 1.0, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 5.75, 6, 6.26, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 9.25, 9.5, 9.75, or 10 or more;

(i) a reduction in the onset of influenza-like illness or chills about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after cyclophosphamide administration;

(j) a reduction in the duration of influenza-like illness or chills about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after cyclophosphamide administration;

(k) a reduction in anorexia compared to baseline or control measured by an increase in body mass index by about 0.25, 0.5, 1.0, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 5.75, 6, 6.26, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 9.25, 9.5, 9.75, or 10 or more;

(l) an increase in appetite compared to baseline or control, which may be measured by an increase in calorie consumption by about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 125%, 150%, 175%, 200%, 250%, 300%, 350%, 400%, 450%, or 500% or more;

(m) a reduction in fatigue compared to baseline or control, which may be measured by an increase in perceived energy or reduced energy expenditure about 1 hour, about 2

hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after cyclophosphamide administration;

(n) a reduction in diarrhea compared to baseline or control about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after cyclophosphamide administration;

(o) an increase in body weight compared to baseline or control measured by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 225%, 250%, 275%, 300%, 350%, 400%, 450%, or 500%;

(p) a reduced rate of weight loss compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(q) an increase in skeletal mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(r) a reduction in rate of loss of skeletal mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(s) an increase in cardiac mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(t) a reduction in rate of loss of cardiac mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(u) an increase in fat mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(v) a reduction in rate of loss of fat mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(w) an increase in bone density compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(x) a reduction in rate of loss of bone density compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(y) a reduction in general weakness compared to baseline or control as measured by an increase perceived or exerted force without increased energy expenditure about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after administration of cyclophosphamide;

(z) a maintenance in ECOG performance score or a reduction in ECOG performance score compared to baseline or control by about 1, 2, or 3;

(aa) a maintenance in KPS score or an increase in KPS score compared to baseline or control by about 100, 90, 80, 70, 60, 50, 40, or 30;

(bb) a reduction in titration of cyclophosphamide treatment by about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% compared to baseline or control;

(cc) an increase in tolerance of administered dose of cyclophosphamide treatment compared to baseline or control by about 0.5 mg/kg per day, 1 mg/kg per day, 1.5 mg/kg per day, 2.0 mg/kg per day, 2.5 mg/kg per day, 3.0 mg/kg per day, 3.5 mg/kg per day, 4.0 mg/kg per day, 4.5 mg/kg per day, 5.0 mg/kg per day, 5.5 mg/kg per day, 6.0 mg/kg

per day, 6.5 mg/kg per day, 7.0 mg/kg per day, 7.5 mg/kg per day, 8.0 mg/kg per day, 8.5 mg/kg per day, 9.0 mg/kg per day, 9.5 mg/kg per day, 10.0 mg/kg per day, 11 mg/kg per day, 12 mg/kg per day, 13 mg/kg per day, 14 mg/kg per day, 15 mg/kg per day, 16 mg/kg per day, 17 mg/kg per day, 18 mg/kg per day, 19 mg/kg per day, 20 mg/kg per day or more;

(dd) an increase in frequency of administration of cyclophosphamide treatment compared to baseline or control by about 1 hour, 12 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 2 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, or 6 months;

(ee) a reduction iatrogenic injury by about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% compared to baseline or control;

(ff) an increase in cumulative mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(gg) a reduction in rate of loss of cumulative mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(hh) an increase in net weight gain compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(ii) an increase in cumulative food intake compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(jj) an increase in BMI compared to baseline or control by at least about 0.5 kg/m^2, 1.0 kg/m^2, 1.5 kg/m^2, 2.0 kg/m^2, 2.5 kg/m^2, 3.0 kg/m^2, 3.5 kg/m^2, 4.0 kg/m^2, 4.5 kg/m^2, 5.0 kg/m^2, 5.5 kg/m^2, 6.0 kg/m^2, 6.5 kg/m^2, 7.0 kg/m^2, 7.5 kg/m^2, 8.0 kg/m^2, 8.5 kg/m^2, 9.0 kg/m^2, 9.5 kg/m^2, 10.0 kg/m^2, 10.5 kg/m^2, 11.0 kg/m^2, 11.5 kg/m^2, or 12.0 kg/m^2 ;

(kk) a reduction in an inflammatory transcript level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(ll) a reduction in an inflammatory protein level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(mm) an increase in FAACT score compared to baseline or control by at least 1, 2, 3, 4, or 5 points;

(nn) an increase in OS compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(oo) an increase in PFS compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(pp) an increase in BMI durability compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(qq) a reduction in time to cancer treatment failure compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%; and

(rr) a reduction in ctDNA levels compared to baseline or control by at least about 10%, 20%, 30%m 40%, 50%, 60%, 70%, 80%, 90%, or 100%.

Temozolomide

[0716] In some embodiments, the anti-cancer agent is an alkylating agent. In some embodiments, the alkylating agent is an antineoplastic. In some embodiments, the antineoplastic is temozolomide.

[0717] In some embodiments, temozolomide is administered hourly, daily, weekly, biweekly, monthly, or bimonthly. In some embodiments, temozolomide is administered through continuous infusion. In some embodiments, temozolomide is administered per day or per cycle at a dose of about 10 mg/m^2 to about 500 mg/m^2.

[0718] In some embodiments, temozolomide is administered per cycle at a dose of at least 10 mg/m^2 to at least 500 mg/m^2.

[0719] In some embodiments, temozolomide is administered per cycle at a dose of at least about 10 mg/m^2 to at least about 500 mg/m^2.

[0720] In some embodiments, temozolomide is administered a dose of about 10 mg/m^2, 20 mg/m^2, 30 mg/m^2, 40 mg/m^2, 50 mg/m^2, 75 mg/m^2, 100 mg/m^2, 125 mg/m^2,

150 mg/m^2, 175 mg/m^2, 200 mg/m^2, 225 mg/m^2, 250 mg/m^2, 275 mg/m^2, 300 mg/m^2, 350 mg/m^2, 400 mg/m^2, 450 mg/m^2, or 500 mg/m^2 or more per day or per cycle.

[0721] In some embodiments, the temozolomide is administered once daily. In some embodiments, the temozolomide is administered once daily for 5 days to 25 weeks. In some embodiments, temozolomide is administered when the absolute neutrophil count of the subject is greater than or equal to 1.5 x 10 /L or the platelet count of the subject is greater than or equal to 100 x 10^9 /L.

[0722] In some embodiments, temozolomide is administered at a dose of about 75 mg/m^2 once daily for 42 days. In some embodiments, temozolomide is administered at a dose of 150 mg/m^2 once daily on days 1 to 5 of each 28-day cycle for 6 cycles. In some embodiments, temozolomide is administered at a dose of 200 mg/m^2 for cycles 2 to 6. In some embodiments, temozolomide is administered at a dose of 140 mg/m^2 once daily on days 1 to 5 of each 28-day cycle.

[0723] In some embodiments, administration of temozolomide is associated with one or more symptoms selected from the group consisting of vomiting, nausea, abdominal discomfort or pain, anorexia, fatigue, diarrhea, weight loss, fat mass loss, muscle mass loss, cardiac muscle loss, and general weakness. In some embodiments, nausea or vomiting may begin within 1 minute to 24 hours after administration of temozolomide. In some embodiments, nausea or vomiting lasts up to 1 hour to one week after administration of temozolomide. In some embodiments, nausea or vomiting beings or persists 1 minute to one week after administration of temozolomide. In some embodiments, the administration of temozolomide and a non-naturally occurring melanocortin analog reduces or prevents one or more of these symptoms.

[0724] In some embodiments, nausea or vomiting may begin within 1 to 24 hours after administration of temozolomide. In some embodiments, nausea or vomiting lasts up to 1 hour to 24 hours after administration of temozolomide. In some embodiments, nausea or vomiting begins or persists 24 hours or more after administration of temozolomide. In some embodiments, the administration of temozolomide and a non-naturally occurring melanocortin analog reduces or prevents one or more of these symptoms.

[0725] In some embodiments, temozolomide is administered before, during, or after administration of a non-naturally occurring melanocortin analog. In some

embodiments, temozolomide is administered at a dose of about 10 mg/m^2 to about 500 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0726] In some embodiments, temozolomide is administered at a dose of at least 10 mg/m^2 to about 500 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0727] In some embodiments, temozolomide is administered at a dose of at least about 10 mg/m^2 to about 500 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0728] In some embodiments, temozolomide is administered at a dose of about 10 mg/m^2. 20 mg/m^2, 30 mg/m^2, 40 mg/m^2, 50 mg/m^2, 75 mg/m^2, 100 mg/m^2, 125 mg/m^2, 150 mg/m^2, 175 mg/m^2, 200 mg/m^2, 225 mg/m^2, 250 mg/m^2, 275 mg/m^2, 300 mg/m^2, 350 mg/m^2, 400 mg/m^2, 450 mg/m^2, or 500 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0729] In some embodiments, temozolomide is administered at a dose of at least 10 mg/m^2. 20 mg/m^2, 30 mg/m^2, 40 mg/m^2, 50 mg/m^2, 75 mg/m^2, 100 mg/m^2, 125 mg/m^2, 150 mg/m^2, 175 mg/m^2, 200 mg/m^2, 225 mg/m^2, 250 mg/m^2, 275 mg/m^2, 300 mg/m^2, 350 mg/m^2, 400 mg/m^2, 450 mg/m^2, or 500 mg/m^2 mg/kg per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0730] In some embodiments, temozolomide is administered at a dose of at least about 10 mg/m^2. 20 mg/m^2, 30 mg/m^2, 40 mg/m^2, 50 mg/m^2, 75 mg/m^2, 100 mg/m^2, 125 mg/m^2, 150 mg/m^2, 175 mg/m^2, 200 mg/m^2, 225 mg/m^2, 250 mg/m^2, 275 mg/m^2, 300 mg/m^2, 350 mg/m^2, 400 mg/m^2, 450 mg/m^2, or 500 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0731] In some embodiments, the temozolomide is administered hourly, twice daily, once daily, once every 2 days, once every 3 days, once every 4 days, once every 5 days, or once a week.

[0732] In some embodiments, the temozolomide is administered by continuous 1-hour, 2-hour, 3-hour, 4-hour, 5-hour, 6-hour, 7-hour, 8-hour, 9-hour, 10-hour, 12-hour, 14-hour, 16-hour, 18-hour, 20-hour, 22-hour, 24-hour, 36-hour, or 72-hour infusion. In some embodiments, temozolomide is administered by daily pulse doses.

[0733] In some embodiments, the subject has received one or more of a nutritive therapy, a nutritional supplement, an antiemetic, or a therapeutic for preventing cancer associated wasting before during, or after administration of temozolomide or the non-naturally occurring melanocortin analog.

[0734] In some embodiments, the subject administered the non-naturally occurring melanocortin analog before, during, or after administration of the temozolomide exhibits one or more of a reduction in vomiting or nausea compared to baseline or control, a reduction in gastrointestinal side effects that are not vomiting or nausea compared to baseline or control, a reduction in asthenia compared to baseline or control, a reduction in anorexia compared to baseline or control, an increase in appetite compared to baseline or control, a reduction in fatigue compared to baseline or control, a reduction in diarrhea compared to baseline or control, an increase in body weight compared to baseline or control, a reduced rate of weight loss compared to baseline or control, an increase in skeletal muscle mass compared to baseline or control, a reduced rate of loss of skeletal muscle mass compared to baseline or control, an increase in cardiac muscle mass compared to baseline or control, a reduced rate of loss of cardiac muscle mass compared to baseline or control, an increase in fat mass compared to baseline or control, a reduced rate of loss of fat mass compared to baseline or control, an increase in bone density compared to baseline or control, a reduction in rate of loss of bone density compared to baseline or control, a reduction in general weakness compared to baseline or control, a reduction of ECOG performance score compared to baseline or control, a maintenance in ECOG performance score, an increase in KPS score compared to baseline or control, a maintenance in KPS score, no titration of temozolomide treatment, a reduced titration of temozolomide treatment compared to baseline or control, a reduction in iatrogenic injury, an increase in cumulative mass compared to baseline or control, a reduction in rate of loss of cumulative mass compared to baseline or control, an increase in net weight gain compared to baseline or control, an increase in cumulative food intake compared to baseline or control, an increase in BMI compared to baseline or control, a reduced BMI decline compared to baseline or control, or a reduced proinflammatory transcript/protein level compared to baseline or control.

[0735] In some embodiments, the subject administered the non-naturally occurring melanocortin analog before, during, or after administration of the temozolomide exhibits one or more of

(a) a reduction in the onset of vomiting or nausea compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after temozolomide administration;

(b) a reduction in the duration of vomiting or nausea compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 24 hours, 48 hours, 72 hours, 96 hours, 5 days, 6 days, or 7 days after temozolomide administration;

(c) a reduction in the onset of abdominal discomfort or pain compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after temozolomide administration;

(d) a reduction in the duration of abdominal discomfort or pain compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 24 hours, 48 hours, 72 hours, 96 hours, 5 days, 6 days, or 7 days after temozolomide administration;

(e) a reduction in the onset of hemorrhagic colitis compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after temozolomide administration;

(f) a reduction in the duration of hemorrhagic colitis compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours,

19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after temozolomide administration;

(g) a reduction in asthenia compared to baseline or control compared to control within about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after temozolomide administration;

(h) a reduction in general physical deterioration to baseline or control compared to control measured by an increase in body mass index by about 0.25, 0.5, 1.0, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 5.75, 6, 6.26, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 9.25, 9.5, 9.75, or 10 or more;

(i) a reduction in the onset of influenza-like illness or chills about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after temozolomide administration;

(j) a reduction in the duration of influenza-like illness or chills about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after temozolomide administration;

(k) a reduction in anorexia compared to baseline or control measured by an increase in body mass index by about 0.25, 0.5, 1.0, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 5.75, 6, 6.26, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 9.25, 9.5, 9.75, or 10 or more;

(l) an increase in appetite compared to baseline or control, which may be measured by an increase in calorie consumption by about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 125%, 150%, 175%, 200%, 250%, 300%, 350%, 400%, 450%, or 500% or more;

(m) a reduction in fatigue compared to baseline or control, which may be measured by an increase in perceived energy or reduced energy expenditure about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about

8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after temozolomide administration;

(n) a reduction in diarrhea compared to baseline or control about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after temozolomide administration;

(o) an increase in body weight compared to baseline or control measured by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 225%, 250%, 275%, 300%, 350%, 400%, 450%, or 500%;

(p) a reduced rate of weight loss compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(q) an increase in skeletal mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(r) a reduction in rate of loss of skeletal mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(s) an increase in cardiac mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(t) a reduction in rate of loss of cardiac mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(u) an increase in fat mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(v) a reduction in rate of loss of fat mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(w) an increase in bone density compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(x) a reduction in rate of loss of bone density compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(y) a reduction in general weakness compared to baseline or control as measured by an increase perceived or exerted force without increased energy expenditure about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after administration of temozolomide;

(z) a maintenance in ECOG performance score or a reduction in ECOG performance score compared to baseline or control by about 1, 2, or 3;

(aa) a maintenance in KPS score or an increase in KPS score compared to baseline or control by about 100, 90, 80, 70, 60, 50, 40, or 30;

(bb) a reduction in titration of temozolomide treatment by about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% compared to baseline or control;

(cc) an increase in tolerance of administered dose of temozolomide treatment compared to baseline or control by about 1 mg/m^2, 2 mg/m^2, 5 mg/m^2, 10 mg/m^2, 25 mg/m^2, 50 mg/m^2, 75 mg/m^2, 100 mg/m^2, 150 mg/m^2, 200 mg/m^2, 250 mg/m^2, 300 mg/m^2, 350 mg/m^2, 400 mg/m^2, 450 mg/m^2, 500 mg/m^2, 600 mg/m^2, 700 mg/m^2, 800 mg/m^2, 900

mg/m^2, 1000 mg/m^2, 1250 mg/m^2, 1500 mg/m^2, 1750 mg/m^2, 2000 mg/m^2, 2500 mg/m^2, 3000 mg/m^2, 3500 mg/m^2, 4000 mg/m^2, 4500 mg/m^2, 5000 mg/m^2 or more;

(dd) an increase in frequency of administration of temozolomide treatment compared to baseline or control by about 1 hour, 12 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 2 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, or 6 months;

(ee) a reduction iatrogenic injury by about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% compared to baseline or control;

(ff) an increase in cumulative mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(gg) a reduction in rate of loss of cumulative mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(hh) an increase in net weight gain compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(ii) an increase in cumulative food intake compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(jj) an increase in BMI compared to baseline or control by at least about 0.5 kg/m^2, 1.0 kg/m^2, 1.5 kg/m^2, 2.0 kg/m^2, 2.5 kg/m^2, 3.0 kg/m^2, 3.5 kg/m^2, 4.0 kg/m^2, 4.5 kg/m^2, 5.0 kg/m^2, 5.5 kg/m^2, 6.0 kg/m^2, 6.5 kg/m^2, 7.0 kg/m^2, 7.5 kg/m^2, 8.0 kg/m^2, 8.5 kg/m^2, 9.0 kg/m^2, 9.5 kg/m^2, 10.0 kg/m^2, 10.5 kg/m^2, 11.0 kg/m^2, 11.5 kg/m^2, or 12.0 kg/m^2 ;

(kk) a reduction in an inflammatory transcript level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(ll) a reduction in an inflammatory protein level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(mm) an increase in FAACT score compared to baseline or control by at least 1, 2, 3, 4, or 5 points;

(nn) an increase in OS compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(oo) an increase in PFS compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(pp) an increase in BMI durability compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(qq) a reduction in time to cancer treatment failure compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%; and

(rr) a reduction in ctDNA levels compared to baseline or control by at least about 10%, 20%, 30%m 40%, 50%, 60%, 70%, 80%, 90%, or 100%.

Fluorouracil

[0736] In some embodiments, the anti-cancer agent is an antimetabolite agent. In some embodiments, the antimetabolite agent is a fluorouracil. In some embodiments, the fluorouracil is 5-fluorouracil (5-FU).

[0737] In some embodiments, fluorouracil is administered hourly, daily, weekly, biweekly, monthly, or bimonthly. In some embodiments, fluorouracil is administered through continuous infusion. In some embodiments, fluorouracil is administered per day or per cycle at a dose of about 50 mg/m^2 to about 7500 mg/m^2. In some embodiments, fluorouracil is administered per cycle at a dose of at least 50 mg/m^2 to at least 7500 mg/m^2. In some embodiments, fluorouracil is administered per cycle at a dose of at least about 50 mg/m^2 to at least about 7500 mg/m^2.

[0738] In some embodiments, fluorouracil is administered a dose of about 50 mg/m^2, 60 mg/m^2, 70 mg/m^2, 80 mg/m^2, 90 mg/m^2, 100 mg/m^2, 125 mg/m^2, 150 mg/m^2, 175 mg/m^2, 200 mg/m^2, 225 mg/m^2, 250 mg/m^2, 275 mg/m^2, 300 mg/m^2, 325 mg/m^2, 350 mg/m^2, 375 mg/m^2, 400 mg/m^2, 425 mg/m^2, 450 mg/m^2, 475 mg/m^2, 500 mg/m^2, 550 mg/m^2, 600 mg/m^2, 650 mg/m^2, or 700 mg/m^2 or more per day or per cycle. In

some embodiments, the fluorouracil is administered once daily. In some embodiments, the fluorouracil is administered once daily for 1 day to 10 weeks.

[0739] In some embodiments, fluorouracil is administered at a dose of about 400 mg/m^2, followed by 2400 mg/m^2 to 3000 mg/m^2.

[0740] In some embodiments, fluorouracil is administered at a dose of 2400 mg/m^2 to 3000 mg/m^2 over 46 hours every two weeks. In some embodiments, fluorouracil is administered over 46 hours every two weeks. In some embodiments, fluorouracil is administered at a dose of 500 mg/m^2 on days 1, 8, 15, 22, 29, and 36 in 8-week cycles. In some embodiments, fluorouracil is administered at a dose of 500 mg/m^2 or 600 mg/m^2 on days 1 and 8 every 28 days for 6 cycles. In some embodiments, fluorouracil is administered at a dose of 200 mg/m^2 to 1000 mg/m^2 over 24 hours.

[0741] In some embodiments, administration of the fluorouracil is associated with one or more symptoms selected from the group consisting of vomiting, nausea, abdominal discomfort or pain, anorexia, fatigue, diarrhea, weight loss, fat mass loss, muscle mass loss, cardiac muscle loss, and general weakness. In some embodiments, nausea or vomiting may begin within 1 minute to 24 hours after administration of fluorouracil. In some embodiments, nausea or vomiting lasts up to 1 hour to one week after administration of fluorouracil. In some embodiments, nausea or vomiting beings or persists 1 minute to one week after administration of fluorouracil. In some embodiments, the administration of fluorouracil and a non-naturally occurring melanocortin analog reduces or prevents one or more of these symptoms.

[0742] In some embodiments, nausea or vomiting may begin within 1 to 24 hours after administration of fluorouracil. In some embodiments, nausea or vomiting lasts up to 1 hour to 24 hours after administration of fluorouracil. In some embodiments, nausea or vomiting begins or persists 24 hours or more after administration of fluorouracil. In some embodiments, the administration of fluorouracil and a non-naturally occurring melanocortin analog reduces or prevents one or more of these symptoms.

[0743] In some embodiments, fluorouracil is administered before, during, or after administration of a non-naturally occurring melanocortin analog. In some embodiments, fluorouracil is administered at a dose of 50 mg/m^2 to about 7500 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0744] In some embodiments, fluorouracil is administered at a dose of at least 50 mg/m^2 to at least 7500 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0745] In some embodiments, fluorouracil is administered at a dose of at least about 50 mg/m^2 to at least about 7500 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0746] In some embodiments, fluorouracil is administered at a dose of about 50 mg/m^2, 60 mg/m^2, 70 mg/m^2, 80 mg/m^2, 90 mg/m^2, 100 mg/m^2, 125 mg/m^2, 150 mg/m^2, 175 mg/m^2, 200 mg/m^2, 225 mg/m^2, 250 mg/m^2, 275 mg/m^2, 300 mg/m^2, 325 mg/m^2, 350 mg/m^2, 375 mg/m^2, 400 mg/m^2, 425 mg/m^2, 450 mg/m^2, 475 mg/m^2, 500 mg/m^2, 550 mg/m^2, 600 mg/m^2, 650 mg/m^2, or 700 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0747] In some embodiments, fluorouracil is administered at a dose of at least 50 mg/m^2, 60 mg/m^2, 70 mg/m^2, 80 mg/m^2, 90 mg/m^2, 100 mg/m^2, 125 mg/m^2, 150 mg/m^2, 175 mg/m^2, 200 mg/m^2, 225 mg/m^2, 250 mg/m^2, 275 mg/m^2, 300 mg/m^2, 325 mg/m^2, 350 mg/m^2, 375 mg/m^2, 400 mg/m^2, 425 mg/m^2, 450 mg/m^2, 475 mg/m^2, 500 mg/m^2, 550 mg/m^2, 600 mg/m^2, 650 mg/m^2, or 700 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0748] In some embodiments, fluorouracil is administered at a dose of at least about 50 mg/m^2, 60 mg/m^2, 70 mg/m^2, 80 mg/m^2, 90 mg/m^2, 100 mg/m^2, 125 mg/m^2, 150 mg/m^2, 175 mg/m^2, 200 mg/m^2, 225 mg/m^2, 250 mg/m^2, 275 mg/m^2, 300 mg/m^2, 325 mg/m^2, 350 mg/m^2, 375 mg/m^2, 400 mg/m^2, 425 mg/m^2, 450 mg/m^2, 475 mg/m^2, 500 mg/m^2, 550 mg/m^2, 600 mg/m^2, 650 mg/m^2, or 700 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0749] In some embodiments, the fluorouracil is administered hourly, twice daily, once daily, once every 2 days, once every 3 days, once every 4 days, once every 5 days, or once a week.

[0750] In some embodiments, the fluorouracil is administered by continuous 1-hour, 2-hour, 3-hour, 4-hour, 5-hour, 6-hour, 7-hour, 8-hour, 9-hour, 10-hour, 12-hour, 14-hour, 16-hour, 18-hour, 20-hour, 22-hour, 24-hour, 36-hour, or 72-hour infusion. In some embodiments, fluorouracil is administered by daily pulse doses. In some

embodiments, the subject has received one or more of a nutritive therapy, a nutritional supplement, an antiemetic, or a therapeutic for preventing cancer associated wasting before during, or after administration of fluorouracil or the non-naturally occurring melanocortin analog.

[0751] In some embodiments, the subject administered the non-naturally occurring melanocortin analog before, during, or after administration of the fluorouracil exhibits one or more of a reduction in vomiting or nausea compared to baseline or control, a reduction in gastrointestinal side effects that are not vomiting or nausea compared to baseline or control, a reduction in asthenia compared to baseline or control, a reduction in anorexia compared to baseline or control, an increase in appetite compared to baseline or control, a reduction in fatigue compared to baseline or control, a reduction in diarrhea compared to baseline or control, an increase in body weight compared to baseline or control, a reduced rate of weight loss compared to baseline or control, an increase in skeletal muscle mass compared to baseline or control, a reduced rate of loss of skeletal muscle mass compared to baseline or control, an increase in cardiac muscle mass compared to baseline or control, a reduced rate of loss of cardiac muscle mass compared to baseline or control, an increase in fat mass compared to baseline or control, a reduced rate of loss of fat mass compared to baseline or control, an increase in bone density compared to baseline or control, a reduction in rate of loss of bone density compared to baseline or control, a reduction in general weakness compared to baseline or control, a reduction of ECOG performance score compared to baseline or control, a maintenance in ECOG performance score, an increase in KPS score compared to baseline or control, a maintenance in KPS score, no titration of fluorouracil treatment, a reduced titration of fluorouracil treatment compared to baseline or control, a reduction in iatrogenic injury, an increase in cumulative mass compared to baseline or control, a reduction in rate of loss of cumulative mass compared to baseline or control, an increase in net weight gain compared to baseline or control, an increase in cumulative food intake compared to baseline or control, an increase in BMI compared to baseline or control, a reduced BMI decline compared to baseline or control, or a reduced proinflammatory transcript/protein level compared to baseline or control.

[0752] In some embodiments, the subject administered the non-naturally occurring melanocortin analog before, during, or after administration of the fluorouracil exhibits one or more of

(a) a reduction in the onset of vomiting or nausea compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after fluorouracil administration;

(b) a reduction in the duration of vomiting or nausea compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 24 hours, 48 hours, 72 hours, 96 hours, 5 days, 6 days, or 7 days after fluorouracil administration;

(c) a reduction in the onset of abdominal discomfort or pain compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after fluorouracil administration;

(d) a reduction in the duration of abdominal discomfort or pain compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 24 hours, 48 hours, 72 hours, 96 hours, 5 days, 6 days, or 7 days after fluorouracil administration;

(e) a reduction in the onset of hemorrhagic colitis compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after fluorouracil administration;

(f) a reduction in the duration of hemorrhagic colitis compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after fluorouracil administration;

(g) a reduction in asthenia compared to baseline or control compared to control within about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after fluorouracil administration;

(h) a reduction in general physical deterioration to baseline or control compared to control measured by an increase in body mass index by about 0.25, 0.5, 1.0, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 5.75, 6, 6.26, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 9.25, 9.5, 9.75, or 10 or more;

(i) a reduction in the onset of influenza-like illness or chills about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after fluorouracil administration;

(j) a reduction in the duration of influenza-like illness or chills about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after fluorouracil administration;

(k) a reduction in anorexia compared to baseline or control measured by an increase in body mass index by about 0.25, 0.5, 1.0, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 5.75, 6, 6.26, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 9.25, 9.5, 9.75, or 10 or more;

(l) an increase in appetite compared to baseline or control, which may be measured by an increase in calorie consumption by about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 125%, 150%, 175%, 200%, 250%, 300%, 350%, 400%, 450%, or 500% or more;

(m) a reduction in fatigue compared to baseline or control, which may be measured by an increase in perceived energy or reduced energy expenditure about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about

48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after fluorouracil administration;

(n) a reduction in diarrhea compared to baseline or control about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after fluorouracil administration;

(o) an increase in body weight compared to baseline or control measured by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 225%, 250%, 275%, 300%, 350%, 400%, 450%, or 500%;

(p) a reduced rate of weight loss compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(q) an increase in skeletal mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(r) a reduction in rate of loss of skeletal mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(s) an increase in cardiac mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(t) a reduction in rate of loss of cardiac mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(u) an increase in fat mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(v) a reduction in rate of loss of fat mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(w) an increase in bone density compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(x) a reduction in rate of loss of bone density compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(y) a reduction in general weakness compared to baseline or control as measured by an increase perceived or exerted force without increased energy expenditure about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after administration of fluorouracil;

(z) a maintenance in ECOG performance score or a reduction in ECOG performance score compared to baseline or control by about 1, 2, or 3;

(aa) a maintenance in KPS score or an increase in KPS score compared to baseline or control by about 100, 90, 80, 70, 60, 50, 40, or 30;

(bb) a reduction in titration of fluorouracil treatment by about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% compared to baseline or control;

(cc) an increase in tolerance of administered dose of fluorouracil treatment compared to baseline or control by about 1 mg/m^2, 2 mg/m^2, 5 mg/m^2, 10 mg/m^2, 25 mg/m^2, 50 mg/m^2, 75 mg/m^2, 100 mg/m^2, 150 mg/m^2, 200 mg/m^2, 250 mg/m^2, 300 mg/m^2, 350 mg/m^2, 400 mg/m^2, 450 mg/m^2, 500 mg/m^2, 600 mg/m^2, 700 mg/m^2, 800 mg/m^2, 900 mg/m^2, 1000 mg/m^2, 1250 mg/m^2, 1500 mg/m^2, 1750 mg/m^2, 2000 mg/m^2, 2500 mg/m^2, 3000 mg/m^2, 3500 mg/m^2, 4000 mg/m^2, 4500 mg/m^2, 5000 mg/m^2, 5500 mg/m^2, 6000 mg/m^2, 6500 mg/m^2, 7000 mg/m^2, 7500 mg/m^2 or more;

(dd) an increase in frequency of administration of fluorouracil treatment compared to baseline or control by about 1 hour, 12 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 2 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, or 6 months;

(ee) a reduction iatrogenic injury by about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% compared to baseline or control;

(ff) an increase in cumulative mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(gg) a reduction in rate of loss of cumulative mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(hh) an increase in net weight gain compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(ii) an increase in cumulative food intake compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(jj) an increase in BMI compared to baseline or control by at least about 0.5 kg/m^2, 1.0 kg/m^2, 1.5 kg/m^2, 2.0 kg/m^2, 2.5 kg/m^2, 3.0 kg/m^2, 3.5 kg/m^2, 4.0 kg/m^2, 4.5 kg/m^2, 5.0 kg/m^2, 5.5 kg/m^2, 6.0 kg/m^2, 6.5 kg/m^2, 7.0 kg/m^2, 7.5 kg/m^2, 8.0 kg/m^2, 8.5 kg/m^2, 9.0 kg/m^2, 9.5 kg/m^2, 10.0 kg/m^2, 10.5 kg/m^2, 11.0 kg/m^2, 11.5 kg/m^2, or 12.0 kg/m^2 ;

(kk) a reduction in an inflammatory transcript level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(ll) a reduction in an inflammatory protein level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(mm) an increase in FAACT score compared to baseline or control by at least 1, 2, 3, 4, or 5 points;

(nn) an increase in OS compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(oo) an increase in PFS compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(pp) an increase in BMI durability compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(qq) a reduction in time to cancer treatment failure compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%; and

(rr) a reduction in ctDNA levels compared to baseline or control by at least about 10%, 20%, 30%m 40%, 50%, 60%, 70%, 80%, 90%, or 100%.

Capecitabine

[0753] In some embodiments, the anti-cancer agent is an antimetabolite agent. In some embodiments, the antimetabolite agent is a capecitabine.

[0754] In some embodiments, capecitabine is administered hourly, daily, weekly, biweekly, monthly, or bimonthly. In some embodiments, capecitabine is administered through continuous infusion. In some embodiments, capecitabine is administered per day or per cycle at a dose of about 50 mg/m^2 to about 1500 mg/m^2. In some embodiments, capecitabine is administered per cycle at a dose of at least 50 mg/m^2 to at least 1500 mg/m^2. In some embodiments, capecitabine is administered per cycle at a dose of at least about 50 mg/m^2 to at least about 1500 mg/m^2.

[0755] In some embodiments, capecitabine is administered a dose of about 50 mg/m^2, 60 mg/m^2, 70 mg/m^2, 80 mg/m^2, 90 mg/m^2, 100 mg/m^2, 125 mg/m^2, 150 mg/m^2, 175 mg/m^2, 200 mg/m^2, 225 mg/m^2, 250 mg/m^2, 275 mg/m^2, 300 mg/m^2, 325 mg/m^2, 350 mg/m^2, 375 mg/m^2, 400 mg/m^2, 425 mg/m^2, 450 mg/m^2, 475 mg/m^2, 500 mg/m^2, 550 mg/m^2, 600 mg/m^2, 650 mg/m^2, 700 mg/m^2, 800 mg/m^2, 900 mg/m^2, 1000 mg/m^2, 1100 mg/m^2, 1200 mg/m^2, 1300 mg/m^2, 1400 mg/m^2, 1500 mg/m^2 or more per day or per cycle. In some embodiments, the capecitabine is administered once daily. In some embodiments, the capecitabine is administered once daily for 1 day to 3 weeks.

[0756] In some embodiments, capecitabine is administered at a dose of about 1250 mg/m^2 twice daily for 2 weeks followed by a one-week rest period in 3-week cycles. In some embodiments, capecitabine is administered at a dose of about 937.5 mg/m^2, 625 mg/m^2, or 312.5 mg/m^2 twice daily.

[0757] In some embodiments, administration of the capecitabine is associated with one or more symptoms selected from the group consisting of vomiting, nausea, abdominal discomfort or pain, anorexia, fatigue, diarrhea, weight loss, fat mass loss, muscle mass loss, cardiac muscle loss, and general weakness. In some embodiments, nausea or vomiting may begin within 1 minute to 24 hours after administration of capecitabine. In some embodiments, nausea or vomiting lasts up to 1 hour to one week after administration of capecitabine. In some embodiments, nausea or vomiting beings or persists 1 minute to one week after administration of capecitabine. In some embodiments, the administration of capecitabine and a non-naturally occurring melanocortin analog reduces or prevents one or more of these symptoms.

[0758] In some embodiments, nausea or vomiting may begin within 1 to 24 hours after administration of capecitabine. In some embodiments, nausea or vomiting lasts up to 1 hour to 24 hours after administration of capecitabine. In some embodiments, nausea or vomiting begins or persists 24 hours or more after administration of capecitabine. In some embodiments, the administration of capecitabine and a non-naturally occurring melanocortin analog reduces or prevents one or more of these symptoms.

[0759] In some embodiments, capecitabine is administered before, during, or after administration of a non-naturally occurring melanocortin analog. In some embodiments, capecitabine is administered at a dose of 50 mg/m^2 to about 4000 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0760] In some embodiments, capecitabine is administered at a dose of at least 50 mg/m^2 to at least 3000 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0761] In some embodiments, capecitabine is administered at a dose of at least about 50 mg/m^2 to at least about 3000 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0762] In some embodiments, capecitabine is administered at a dose of about 50 mg/m^2, 60 mg/m^2, 70 mg/m^2, 80 mg/m^2, 90 mg/m^2, 100 mg/m^2, 125 mg/m^2, 150 mg/m^2, 175 mg/m^2, 200 mg/m^2, 225 mg/m^2, 250 mg/m^2, 275 mg/m^2, 300 mg/m^2, 325 mg/m^2, 350 mg/m^2, 375 mg/m^2, 400 mg/m^2, 425 mg/m^2, 450 mg/m^2, 475 mg/m^2, 500 mg/m^2, 550 mg/m^2, 600 mg/m^2, 650 mg/m^2, 700 mg/m^2, 750 mg/m^2, 800 mg/m^2, 850 mg/m^2, 900 mg/m^2, 1000 mg/m^2, 1100 mg/m^2, 1200 mg/m^2, 1250 mg/m^2, 2000 mg/m^2, 2500 mg/m^2, 3000 mg/m^2, or 4000 mg/m^2 or more per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0763] In some embodiments, capecitabine is administered at a dose of at least 50 mg/m^2, 60 mg/m^2, 70 mg/m^2, 80 mg/m^2, 90 mg/m^2, 100 mg/m^2, 125 mg/m^2, 150 mg/m^2, 175 mg/m^2, 200 mg/m^2, 225 mg/m^2, 250 mg/m^2, 275 mg/m^2, 300 mg/m^2, 325 mg/m^2, 350 mg/m^2, 375 mg/m^2, 400 mg/m^2, 425 mg/m^2, 450 mg/m^2, 475 mg/m^2, 500 mg/m^2, 550 mg/m^2, 600 mg/m^2, 650 mg/m^2, 700 mg/m^2, 750 mg/m^2, 800 mg/m^2, 850 mg/m^2, 900 mg/m^2, 1000 mg/m^2, 1100 mg/m^2, 1200 mg/m^2, 1250 mg/m^2, 2000 mg/m^2, 2500 mg/m^2, 3000 mg/m^2, or 4000 mg/m^2 or more per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0764] In some embodiments, capecitabine is administered at a dose of at least about 50 mg/m^2, 60 mg/m^2, 70 mg/m^2, 80 mg/m^2, 90 mg/m^2, 100 mg/m^2, 125 mg/m^2, 150 mg/m^2, 175 mg/m^2, 200 mg/m^2, 225 mg/m^2, 250 mg/m^2, 275 mg/m^2, 300 mg/m^2, 325 mg/m^2, 350 mg/m^2, 375 mg/m^2, 400 mg/m^2, 425 mg/m^2, 450 mg/m^2, 475 mg/m^2, 500 mg/m^2, 550 mg/m^2, 600 mg/m^2, 650 mg/m^2, 700 mg/m^2, 750 mg/m^2, 800 mg/m^2, 850 mg/m^2, 900 mg/m^2, 1000 mg/m^2, 1100 mg/m^2, 1200 mg/m^2, 1250 mg/m^2, 2000 mg/m^2, 2500 mg/m^2, 3000 mg/m^2, or 4000 mg/m^2 or more per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0765] In some embodiments, the capecitabine is administered hourly, twice daily, once daily, once every 2 days, once every 3 days, once every 4 days, once every 5 days, or once a week.

[0766] In some embodiments, the capecitabine is administered by continuous 1-hour, 2-hour, 3-hour, 4-hour, 5-hour, 6-hour, 7-hour, 8-hour, 9-hour, 10-hour, 12-hour, 14-hour, 16-hour, 18-hour, 20-hour, 22-hour, 24-hour, 36-hour, or 72-hour infusion.

[0767] In some embodiments, capecitabine is administered by daily pulse doses. In some embodiments, the subject has received one or more of a nutritive therapy, a

nutritional supplement, an antiemetic, or a therapeutic for preventing cancer associated wasting before during, or after administration of capecitabine or the non-naturally occurring melanocortin analog.

[0768] In some embodiments, the subject administered the non-naturally occurring melanocortin analog before, during, or after administration of the capecitabine exhibits one or more of a reduction in vomiting or nausea compared to baseline or control, a reduction in gastrointestinal side effects that are not vomiting or nausea compared to baseline or control, a reduction in asthenia compared to baseline or control, a reduction in anorexia compared to baseline or control, an increase in appetite compared to baseline or control, a reduction in fatigue compared to baseline or control, a reduction in diarrhea compared to baseline or control, an increase in body weight compared to baseline or control, a reduced rate of weight loss compared to baseline or control, an increase in skeletal muscle mass compared to baseline or control, a reduced rate of loss of skeletal muscle mass compared to baseline or control, an increase in cardiac muscle mass compared to baseline or control, a reduced rate of loss of cardiac muscle mass compared to baseline or control, an increase in fat mass compared to baseline or control, a reduced rate of loss of fat mass compared to baseline or control, an increase in bone density compared to baseline or control, a reduction in rate of loss of bone density compared to baseline or control, a reduction in general weakness compared to baseline or control, a reduction of ECOG performance score compared to baseline or control, a maintenance in ECOG performance score, an increase in KPS score compared to baseline or control, a maintenance in KPS score, no titration of capecitabine treatment, a reduced titration of capecitabine treatment compared to baseline or control, a reduction in iatrogenic injury, an increase in cumulative mass compared to baseline or control, a reduction in rate of loss of cumulative mass compared to baseline or control, an increase in net weight gain compared to baseline or control, an increase in cumulative food intake compared to baseline or control, an increase in BMI compared to baseline or control, a reduced BMI decline compared to baseline or control, or a reduced proinflammatory transcript/protein level compared to baseline or control.

[0769] In some embodiments, the subject administered the non-naturally occurring melanocortin analog before, during, or after administration of capecitabine exhibits one or more of

(a) a reduction in the onset of vomiting or nausea compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after capecitabine administration;

(b) a reduction in the duration of vomiting or nausea compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 24 hours, 48 hours, 72 hours, 96 hours, 5 days, 6 days, or 7 days after capecitabine administration;

(c) a reduction in the onset of abdominal discomfort or pain compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after capecitabine administration;

(d) a reduction in the duration of abdominal discomfort or pain compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 24 hours, 48 hours, 72 hours, 96 hours, 5 days, 6 days, or 7 days after capecitabine administration;

(e) a reduction in the onset of hemorrhagic colitis compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after capecitabine administration;

(f) a reduction in the duration of hemorrhagic colitis compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after capecitabine administration;

(g) a reduction in asthenia compared to baseline or control compared to control within about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after capecitabine administration;

(h) a reduction in general physical deterioration to baseline or control compared to control measured by an increase in body mass index by about 0.25, 0.5, 1.0, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 5.75, 6, 6.26, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 9.25, 9.5, 9.75, or 10 or more;

(i) a reduction in the onset of influenza-like illness or chills about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after capecitabine administration;

(j) a reduction in the duration of influenza-like illness or chills about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after capecitabine administration;

(k) a reduction in anorexia compared to baseline or control measured by an increase in body mass index by about 0.25, 0.5, 1.0, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 5.75, 6, 6.26, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 9.25, 9.5, 9.75, or 10 or more;

(l) an increase in appetite compared to baseline or control, which may be measured by an increase in calorie consumption by about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 125%, 150%, 175%, 200%, 250%, 300%, 350%, 400%, 450%, or 500% or more;

(m) a reduction in fatigue compared to baseline or control, which may be measured by an increase in perceived energy or reduced energy expenditure about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about

48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after capecitabine administration;

(n) a reduction in diarrhea compared to baseline or control about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after capecitabine administration;

(o) an increase in body weight compared to baseline or control measured by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 225%, 250%, 275%, 300%, 350%, 400%, 450%, or 500%;

(p) a reduced rate of weight loss compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(q) an increase in skeletal mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(r) a reduction in rate of loss of skeletal mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(s) an increase in cardiac mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(t) a reduction in rate of loss of cardiac mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(u) an increase in fat mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(v) a reduction in rate of loss of fat mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(w) an increase in bone density compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(x) a reduction in rate of loss of bone density compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(y) a reduction in general weakness compared to baseline or control as measured by an increase perceived or exerted force without increased energy expenditure about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after administration of capecitabine;

(z) a maintenance in ECOG performance score or a reduction in ECOG performance score compared to baseline or control by about 1, 2, or 3;

(aa) a maintenance in KPS score or an increase in KPS score compared to baseline or control by about 100, 90, 80, 70, 60, 50, 40, or 30;

(bb) a reduction in titration of capecitabine treatment by about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% compared to baseline or control;

(cc) an increase in tolerance of administered dose of capecitabine treatment compared to baseline or control by about 1 mg/m^2, 2 mg/m^2, 5 mg/m^2, 10 mg/m^2, 25 mg/m^2, 50 mg/m^2, 75 mg/m^2, 100 mg/m^2, 150 mg/m^2, 200 mg/m^2, 250 mg/m^2, 300 mg/m^2, 350 mg/m^2, 400 mg/m^2, 450 mg/m^2, 500 mg/m^2, 600 mg/m^2, 700 mg/m^2, 800 mg/m^2, 900 mg/m^2, 1000 mg/m^2, 1250 mg/m^2, 1500 mg/m^2, or more;

(dd) an increase in frequency of administration of capecitabine treatment compared to baseline or control by about 1 hour, 12 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6

days, 7 days, 10 days, 2 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, or 6 months;

(ee) a reduction iatrogenic injury by about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% compared to baseline or control;

(ff) an increase in cumulative mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(gg) a reduction in rate of loss of cumulative mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(hh) an increase in net weight gain compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(ii) an increase in cumulative food intake compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(jj) an increase in BMI compared to baseline or control by at least about 0.5 kg/m^2, 1.0 kg/m^2, 1.5 kg/m^2, 2.0 kg/m^2, 2.5 kg/m^2, 3.0 kg/m^2, 3.5 kg/m^2, 4.0 kg/m^2, 4.5 kg/m^2, 5.0 kg/m^2, 5.5 kg/m^2, 6.0 kg/m^2, 6.5 kg/m^2, 7.0 kg/m^2, 7.5 kg/m^2, 8.0 kg/m^2, 8.5 kg/m^2, 9.0 kg/m^2, 9.5 kg/m^2, 10.0 kg/m^2, 10.5 kg/m^2, 11.0 kg/m^2, 11.5 kg/m^2, or 12.0 kg/m^2 ;

(kk) a reduction in an inflammatory transcript level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(ll) a reduction in an inflammatory protein level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(mm) an increase in FAACT score compared to baseline or control by at least 1, 2, 3, 4, or 5 points;

(nn) an increase in OS compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(oo) an increase in PFS compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(pp) an increase in BMI durability compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(qq) a reduction in time to cancer treatment failure compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%; and

(rr) a reduction in ctDNA levels compared to baseline or control by at least about 10%, 20%, 30%m 40%, 50%, 60%, 70%, 80%, 90%, or 100%.

Fludarabine

[0770] In some embodiments, the anti-cancer agent is an antimetabolite agent. In some embodiments, the antimetabolite agent is a fludarabine. In some embodiments, the fludarabine is fludarabine phosphate or fludarabine nucleotide analog.

[0771] In some embodiments, fludarabine is administered hourly, daily, weekly, biweekly, monthly, or bimonthly. In some embodiments, fludarabine is administered through continuous infusion. In some embodiments, fludarabine is administered per day or per cycle at a dose of about 5 mg/m^2 to about 100 mg/m^2. In some embodiments, fludarabine is administered per cycle at a dose of at least 5 mg/m^2 to at least 100 mg/m^2. In some embodiments, fludarabine is administered per cycle at a dose of at least about 5 mg/m^2 to at least about 100 mg/m^2.

[0772] In some embodiments, fludarabine is administered a dose of about 10 mg/m^2, 15 mg/m^2, 20 mg/m^2, 25 mg/m^2, 30 mg/m^2, 35 mg/m^2, 40 mg/m^2, 45 mg/m^2, 50 mg/m^2, 55 mg/m^2, 60 mg/m^2, 65 mg/m^2, 70 mg/m^2, 75 mg/m^2, 80 mg/m^2, 85 mg/m^2, 90 mg/m^2, 95 mg/m^2, or 100 mg/m^2 or more per day or per cycle. In some embodiments, the fludarabine is administered once daily. In some embodiments, the fludarabine is administered once daily for 1 day to 3 weeks.

[0773] In some embodiments, fludarabine is administered at a dose of about 96 mg/m^2 per day for 5 to 7 days. In some embodiments, fludarabine is administered at a dose of about 22 to 40 mg/m^2 daily for 5 days every 28 days. In some embodiments, fludarabine is administered at a dose of about 15 to 25 mg/m^2 daily for 5 days every 28

days. In some embodiments, fludarabine is administered at a dose of about 1, 10, or 30 mg/kg per day.

[0774] In some embodiments, administration of the fludarabine is associated with one or more symptoms selected from the group consisting of vomiting, nausea, abdominal discomfort or pain, anorexia, fatigue, diarrhea, weight loss, fat mass loss, muscle mass loss, cardiac muscle loss, and general weakness. In some embodiments, nausea or vomiting may begin within 1 minute to 24 hours after administration of fludarabine. In some embodiments, nausea or vomiting lasts up to 1 hour to one week after administration of fludarabine. In some embodiments, nausea or vomiting beings or persists 1 minute to one week after administration of fludarabine. In some embodiments, the administration of fludarabine and a non-naturally occurring melanocortin analog reduces or prevents one or more of these symptoms.

[0775] In some embodiments, nausea or vomiting may begin within 1 to 24 hours after administration of fludarabine. In some embodiments, nausea or vomiting lasts up to 1 hour to 24 hours after administration of fludarabine. In some embodiments, nausea or vomiting begins or persists 24 hours or more after administration of fludarabine. In some embodiments, the administration of fludarabine and a non-naturally occurring melanocortin analog reduces or prevents one or more of these symptoms.

[0776] In some embodiments, fludarabine is administered before, during, or after administration of a non-naturally occurring melanocortin analog. In some embodiments, fludarabine is administered at a dose of 10 mg/m^2 to about 300 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog. In some embodiments, fludarabine is administered at a dose of at least 50 mg/m^2 to at least 3000 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog. In some embodiments, fludarabine is administered at a dose of at least about 10 mg/m^2 to at least about 300 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog. In some embodiments, fludarabine is administered at a dose of about 10 mg/m^2, 15 mg/m^2, 20 mg/m^2, 25 mg/m^2, 30 mg/m^2, 35 mg/m^2, 40 mg/m^2, 45 mg/m^2, 50 mg/m^2, 55 mg/m^2, 60 mg/m^2, 65 mg/m^2, 70 mg/m^2, 75 mg/m^2, 80 mg/m^2, 85 mg/m^2, 90 mg/m^2, 95 mg/m^2, 100 mg/m^2, 125 mg/m^2, 150 mg/m^2, 175 mg/m^2, 200 mg/m^2, 225 mg/m^2, 250 mg/m^2, 275 mg/m^2, 300 mg/m^2, 325 mg/m^2, 350 mg/m^2, 375 mg/m^2, 400 mg/m^2, 425 mg/m^2, 450

mg/m^2, 475 mg/m^2, 500 mg/m^2, 550 mg/m^2, 600 mg/m^2, 650 mg/m^2, 700 mg/m^2, 750 mg/m^2, 800 mg/m^2, 850 mg/m^2, 900 mg/m^2, 1000 mg/m^2, 1100 mg/m^2, 1200 mg/m^2, 1250 mg/m^2, 2000 mg/m^2, 2500 mg/m^2, 3000 mg/m^2, or 4000 mg/m^2 or more per day before, during, or after administration of the non-naturally occurring melanocortin analog. In some embodiments, fludarabine is administered at a dose of at 10 mg/m^2, 15 mg/m^2, 20 mg/m^2, 25 mg/m^2, 30 mg/m^2, 35 mg/m^2, 40 mg/m^2, 45 mg/m^2, 50 mg/m^2, 55 mg/m^2, 60 mg/m^2, 65 mg/m^2, 70 mg/m^2, 75 mg/m^2, 80 mg/m^2, 85 mg/m^2, 90 mg/m^2, 95 mg/m^2, 100 mg/m^2, 125 mg/m^2, 150 mg/m^2, 175 mg/m^2, 200 mg/m^2, 225 mg/m^2, 250 mg/m^2, 275 mg/m^2, 300 mg/m^2, 325 mg/m^2, 350 mg/m^2, 375 mg/m^2, 400 mg/m^2, 425 mg/m^2, 450 mg/m^2, 475 mg/m^2, 500 mg/m^2, 550 mg/m^2, 600 mg/m^2, 650 mg/m^2, 700 mg/m^2, 750 mg/m^2, 800 mg/m^2, 850 mg/m^2, 900 mg/m^2, 1000 mg/m^2, 1100 mg/m^2, 1200 mg/m^2, 1250 mg/m^2, 2000 mg/m^2, 2500 mg/m^2, 3000 mg/m^2, or 4000 mg/m^2 or more per day before, during, or after administration of the non-naturally occurring melanocortin analog. In some embodiments, fludarabine is administered at a dose of at least about 10 mg/m^2, 15 mg/m^2, 20 mg/m^2, 25 mg/m^2, 30 mg/m^2, 35 mg/m^2, 40 mg/m^2, 45 mg/m^2, 50 mg/m^2, 55 mg/m^2, 60 mg/m^2, 65 mg/m^2, 70 mg/m^2, 75 mg/m^2, 80 mg/m^2, 85 mg/m^2, 90 mg/m^2, 95 mg/m^2, 100 mg/m^2, 125 mg/m^2, 150 mg/m^2, 175 mg/m^2, 200 mg/m^2, 225 mg/m^2, 250 mg/m^2, 275 mg/m^2, 300 mg/m^2, 325 mg/m^2, 350 mg/m^2, 375 mg/m^2, 400 mg/m^2, 425 mg/m^2, 450 mg/m^2, 475 mg/m^2, 500 mg/m^2, 550 mg/m^2, 600 mg/m^2, 650 mg/m^2, 700 mg/m^2, 750 mg/m^2, 800 mg/m^2, 850 mg/m^2, 900 mg/m^2, 1000 mg/m^2, 1100 mg/m^2, 1200 mg/m^2, 1250 mg/m^2, 2000 mg/m^2, 2500 mg/m^2, 3000 mg/m^2, or 4000 mg/m^2 or more per day before, during, or after administration of the non-naturally occurring melanocortin analog. In some embodiments, the fludarabine is administered hourly, twice daily, once daily, once every 2 days, once every 3 days, once every 4 days, once every 5 days, or once a week. In some embodiments, the fludarabine is administered by continuous 1-hour, 2-hour, 3-hour, 4-hour, 5-hour, 6-hour, 7-hour, 8-hour, 9-hour, 10-hour, 12-hour, 14-hour, 16-hour, 18-hour, 20-hour, 22-hour, 24-hour, 36-hour, or 72-hour infusion. In some embodiments, fludarabine is administered by daily pulse doses. In some embodiments, the subject has received one or more of a nutritive therapy, a nutritional supplement, an antiemetic, or a therapeutic for preventing cancer associated wasting before during, or after administration of fludarabine or the non-naturally occurring melanocortin analog.

[0777] In some embodiments, the subject administered the non-naturally occurring melanocortin analog before, during, or after administration of the fludarabine exhibits one or more of a reduction in vomiting or nausea compared to baseline or control, a reduction in gastrointestinal side effects that are not vomiting or nausea compared to baseline or control, a reduction in asthenia compared to baseline or control, a reduction in anorexia compared to baseline or control, an increase in appetite compared to baseline or control, a reduction in fatigue compared to baseline or control, a reduction in diarrhea compared to baseline or control, an increase in body weight compared to baseline or control, a reduced rate of weight loss compared to baseline or control, an increase in skeletal muscle mass compared to baseline or control, a reduced rate of loss of skeletal muscle mass compared to baseline or control, an increase in cardiac muscle mass compared to baseline or control, a reduced rate of loss of cardiac muscle mass compared to baseline or control, an increase in fat mass compared to baseline or control, a reduced rate of loss of fat mass compared to baseline or control, an increase in bone density compared to baseline or control, a reduction in rate of loss of bone density compared to baseline or control, a reduction in general weakness compared to baseline or control, a reduction of ECOG performance score compared to baseline or control, a maintenance in ECOG performance score, an increase in KPS score compared to baseline or control, a maintenance in KPS score, no titration of fludarabine treatment, a reduced titration of fludarabine treatment compared to baseline or control, a reduction in iatrogenic injury, an increase in cumulative mass compared to baseline or control, a reduction in rate of loss of cumulative mass compared to baseline or control, an increase in net weight gain compared to baseline or control, an increase in cumulative food intake compared to baseline or control, an increase in BMI compared to baseline or control, a reduced BMI decline compared to baseline or control, or a reduced proinflammatory transcript/protein level compared to baseline or control.

[0778] In some embodiments, the subject administered the non-naturally occurring melanocortin analog before, during, or after administration of fludarabine exhibits one or more of

(a) a reduction in the onset of vomiting or nausea compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19

hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after fludarabine administration;

(b) a reduction in the duration of vomiting or nausea compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 24 hours, 48 hours, 72 hours, 96 hours, 5 days, 6 days, or 7 days after fludarabine administration;

(c) a reduction in the onset of abdominal discomfort or pain compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after fludarabine administration;

(d) a reduction in the duration of abdominal discomfort or pain compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 24 hours, 48 hours, 72 hours, 96 hours, 5 days, 6 days, or 7 days after fludarabine administration;

(e) a reduction in the onset of hemorrhagic colitis compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after fludarabine administration;

(f) a reduction in the duration of hemorrhagic colitis compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after fludarabine administration;

(g) a reduction in asthenia compared to baseline or control compared to control within about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours,

about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after fludarabine administration;

(h) a reduction in general physical deterioration to baseline or control compared to control measured by an increase in body mass index by about 0.25, 0.5, 1.0, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 5.75, 6, 6.26, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 9.25, 9.5, 9.75, or 10 or more;

(i) a reduction in the onset of influenza-like illness or chills about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after fludarabine administration;

(j) a reduction in the duration of influenza-like illness or chills about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after fludarabine administration;

(k) a reduction in anorexia compared to baseline or control measured by an increase in body mass index by about 0.25, 0.5, 1.0, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 5.75, 6, 6.26, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 9.25, 9.5, 9.75, or 10 or more;

(l) an increase in appetite compared to baseline or control, which may be measured by an increase in calorie consumption by about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 125%, 150%, 175%, 200%, 250%, 300%, 350%, 400%, 450%, or 500% or more;

(m) a reduction in fatigue compared to baseline or control, which may be measured by an increase in perceived energy or reduced energy expenditure about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after fludarabine administration;

(n) a reduction in diarrhea compared to baseline or control about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8

hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after fludarabine administration;

(o) an increase in body weight compared to baseline or control measured by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 225%, 250%, 275%, 300%, 350%, 400%, 450%, or 500%;

(p) a reduced rate of weight loss compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(q) an increase in skeletal mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(r) a reduction in rate of loss of skeletal mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(s) an increase in cardiac mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(t) a reduction in rate of loss of cardiac mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(u) an increase in fat mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(v) a reduction in rate of loss of fat mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(w) an increase in bone density compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(x) a reduction in rate of loss of bone density compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(y) a reduction in general weakness compared to baseline or control as measured by an increase perceived or exerted force without increased energy expenditure about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after administration of fludarabine;

(z) a maintenance in ECOG performance score or a reduction in ECOG performance score compared to baseline or control by about 1, 2, or 3;

(aa) a maintenance in KPS score or an increase in KPS score compared to baseline or control by about 100, 90, 80, 70, 60, 50, 40, or 30;

(bb) a reduction in titration of fludarabine treatment by about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% compared to baseline or control;

(cc) an increase in tolerance of administered dose of fludarabine treatment compared to baseline or control by about 1 mg/m^2, 2 mg/m^2, 5 mg/m^2, 10 mg/m^2, 15 mg/m^2, 20 mg/m^2, 25 mg/m^2, 30 mg/m^2, 40 mg/m^2, 50 mg/m^2, 60 mg/m^2, 70 mg/m^2, 75 mg/m^2, 80 mg/m^2, 90 mg/m^2, 100 mg/m^2, or more;

(dd) an increase in frequency of administration of fludarabine treatment compared to baseline or control by about 1 hour, 12 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 2 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, or 6 months;

(ee) a reduction in iatrogenic injury by about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% compared to baseline or control;

(ff) an increase in cumulative mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(gg) a reduction in rate of loss of cumulative mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(hh) an increase in net weight gain compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(ii) an increase in cumulative food intake compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(jj) an increase in BMI compared to baseline or control by at least about 0.5 kg/m^2, 1.0 kg/m^2, 1.5 kg/m^2, 2.0 kg/m^2, 2.5 kg/m^2, 3.0 kg/m^2, 3.5 kg/m^2, 4.0 kg/m^2, 4.5 kg/m^2, 5.0 kg/m^2, 5.5 kg/m^2, 6.0 kg/m^2, 6.5 kg/m^2, 7.0 kg/m^2, 7.5 kg/m^2, 8.0 kg/m^2, 8.5 kg/m^2, 9.0 kg/m^2, 9.5 kg/m^2, 10.0 kg/m^2, 10.5 kg/m^2, 11.0 kg/m^2, 11.5 kg/m^2, or 12.0 kg/m^2 ;

(kk) a reduction in an inflammatory transcript level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(ll) a reduction in an inflammatory protein level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(mm) an increase in FAACT score compared to baseline or control by at least 1, 2, 3, 4, or 5 points;

(nn) an increase in OS compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(oo) an increase in PFS compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(pp) an increase in BMI durability compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(qq) a reduction in time to cancer treatment failure compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%; and

(rr) a reduction in ctDNA levels compared to baseline or control by at least about 10%, 20%, 30%m 40%, 50%, 60%, 70%, 80%, 90%, or 100%.

Gemcitabine

[0779] In some embodiments, the anti-cancer agent is an antimetabolite agent. In some embodiments, the antimetabolite agent is gemcitabine. In some embodiments, gemcitabine is gemcitabine hydrochloride.

[0780] In some embodiments, gemcitabine is administered hourly, daily, weekly, biweekly, monthly, or bimonthly. In some embodiments, gemcitabine is administered through continuous infusion. In some embodiments, gemcitabine is administered per day or per cycle at a dose of about 500 mg/m^2 to about 5000 mg/m^2.

[0781] In some embodiments, gemcitabine is administered per cycle at a dose of at least 500 mg/m^2 to at least 5000 mg/m^2.

[0782] In some embodiments gemcitabine is administered per cycle at a dose of at least about 500 mg/m^2 to at least about 5000 mg/m^2.

[0783] In some embodiments, gemcitabine is administered a dose of about 500 mg/m^2, 550 mg/m^2, 600 mg/m^2, 650 mg/m^2, 700 mg/m^2, 750 mg/m^2, 800 mg/m^2, 850 mg/m^2, 900 mg/m^2, 950 mg/m^2, 1000 mg/m^2, 1250 mg/m^2, 1500 mg/m^2, 1750 mg/m^2, 2000 mg/m^2, 2500 mg/m^2, 3000 mg/m^2, 4000 mg/m^2, or 5000 mg/m^2 or more per day or per cycle. In some embodiments, gemcitabine is administered once daily. In some embodiments, the gemcitabine is administered once daily for 1 day to 8 weeks.

[0784] In some embodiments, gemcitabine is administered at a dose of about 1000 mg/m² on days 1 and 8 per 21-day cycle.

[0785] In some embodiments, gemcitabine is administered at a dose of about 1250 mg/m² on days 1 and 8 per 21-day cycle.

[0786] In some embodiments, gemcitabine is administered at a dose of about 1000 mg/m² on days 1, 8, and 15 per 21-day cycle.

[0787] In some embodiments, gemcitabine is administered at a dose of about 1250 mg/m² on days 1, 8, and 15 per 21-day cycle.

[0788] In some embodiments, gemcitabine is administered at a dose of about 1000 mg/m² for 7 weeks. In some embodiments, gemcitabine is administered at a dose of about 1000 mg/m² for 3 weeks.

[0789] In some embodiments, administration of the gemcitabine is associated with one or more symptoms selected from the group consisting of vomiting, nausea, abdominal discomfort or pain, anorexia, fatigue, diarrhea, weight loss, fat mass loss, muscle mass loss, cardiac muscle loss, and general weakness. In some embodiments, nausea or vomiting may begin within 1 minute to 24 hours after administration of gemcitabine. In some embodiments, nausea or vomiting lasts up to 1 hour to one week after administration of gemcitabine. In some embodiments, nausea or vomiting beings or persists 1 minute to one week after administration of gemcitabine. In some embodiments, the administration of gemcitabine and a non-naturally occurring melanocortin analog reduces or prevents one or more of these symptoms.

[0790] In some embodiments, nausea or vomiting may begin within 1 to 24 hours after administration of gemcitabine. In some embodiments, nausea or vomiting lasts up to 1 hour to 24 hours after administration of gemcitabine. In some embodiments, nausea or vomiting begins or persists 24 hours or more after administration of gemcitabine. In some embodiments, the administration of gemcitabine and a non-naturally occurring melanocortin analog reduces or prevents one or more of these symptoms.

[0791] In some embodiments, gemcitabine is administered before, during, or after administration of a non-naturally occurring melanocortin analog. In some embodiments, fludarabine is administered at a dose of 50 mg/m^2 to about 5000 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0792] In some embodiments, gemcitabine is administered at a dose of at least 50 mg/m^2 to at least 5000 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0793] In some embodiments, gemcitabine is administered at a dose of at least about 50 mg/m^2 to at least about 5000 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0794] In some embodiments, gemcitabine is administered at a dose of about 50 mg/m^2, 55 mg/m^2, 60 mg/m^2, 65 mg/m^2, 70 mg/m^2, 75 mg/m^2, 80 mg/m^2, 85 mg/m^2, 90 mg/m^2, 95 mg/m^2, 100 mg/m^2, 125 mg/m^2, 150 mg/m^2, 175 mg/m^2, 200 mg/m^2, 225 mg/m^2, 250 mg/m^2, 275 mg/m^2, 300 mg/m^2, 325 mg/m^2, 350 mg/m^2, 375 mg/m^2, 400 mg/m^2, 425 mg/m^2, 450 mg/m^2, 475 mg/m^2, 500 mg/m^2, 550 mg/m^2, 600 mg/m^2, 650 mg/m^2, 700 mg/m^2, 750 mg/m^2, 800 mg/m^2, 850 mg/m^2, 900 mg/m^2, 1000 mg/m^2, 1100 mg/m^2, 1200 mg/m^2, 1250 mg/m^2, 2000 mg/m^2, 2500 mg/m^2, 3000 mg/m^2, 4000 mg/m^2, or 5000 mg/m^2 or more per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0795] In some embodiments, gemcitabine is administered at a dose of at 50 mg/m^2, 55 mg/m^2, 60 mg/m^2, 65 mg/m^2, 70 mg/m^2, 75 mg/m^2, 80 mg/m^2, 85 mg/m^2, 90 mg/m^2, 95 mg/m^2, 100 mg/m^2, 125 mg/m^2, 150 mg/m^2, 175 mg/m^2, 200 mg/m^2, 225 mg/m^2, 250 mg/m^2, 275 mg/m^2, 300 mg/m^2, 325 mg/m^2, 350 mg/m^2, 375 mg/m^2, 400 mg/m^2, 425 mg/m^2, 450 mg/m^2, 475 mg/m^2, 500 mg/m^2, 550 mg/m^2, 600 mg/m^2, 650 mg/m^2, 700 mg/m^2, 750 mg/m^2, 800 mg/m^2, 850 mg/m^2, 900 mg/m^2, 1000 mg/m^2, 1100 mg/m^2, 1200 mg/m^2, 1250 mg/m^2, 2000 mg/m^2, 2500 mg/m^2, 3000 mg/m^2, 4000 mg/m^2, or 5000 mg/m^2 or more per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0796] In some embodiments, gemcitabine is administered at a dose of at least about 50 mg/m^2, 55 mg/m^2, 60 mg/m^2, 65 mg/m^2, 70 mg/m^2, 75 mg/m^2, 80 mg/m^2, 85 mg/m^2, 90 mg/m^2, 95 mg/m^2, 100 mg/m^2, 125 mg/m^2, 150 mg/m^2, 175 mg/m^2, 200 mg/m^2, 225 mg/m^2, 250 mg/m^2, 275 mg/m^2, 300 mg/m^2, 325 mg/m^2, 350 mg/m^2, 375 mg/m^2, 400 mg/m^2, 425 mg/m^2, 450 mg/m^2, 475 mg/m^2, 500 mg/m^2, 550 mg/m^2, 600 mg/m^2, 650 mg/m^2, 700 mg/m^2, 750 mg/m^2, 800 mg/m^2, 850 mg/m^2, 900 mg/m^2, 1000 mg/m^2, 1100 mg/m^2, 1200 mg/m^2, 1250 mg/m^2, 2000 mg/m^2, 2500 mg/m^2, 3000 mg/m^2, 4000 mg/m^2, or 5000 mg/m^2 or more per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0797] In some embodiments, the gemcitabine is administered hourly, twice daily, once daily, once every 2 days, once every 3 days, once every 4 days, once every 5 days, or once a week.

[0798] In some embodiments, the gemcitabine is administered by continuous 1-hour, 2-hour, 3-hour, 4-hour, 5-hour, 6-hour, 7-hour, 8-hour, 9-hour, 10-hour, 12-hour, 14-hour, 16-hour, 18-hour, 20-hour, 22-hour, 24-hour, 36-hour, or 72-hour infusion. In some embodiments, gemcitabine is administered by daily pulse doses. In some embodiments, the subject has received one or more of a nutritive therapy, a nutritional supplement, an antiemetic, or a therapeutic for preventing cancer associated wasting before during, or after administration of gemcitabine or the non-naturally occurring melanocortin analog.

[0799] In some embodiments, the subject administered the non-naturally occurring melanocortin analog before, during, or after administration of the gemcitabine exhibits one or more of a reduction in vomiting or nausea compared to baseline or control, a reduction in gastrointestinal side effects that are not vomiting or nausea compared to baseline or control, a reduction in asthenia compared to baseline or control, a reduction in anorexia compared to baseline or control, an increase in appetite compared to baseline or control, a reduction in fatigue compared to baseline or control, a reduction in diarrhea compared to baseline or control, an increase in body weight compared to baseline or control, a reduced rate of weight loss compared to baseline or control, an increase in skeletal muscle mass compared to baseline or control, a reduced rate of loss of skeletal muscle mass compared to baseline or control, an increase in cardiac muscle mass compared to baseline or control, a reduced rate of loss of cardiac muscle mass compared to baseline or control, an increase in fat mass compared to baseline or control, a reduced rate of loss of fat mass compared to baseline or control, an increase in bone density compared to baseline or control, a reduction in rate of loss of bone density compared to baseline or control, a reduction in general weakness compared to baseline or control, a reduction of ECOG performance score compared to baseline or control, a maintenance in ECOG performance score, an increase in KPS score compared to baseline or control, a maintenance in KPS score, no titration of gemcitabine treatment, a reduced titration of gemcitabine treatment compared to baseline or control, a reduction in iatrogenic injury, an increase in cumulative mass compared to baseline or control, a reduction in rate of loss of cumulative mass

compared to baseline or control, an increase in net weight gain compared to baseline or control, an increase in cumulative food intake compared to baseline or control, an increase in BMI compared to baseline or control, a reduced BMI decline compared to baseline or control, or a reduced proinflammatory transcript/protein level compared to baseline or control.

[0800] In some embodiments, the subject administered the non-naturally occurring melanocortin analog before, during, or after administration of gemcitabine exhibits one or more of

(a) a reduction in the onset of vomiting or nausea compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after gemcitabine administration;

(b) a reduction in the duration of vomiting or nausea compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 24 hours, 48 hours, 72 hours, 96 hours, 5 days, 6 days, or 7 days after gemcitabine administration;

(c) a reduction in the onset of abdominal discomfort or pain compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after gemcitabine administration;

(d) a reduction in the duration of abdominal discomfort or pain compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 24 hours, 48 hours, 72 hours, 96 hours, 5 days, 6 days, or 7 days after gemcitabine administration;

(e) a reduction in the onset of hemorrhagic colitis compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19

hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after gemcitabine administration;

(f) a reduction in the duration of hemorrhagic colitis compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after gemcitabine administration;

(g) a reduction in asthenia compared to baseline or control compared to control within about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after gemcitabine administration;

(h) a reduction in general physical deterioration to baseline or control compared to control measured by an increase in body mass index by about 0.25, 0.5, 1.0, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 5.75, 6, 6.26, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 9.25, 9.5, 9.75, or 10 or more;

(i) a reduction in the onset of influenza-like illness or chills about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after gemcitabine administration;

(j) a reduction in the duration of influenza-like illness or chills about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after gemcitabine administration;

(k) a reduction in anorexia compared to baseline or control measured by an increase in body mass index by about 0.25, 0.5, 1.0, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 5.75, 6, 6.26, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 9.25, 9.5, 9.75, or 10 or more;

(l) an increase in appetite compared to baseline or control, which may be measured by an increase in calorie consumption by about 5%, 10%, 15%, 20%, 25%, 30%, 35%,

40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 125%, 150%, 175%, 200%, 250%, 300%, 350%, 400%, 450%, or 500% or more;

(m) an reduction in fatigue compared to baseline or control, which may be measured by an increase in perceived energy or reduced energy expenditure about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after gemcitabine administration;

(n) a reduction in diarrhea compared to baseline or control about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after gemcitabine administration;

(o) an increase in body weight compared to baseline or control measured by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 225%, 250%, 275%, 300%, 350%, 400%, 450%, or 500%;

(p) a reduced rate of weight loss compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(q) an increase in skeletal mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(r) a reduction in rate of loss of skeletal mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(s) an increase in cardiac mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(t) a reduction in rate of loss of cardiac mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(u) an increase in fat mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(v) a reduction in rate of loss of fat mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(w) an increase in bone density compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(x) a reduction in rate of loss of bone density compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(y) a reduction in general weakness compared to baseline or control as measured by an increase perceived or exerted force without increased energy expenditure about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after administration of gemcitabine;

(z) a maintenance in ECOG performance score or a reduction in ECOG performance score compared to baseline or control by about 1, 2, or 3;

(aa) a maintenance in KPS score or an increase in KPS score compared to baseline or control by about 100, 90, 80, 70, 60, 50, 40, or 30;

(bb) a reduction in titration of gemcitabine treatment by about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% compared to baseline or control;

(cc) an increase in tolerance of administered dose of gemcitabine treatment compared to baseline or control by about 500 mg/m^2, 550 mg/m^2,600 mg/m^2, 650 mg/m^2, 700 mg/m^2, 750 mg/m^2, 800 mg/m^2, 850 mg/m^2, 900 mg/m^2, 950 mg/m^2, 1000 mg/m^2, 1500 mg/m^2, 2000 mg/m^2, 2500 mg/m^2, 3000 mg/m^2, 3500 mg/m^2, 4000 mg/m^2, 4500 mg/m^2, 5000 mg/m^2, or more;

(dd) an increase in frequency of administration of gemcitabine treatment compared to baseline or control by about 1 hour, 12 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 2 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, or 6 months;

(ee) a reduction iatrogenic injury by about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% compared to baseline or control;

(ff) an increase in cumulative mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(gg) a reduction in rate of loss of cumulative mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(hh) an increase in net weight gain compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(ii) an increase in cumulative food intake compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(jj) an increase in BMI compared to baseline or control by at least about 0.5 kg/m^2, 1.0 kg/m^2, 1.5 kg/m^2, 2.0 kg/m^2, 2.5 kg/m^2, 3.0 kg/m^2, 3.5 kg/m^2, 4.0 kg/m^2, 4.5 kg/m^2, 5.0 kg/m^2, 5.5 kg/m^2, 6.0 kg/m^2, 6.5 kg/m^2, 7.0 kg/m^2, 7.5 kg/m^2, 8.0 kg/m^2, 8.5 kg/m^2, 9.0 kg/m^2, 9.5 kg/m^2, 10.0 kg/m^2, 10.5 kg/m^2, 11.0 kg/m^2, 11.5 kg/m^2, or 12.0 kg/m^2 ;

(kk) a reduction in an inflammatory transcript level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(ll) a reduction in an inflammatory protein level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(mm) an increase in FAACT score compared to baseline or control by at least 1, 2, 3, 4, or 5 points;

(nn) an increase in OS compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(oo) an increase in PFS compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(pp) an increase in BMI durability compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(qq) a reduction in time to cancer treatment failure compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%; and

(rr) a reduction in ctDNA levels compared to baseline or control by at least about 10%, 20%, 30%m 40%, 50%, 60%, 70%, 80%, 90%, or 100%.

Methotrexate

[0801] In some embodiments, the anti-cancer agent is an antimetabolite agent. In some embodiments, the antimetabolite agent is methotrexate.

[0802] In some embodiments, methotrexate is administered hourly, daily, weekly, biweekly, monthly, or bimonthly. In some embodiments, methotrexate is administered through continuous infusion. In some embodiments, methotrexate is administered per day or per cycle at a dose of about 0.1 mg/m^2 to about 15000 mg/m^2. In some embodiments, methotrexate is administered per cycle at a dose of at least 0.1 mg/m^2 to at least 15000 mg/m^2. In some embodiments methotrexate is administered per cycle at a dose of at least about 0.1 mg/m^2 to at least about 15000 mg/m^2.

[0803] In some embodiments, methotrexate is administered a dose of about 1 mg/m^2, 2 mg/m^2, 5 mg/m^2, 10 mg/m^2, 15 mg/m^2, 20 mg/m^2, 25 mg/m^2, 30 mg/m^2, 40

mg/m^2, 50 mg/m^2, 60 mg/m^2, 70 mg/m^2, 75 mg/m^2, 80 mg/m^2, 90 mg/m^2, 100 mg/m^2, 200 mg/m^2, 300 mg/m^2, 400 mg/m^2, 500 mg/m^2, 550 mg/m^2, 600 mg/m^2, 650 mg/m^2, 700 mg/m^2, 750 mg/m^2, 800 mg/m^2, 850 mg/m^2, 900 mg/m^2, 950 mg/m^2, 1000 mg/m^2, 1250 mg/m^2, 1500 mg/m^2, 1750 mg/m^2, 2000 mg/m^2, 2500 mg/m^2, 3000 mg/m^2, 4000 mg/m^2, 5000 mg/m^2, 6000 mg/m^2, 7000 mg/m^2, 8000 mg/m^2, 9000 mg/m^2, 10000 mg/m^2, 11000 mg/m^2, 12000 mg/m^2, 13000 mg/m^2, 14000 mg/m^2, 15000 mg/m^2 or more per day or per cycle. In some embodiments, the methotrexate is administered once daily. In some embodiments, the methotrexate is administered once daily for 1 day to 8 weeks.

[0804] In some embodiments, methotrexate is administered at a dose of about between 100 mg/m^2 to less than 500 mg/m^2. In some embodiments, methotrexate is administered at a dose of about 500 mg/m^2 or greater. In some embodiments, methotrexate is administered at a dose of about 10 mg/m^2 to 8000 mg/m^2 or greater. In some embodiments, methotrexate is administered at a dose of about 1000 mg/m^2 to 3000 mg/m^2. In some embodiments, methotrexate is administered at a dose of about 3000 mg/m^2 to 8000 mg/m^2. In some embodiments, methotrexate is administered at a dose of about 30 mg/m^2 to 200 mg/m^2. In some embodiments, methotrexate is administered at a dose of about 0.4 mg/kg to about 1 mg/kg. In some embodiments, methotrexate is administered at a dose of less than about 30 mg/m^2 per week.

[0805] In some embodiments, administration of the methotrexate is associated with one or more symptoms selected from the group consisting of vomiting, nausea, abdominal discomfort or pain, anorexia, fatigue, diarrhea, weight loss, fat mass loss, muscle mass loss, cardiac muscle loss, and general weakness. In some embodiments, nausea or vomiting may begin within 1 minute to 24 hours after administration of methotrexate. In some embodiments, nausea or vomiting lasts up to 1 hour to one week after administration of methotrexate. In some embodiments, nausea or vomiting beings or persists 1 minute to one week after administration of methotrexate. In some embodiments, the administration of methotrexate and a non-naturally occurring melanocortin analog reduces or prevents one or more of these symptoms.

[0806] In some embodiments, nausea or vomiting may begin within 1 to 24 hours after administration of methotrexate. In some embodiments, nausea or vomiting lasts up to 1 hour to 24 hours after administration of methotrexate. In some embodiments,

nausea or vomiting begins or persists 24 hours or more after administration methotrexate. In some embodiments, the administration of methotrexate and a non-naturally occurring melanocortin analog reduces or prevents one or more of these symptoms.

[0807] In some embodiments, methotrexate is administered before, during, or after administration of a non-naturally occurring melanocortin analog. In some embodiments, methotrexate is administered at a dose of 0.5 mg/m^2 to about 15000 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0808] In some embodiments, methotrexate is administered at a dose of at least 0.5 mg/m^2 to at least 15000 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0809] In some embodiments, methotrexate is administered at a dose of at least about 0.5 mg/m^2 to at least about 15000 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0810] In some embodiments, methotrexate is administered at a dose of about 1 mg/m^2, 2 mg/m^2, 5 mg/m^2, 10 mg/m^2, 15 mg/m^2, 20 mg/m^2, 25 mg/m^2, 30 mg/m^2, 40 mg/m^2, 50 mg/m^2, 60 mg/m^2, 70 mg/m^2, 75 mg/m^2, 80 mg/m^2, 90 mg/m^2, 100 mg/m^2, 200 mg/m^2, 300 mg/m^2, 400 mg/m^2, 500 mg/m^2, 550 mg/m^2, 600 mg/m^2, 650 mg/m^2, 700 mg/m^2, 750 mg/m^2, 800 mg/m^2, 850 mg/m^2, 900 mg/m^2, 950 mg/m^2, 1000 mg/m^2, 1250 mg/m^2, 1500 mg/m^2, 1750 mg/m^2, 2000 mg/m^2, 2500 mg/m^2, 3000 mg/m^2, 4000 mg/m^2, 5000 mg/m^2, 6000 mg/m^2, 7000 mg/m^2, 8000 mg/m^2, 9000 mg/m^2, 10000 mg/m^2, 11000 mg/m^2, 12000 mg/m^2, 13000 mg/m^2, 14000 mg/m^2, 15000 mg/m^2 or more per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0811] In some embodiments, methotrexate is administered at a dose of 1 mg/m^2, 2 mg/m^2, 5 mg/m^2, 10 mg/m^2, 15 mg/m^2, 20 mg/m^2, 25 mg/m^2, 30 mg/m^2, 40 mg/m^2, 50 mg/m^2, 60 mg/m^2, 70 mg/m^2, 75 mg/m^2, 80 mg/m^2, 90 mg/m^2, 100 mg/m^2, 200 mg/m^2, 300 mg/m^2, 400 mg/m^2, 500 mg/m^2, 550 mg/m^2, 600 mg/m^2, 650 mg/m^2, 700 mg/m^2, 750 mg/m^2, 800 mg/m^2, 850 mg/m^2, 900 mg/m^2, 950 mg/m^2, 1000 mg/m^2, 1250 mg/m^2, 1500 mg/m^2, 1750 mg/m^2, 2000 mg/m^2, 2500 mg/m^2, 3000 mg/m^2, 4000 mg/m^2, 5000 mg/m^2, 6000 mg/m^2, 7000 mg/m^2, 8000 mg/m^2, 9000 mg/m^2, 10000 mg/m^2, 11000

mg/m^2, 12000 mg/m^2, 13000 mg/m^2, 14000 mg/m^2, 15000 mg/m^2 or more per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0812] In some embodiments, methotrexate is administered at a dose of at least about 1 mg/m^2, 2 mg/m^2, 5 mg/m^2, 10 mg/m^2, 15 mg/m^2, 20 mg/m^2, 25 mg/m^2, 30 mg/m^2, 40 mg/m^2, 50 mg/m^2, 60 mg/m^2, 70 mg/m^2, 75 mg/m^2, 80 mg/m^2, 90 mg/m^2, 100 mg/m^2, 200 mg/m^2, 300 mg/m^2, 400 mg/m^2, 500 mg/m^2, 550 mg/m^2, 600 mg/m^2, 650 mg/m^2, 700 mg/m^2, 750 mg/m^2, 800 mg/m^2, 850 mg/m^2, 900 mg/m^2, 950 mg/m^2, 1000 mg/m^2, 1250 mg/m^2, 1500 mg/m^2, 1750 mg/m^2, 2000 mg/m^2, 2500 mg/m^2, 3000 mg/m^2, 4000 mg/m^2, 5000 mg/m^2, 6000 mg/m^2, 7000 mg/m^2, 8000 mg/m^2, 9000 mg/m^2, 10000 mg/m^2, 11000 mg/m^2, 12000 mg/m^2, 13000 mg/m^2, 14000 mg/m^2, 15000 mg/m^2 or more per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0813] In some embodiments, the methotrexate is administered hourly, twice daily, once daily, once every 2 days, once every 3 days, once every 4 days, once every 5 days, or once a week.

[0814] In some embodiments, the methotrexate is administered by continuous 1-hour, 2-hour, 3-hour, 4-hour, 5-hour, 6-hour, 7-hour, 8-hour, 9-hour, 10-hour, 12-hour, 14-hour, 16-hour, 18-hour, 20-hour, 22-hour, 24-hour, 36-hour, or 72-hour infusion. In some embodiments, methotrexate is administered by daily pulse doses. In some embodiments, the subject has received one or more of a nutritive therapy, a nutritional supplement, an antiemetic, or a therapeutic for preventing cancer associated wasting before during, or after administration of methotrexate or the non-naturally occurring melanocortin analog.

[0815] In some embodiments, the subject administered the non-naturally occurring melanocortin analog before, during, or after administration of the methotrexate exhibits one or more of a reduction in vomiting or nausea compared to baseline or control, a reduction in gastrointestinal side effects that are not vomiting or nausea compared to baseline or control, a reduction in asthenia compared to baseline or control, a reduction in anorexia compared to baseline or control, an increase in appetite compared to baseline or control, a reduction in fatigue compared to baseline or control, a reduction in diarrhea compared to baseline or control, an increase in body weight compared to

baseline or control, a reduced rate of weight loss compared to baseline or control, an increase in skeletal muscle mass compared to baseline or control, a reduced rate of loss of skeletal muscle mass compared to baseline or control, an increase in cardiac muscle mass compared to baseline or control, a reduced rate of loss of cardiac muscle mass compared to baseline or control, an increase in fat mass compared to baseline or control, a reduced rate of loss of fat mass compared to baseline or control, an increase in bone density compared to baseline or control, a reduction in rate of loss of bone density compared to baseline or control, a reduction in general weakness compared to baseline or control, a reduction of ECOG performance score compared to baseline or control, a maintenance in ECOG performance score, an increase in KPS score compared to baseline or control, a maintenance in KPS score, no titration of methotrexate treatment, a reduced titration of methotrexate treatment compared to baseline or control, a reduction in iatrogenic injury, an increase in cumulative mass compared to baseline or control, a reduction in rate of loss of cumulative mass compared to baseline or control, an increase in net weight gain compared to baseline or control, an increase in cumulative food intake compared to baseline or control, an increase in BMI compared to baseline or control, a reduced BMI decline compared to baseline or control, or a reduced proinflammatory transcript/protein level compared to baseline or control.

[0816] In some embodiments, the subject administered the non-naturally occurring melanocortin analog before, during, or after administration of methotrexate exhibits one or more of

(a) a reduction in the onset of vomiting or nausea compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after methotrexate administration;

(b) a reduction in the duration of vomiting or nausea compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 24 hours, 48 hours, 72 hours, 96 hours, 5 days, 6 days, or 7 days after methotrexate administration;

(c) a reduction in the onset of abdominal discomfort or pain compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after methotrexate administration;

(d) a reduction in the duration of abdominal discomfort or pain compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 24 hours, 48 hours, 72 hours, 96 hours, 5 days, 6 days, or 7 days after methotrexate administration;

(e) a reduction in the onset of hemorrhagic colitis compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after methotrexate administration;

(f) a reduction in the duration of hemorrhagic colitis compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after methotrexate administration;

(g) a reduction in asthenia compared to baseline or control compared to control within about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after methotrexate administration;

(h) a reduction in general physical deterioration to baseline or control compared to control measured by an increase in body mass index by about 0.25, 0.5, 1.0, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 5.75, 6, 6.26, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 9.25, 9.5, 9.75, or 10 or more;

(i) a reduction in the onset of influenza-like illness or chills about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after methotrexate administration;

(j) a reduction in the duration of influenza-like illness or chills about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after methotrexate administration;

(k) a reduction in anorexia compared to baseline or control measured by an increase in body mass index by about 0.25, 0.5, 1.0, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 5.75, 6, 6.26, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 9.25, 9.5, 9.75, or 10 or more;

(l) an increase in appetite compared to baseline or control, which may be measured by an increase in calorie consumption by about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 125%, 150%, 175%, 200%, 250%, 300%, 350%, 400%, 450%, or 500% or more;

(m) an reduction in fatigue compared to baseline or control, which may be measured by an increase in perceived energy or reduced energy expenditure about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after methotrexate administration;

(n) a reduction in diarrhea compared to baseline or control about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after methotrexate administration;

(o) an increase in body weight compared to baseline or control measured by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%,

30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 225%, 250%, 275%, 300%, 350%, 400%, 450%, or 500%;

(p) a reduced rate of weight loss compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(q) an increase in skeletal mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(r) a reduction in rate of loss of skeletal mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(s) an increase in cardiac mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(t) a reduction in rate of loss of cardiac mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(u) an increase in fat mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(v) a reduction in rate of loss of fat mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(w) an increase in bone density compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(x) a reduction in rate of loss of bone density compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(y) a reduction in general weakness compared to baseline or control as measured by an increase perceived or exerted force without increased energy expenditure about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after administration of methotrexate;

(z) a maintenance in ECOG performance score or a reduction in ECOG performance score compared to baseline or control by about 1, 2, or 3;

(aa) a maintenance in KPS score or an increase in KPS score compared to baseline or control by about 100, 90, 80, 70, 60, 50, 40, or 30;

(bb) a reduction in titration of methotrexate treatment by about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% compared to baseline or control;

(cc) an increase in tolerance of administered dose of methotrexate treatment compared to baseline or control by about 1 mg/m^2, 2 mg/m^2, 5 mg/m^2, 10 mg/m^2, 15 mg/m^2, 20 mg/m^2, 25 mg/m^2, 30 mg/m^2, 40 mg/m^2, 50 mg/m^2, 60 mg/m^2, 70 mg/m^2, 75 mg/m^2, 80 mg/m^2, 90 mg/m^2, 100 mg/m^2, 200 mg/m^2, 300 mg/m^2, 400 mg/m^2, 500 mg/m^2, 550 mg/m^2, 600 mg/m^2, 650 mg/m^2, 700 mg/m^2, 750 mg/m^2, 800 mg/m^2, 850 mg/m^2, 900 mg/m^2, 950 mg/m^2, 1000 mg/m^2, 1250 mg/m^2, 1500 mg/m^2, 1750 mg/m^2, 2000 mg/m^2, 2500 mg/m^2, 3000 mg/m^2, 4000 mg/m^2, 5000 mg/m^2, 6000 mg/m^2, 7000 mg/m^2, 8000 mg/m^2, 9000 mg/m^2, 10000 mg/m^2, 11000 mg/m^2, 12000 mg/m^2, 13000 mg/m^2, 14000 mg/m^2, 15000 mg/m^2 or more;

(dd) an increase in frequency of administration of methotrexate treatment compared to baseline or control by about 1 hour, 12 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 2 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, or 6 months;

(ee) a reduction iatrogenic injury by about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% compared to baseline or control;

(ff) an increase in cumulative mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(gg) a reduction in rate of loss of cumulative mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(hh) an increase in net weight gain compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(ii) an increase in cumulative food intake compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(jj) an increase in BMI compared to baseline or control by at least about 0.5 kg/m^2, 1.0 kg/m^2, 1.5 kg/m^2, 2.0 kg/m^2, 2.5 kg/m^2, 3.0 kg/m^2, 3.5 kg/m^2, 4.0 kg/m^2, 4.5 kg/m^2, 5.0 kg/m^2, 5.5 kg/m^2, 6.0 kg/m^2, 6.5 kg/m^2, 7.0 kg/m^2, 7.5 kg/m^2, 8.0 kg/m^2, 8.5 kg/m^2, 9.0 kg/m^2, 9.5 kg/m^2, 10.0 kg/m^2, 10.5 kg/m^2, 11.0 kg/m^2, 11.5 kg/m^2, or 12.0 kg/m^2 ;

(kk) a reduction in an inflammatory transcript level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(ll) a reduction in an inflammatory protein level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(mm) an increase in FAACT score compared to baseline or control by at least 1, 2, 3, 4, or 5 points;

(nn) an increase in OS compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(oo) an increase in PFS compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(pp) an increase in BMI durability compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(qq) a reduction in time to cancer treatment failure compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%; and

(rr) a reduction in ctDNA levels compared to baseline or control by at least about 10%, 20%, 30%m 40%, 50%, 60%, 70%, 80%, 90%, or 100%.

Vincristine

[0817] In some embodiments, the anti-cancer agent is a plant alkaloid. In some embodiments, the plant alkaloid is vincristine. In some embodiments, the vincristine is vincristine sulfate.

[0818] In some embodiments, vincristine is administered hourly, daily, weekly, biweekly, monthly, or bimonthly. In some embodiments, vincristine is administered through continuous infusion. In some embodiments, vincristine is administered per day or per cycle at a dose of about 0.01 mg/m^2 to about 6 mg/m^2. In some embodiments, vincristine is administered per cycle at a dose of at least 0.01 mg/m^2 to at least 6 mg/m^2. In some embodiments vincristine is administered per cycle at a dose of at least about 0.01 mg/m^2 to at least about 6 mg/m^2.

[0819] In some embodiments, vincristine is administered a dose of about 0.01 mg/m^2, 0.02 mg/m^2, 0.03 mg/m^2, 0.04 mg/m^2, 0.05 mg/m^2, 0.06 mg/m^2, 0.07 mg/m^2, 0.08 mg/m^2, 0.09 mg/m^2, 1 mg/m^2, 1.25 mg/m^2, 1.5 mg/m^2, 1.75 mg/m^2, 2 mg/m^2, 2.5 mg/m^2, 3 mg/m^2, 3.5 mg/m^2, 4 mg/m^2, 4.5 mg/m^2, 5 mg/m^2, 5.5 mg/m^2, 6 mg/m^2, or more per day or per cycle. In some embodiments, the vincristine is administered once daily. In some embodiments, the vincristine is administered once daily for 1 day to 10 weeks.

[0820] In some embodiments, vincristine is administered at a dose of 1.5 mg/m^2 to 2.0 mg/m^2. In some embodiments, vincristine is administered at a starting dose of 0.05 mg/kg, administered once a week. In some embodiments, vincristine is administered at a dose of 1.4 mg/m^2. In some embodiments, vincristine is administered at a dose of 0.7 mg/m^2.

[0821] In some embodiments, administration of the vincristine is associated with one or more symptoms selected from the group consisting of vomiting, nausea, abdominal discomfort or pain, anorexia, fatigue, diarrhea, weight loss, fat mass loss,

muscle mass loss, cardiac muscle loss, and general weakness. In some embodiments, nausea or vomiting may begin within 1 minute to 24 hours after administration of vincristine. In some embodiments, nausea or vomiting lasts up to 1 hour to one week after administration of vincristine. In some embodiments, nausea or vomiting beings or persists 1 minute to one week after administration of vincristine. In some embodiments, the administration of vincristine and a non-naturally occurring melanocortin analog reduces or prevents one or more of these symptoms.

[0822] In some embodiments, nausea or vomiting may begin within 1 to 24 hours after administration of vincristine. In some embodiments, nausea or vomiting lasts up to 1 hour to 24 hours after administration of vincristine. In some embodiments, nausea or vomiting begins or persists 24 hours or more after administration vincristine. In some embodiments, the administration of vincristine and a non-naturally occurring melanocortin analog reduces or prevents one or more of these symptoms.

[0823] In some embodiments, vincristine is administered before, during, or after administration of a non-naturally occurring melanocortin analog. In some embodiments, vincristine is administered at a dose of 0.01 mg/m^2 to about 6 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0824] In some embodiments, vincristine is administered at a dose of at least 0.01 mg/m^2 to at least 6 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0825] In some embodiments, vincristine is administered at a dose of at least about 0.01 mg/m^2 to at least about 6 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0826] In some embodiments, vincristine is administered at a dose of about 0.01 mg/m^2, 0.02 mg/m^2, 0.03 mg/m^2, 0.04 mg/m^2, 0.05 mg/m^2, 0.06 mg/m^2, 0.07 mg/m^2, 0.08 mg/m^2, 0.09 mg/m^2, 1 mg/m^2, 1.25 mg/m^2, 1.5 mg/m^2, 1.75 mg/m^2, 2 mg/m^2, 2.5 mg/m^2, 3 mg/m^2, 3.5 mg/m^2, 4 mg/m^2, 4.5 mg/m^2, 5 mg/m^2, 5.5 mg/m^2, 6 mg/m^2 or more per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0827] In some embodiments, vincristine is administered at a dose of 0.01 mg/m^2, 0.02 mg/m^2, 0.03 mg/m^2, 0.04 mg/m^2, 0.05 mg/m^2, 0.06 mg/m^2, 0.07 mg/m^2, 0.08

mg/m^2, 0.09 mg/m^2, 1 mg/m^2, 1.25 mg/m^2, 1.5 mg/m^2, 1.75 mg/m^2, 2 mg/m^2, 2.5 mg/m^2, 3 mg/m^2, 3.5 mg/m^2, 4 mg/m^2, 4.5 mg/m^2, 5 mg/m^2, 5.5 mg/m^2, 6 mg/m^2 or more per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0828] In some embodiments, vincristine is administered at a dose of at least about 0.01 mg/m^2, 0.02 mg/m^2, 0.03 mg/m^2, 0.04 mg/m^2, 0.05 mg/m^2, 0.06 mg/m^2, 0.07 mg/m^2, 0.08 mg/m^2, 0.09 mg/m^2, 1 mg/m^2, 1.25 mg/m^2, 1.5 mg/m^2, 1.75 mg/m^2, 2 mg/m^2, 2.5 mg/m^2, 3 mg/m^2, 3.5 mg/m^2, 4 mg/m^2, 4.5 mg/m^2, 5 mg/m^2, 5.5 mg/m^2, 6 mg/m^2 or more per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0829] In some embodiments, the vincristine is administered hourly, twice daily, once daily, once every 2 days, once every 3 days, once every 4 days, once every 5 days, or once a week.

[0830] In some embodiments, the vincristine is administered by continuous 1-hour, 2-hour, 3-hour, 4-hour, 5-hour, 6-hour, 7-hour, 8-hour, 9-hour, 10-hour, 12-hour, 14-hour, 16-hour, 18-hour, 20-hour, 22-hour, 24-hour, 36-hour, or 72-hour infusion. In some embodiments, vincristine is administered by daily pulse doses. In some embodiments, the subject has received one or more of a nutritive therapy, a nutritional supplement, an antiemetic, or a therapeutic for preventing cancer associated wasting before during, or after administration of vincristine or the non-naturally occurring melanocortin analog.

[0831] In some embodiments, the subject administered the non-naturally occurring melanocortin analog before, during, or after administration of the vincristine exhibits one or more of a reduction in vomiting or nausea compared to baseline or control, a reduction in gastrointestinal side effects that are not vomiting or nausea compared to baseline or control, a reduction in asthenia compared to baseline or control, a reduction in anorexia compared to baseline or control, an increase in appetite compared to baseline or control, a reduction in fatigue compared to baseline or control, a reduction in diarrhea compared to baseline or control, an increase in body weight compared to baseline or control, a reduced rate of weight loss compared to baseline or control, an increase in skeletal muscle mass compared to baseline or control, a reduced rate of loss of skeletal muscle mass compared to baseline or control, an increase in cardiac

muscle mass compared to baseline or control, a reduced rate of loss of cardiac muscle mass compared to baseline or control, an increase in fat mass compared to baseline or control, a reduced rate of loss of fat mass compared to baseline or control, an increase in bone density compared to baseline or control, a reduction in rate of loss of bone density compared to baseline or control, a reduction in general weakness compared to baseline or control, a reduction of ECOG performance score compared to baseline or control, a maintenance in ECOG performance score, an increase in KPS score compared to baseline or control, a maintenance in KPS score, no titration of vincristine treatment, a reduced titration of vincristine treatment compared to baseline or control, a reduction in iatrogenic injury, an increase in cumulative mass compared to baseline or control, a reduction in rate of loss of cumulative mass compared to baseline or control, an increase in net weight gain compared to baseline or control, an increase in cumulative food intake compared to baseline or control, an increase in BMI compared to baseline or control, a reduced BMI decline compared to baseline or control, or a reduced proinflammatory transcript/protein level compared to baseline or control.

[0832] In some embodiments, the subject administered the non-naturally occurring melanocortin analog before, during, or after administration of vincristine exhibits one or more of

(a) a reduction in the onset of vomiting or nausea compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after vincristine administration;

(b) a reduction in the duration of vomiting or nausea compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 24 hours, 48 hours, 72 hours, 96 hours, 5 days, 6 days, or 7 days after vincristine administration;

(c) a reduction in the onset of abdominal discomfort or pain compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours,

18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after vincristine administration;

(d) a reduction in the duration of abdominal discomfort or pain compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 24 hours, 48 hours, 72 hours, 96 hours, 5 days, 6 days, or 7 days after vincristine administration;

(e) a reduction in the onset of hemorrhagic colitis compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after vincristine administration;

(f) a reduction in the duration of hemorrhagic colitis compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after vincristine administration;

(g) a reduction in asthenia compared to baseline or control compared to control within about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after vincristine administration;

(h) a reduction in general physical deterioration to baseline or control compared to control measured by an increase in body mass index by about 0.25, 0.5, 1.0, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 5.75, 6, 6.26, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 9.25, 9.5, 9.75, or 10 or more;

(i) a reduction in the onset of influenza-like illness or chills about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after vincristine administration;

(j) a reduction in the duration of influenza-like illness or chills about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after vincristine administration;

(k) a reduction in anorexia compared to baseline or control measured by an increase in body mass index by about 0.25, 0.5, 1.0, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 5.75, 6, 6.26, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 9.25, 9.5, 9.75, or 10 or more;

(l) an increase in appetite compared to baseline or control, which may be measured by an increase in calorie consumption by about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 125%, 150%, 175%, 200%, 250%, 300%, 350%, 400%, 450%, or 500% or more;

(m) a reduction in fatigue compared to baseline or control, which may be measured by an increase in perceived energy or reduced energy expenditure about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after vincristine administration;

(n) a reduction in diarrhea compared to baseline or control about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after vincristine administration;

(o) an increase in body weight compared to baseline or control measured by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 225%, 250%, 275%, 300%, 350%, 400%, 450%, or 500%;

(p) a reduced rate of weight loss compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(q) an increase in skeletal mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(r) a reduction in rate of loss of skeletal mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(s) an increase in cardiac mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(t) a reduction in rate of loss of cardiac mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(u) an increase in fat mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(v) a reduction in rate of loss of fat mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(w) an increase in bone density compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(x) a reduction in rate of loss of bone density compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(y) a reduction in general weakness compared to baseline or control as measured by an increase perceived or exerted force without increased energy expenditure about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours,

about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after administration of vincristine;

(z) a maintenance in ECOG performance score or a reduction in ECOG performance score compared to baseline or control by about 1, 2, or 3;

(aa) a maintenance in KPS score or an increase in KPS score compared to baseline or control by about 100, 90, 80, 70, 60, 50, 40, or 30;

(bb) a reduction in titration of vincristine treatment by about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% compared to baseline or control;

(cc) an increase in tolerance of administered dose of vincristine treatment compared to baseline or control by about 0.01 mg/m^2, 0.02 mg/m^2, 0.03 mg/m^2, 0.04 mg/m^2, 0.05 mg/m^2, 0.06 mg/m^2, 0.07 mg/m^2, 0.08 mg/m^2, 0.09 mg/m^2, 1 mg/m^2, 1.25 mg/m^2, 1.5 mg/m^2, 1.75 mg/m^2, 2 mg/m^2, 2.5 mg/m^2, 3 mg/m^2, 3.5 mg/m^2, 4 mg/m^2, 4.5 mg/m^2, 5 mg/m^2, 5.5 mg/m^2, 6 mg/m^2 or more;

(dd) an increase in frequency of administration of vincristine treatment compared to baseline or control by about 1 hour, 12 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 2 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, or 6 months;

(ee) a reduction IN iatrogenic injury by about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% compared to baseline or control;

(ff) an increase in cumulative mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(gg) a reduction in rate of loss of cumulative mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(hh) an increase in net weight gain compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(ii) an increase in cumulative food intake compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(jj) an increase in BMI compared to baseline or control by at least about 0.5 kg/m^2, 1.0 kg/m^2, 1.5 kg/m^2, 2.0 kg/m^2, 2.5 kg/m^2, 3.0 kg/m^2, 3.5 kg/m^2, 4.0 kg/m^2, 4.5 kg/m^2, 5.0 kg/m^2, 5.5 kg/m^2, 6.0 kg/m^2, 6.5 kg/m^2, 7.0 kg/m^2, 7.5 kg/m^2, 8.0 kg/m^2, 8.5 kg/m^2, 9.0 kg/m^2, 9.5 kg/m^2, 10.0 kg/m^2, 10.5 kg/m^2, 11.0 kg/m^2, 11.5 kg/m^2, or 12.0 kg/m^2 ;

(kk) a reduction in an inflammatory transcript level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(ll) a reduction in an inflammatory protein level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(mm) an increase in FAACT score compared to baseline or control by at least 1, 2, 3, 4, or 5 points;

(nn) an increase in OS compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(oo) an increase in PFS compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(pp) an increase in BMI durability compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(qq) a reduction in time to cancer treatment failure compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%; and

(rr) a reduction in ctDNA levels compared to baseline or control by at least about 10%, 20%, 30%m 40%, 50%, 60%, 70%, 80%, 90%, or 100%.

Paclitaxel

[0833] In some embodiments, the anti-cancer agent is a plant alkaloid. In some embodiments, the plant alkaloid is paclitaxel.

[0834] In some embodiments, paclitaxel is administered hourly, daily, weekly, biweekly, monthly, or bimonthly. In some embodiments, paclitaxel is administered through continuous infusion. In some embodiments, paclitaxel is administered per day or per cycle at a dose of about 5 mg/m^2 to about 500 mg/m^2. In some embodiments, paclitaxel is administered per cycle at a dose of at least 5 mg/m^2 to at least 500 mg/m^2. In some embodiments paclitaxel is administered per cycle at a dose of at least about 5 mg/m^2 to at least about 500 mg/m^2.

[0835] In some embodiments, paclitaxel is administered a dose of about 5 mg/m^2, 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 20 mg/m^2, 30 mg/m^2, 40 mg/m^2, 50 mg/m^2, 75 mg/m^2, 100 mg/m^2, 125 mg/m^2, 150 mg/m^2, 175 mg/m^2, 200 mg/m^2, 225 mg/m^2, 250 mg/m^2, 275 mg/m^2, 300 mg/m^2, 350 mg/m^2, 400 mg/m^2, 450 mg/m^2, or 500 mg/m^2, or more per day or per cycle. In some embodiments, the paclitaxel is administered once daily. In some embodiments, the paclitaxel is administered once daily for 1 day to 10 weeks.

[0836] In some embodiments, paclitaxel is administered at a dose of 135 mg/m^2 to 175 mg/m^2. In some embodiments, paclitaxel is administered in single doses of 15 to 135 mg/m^2 given by 1-hour infusions. In some embodiments, paclitaxel is administered at a dose of 30 to 275 mg/m^2 given by 6-hour infusions. In some embodiments, paclitaxel is administered at a dose of 200 to 275 mg/m^2 given by 24-hour infusions. In some embodiments, paclitaxel is administered at a dose of 115 mg/m^2.

[0837] In some embodiments, administration of the paclitaxel is associated with one or more symptoms selected from the group consisting of vomiting, nausea, abdominal discomfort or pain, anorexia, fatigue, diarrhea, weight loss, fat mass loss, muscle mass loss, cardiac muscle loss, and general weakness. In some embodiments, nausea or vomiting may begin within 1 minute to 24 hours after administration of paclitaxel. In some embodiments, nausea or vomiting lasts up to 1 hour to one week after administration of paclitaxel. In some embodiments, nausea or vomiting begins or persists 1 minute to one week after administration of paclitaxel. In some embodiments, the administration of paclitaxel and a non-naturally occurring melanocortin analog reduces or prevents one or more of these symptoms.

[0838] In some embodiments, nausea or vomiting may begin within 1 to 24 hours after administration of paclitaxel. In some embodiments, nausea or vomiting lasts up to 1 hour to 24 hours after administration of paclitaxel. In some embodiments, nausea or vomiting begins or persists 24 hours or more after administration paclitaxel. In some embodiments, the administration of paclitaxel and a non-naturally occurring melanocortin analog reduces or prevents one or more of these symptoms.

[0839] In some embodiments, paclitaxel is administered before, during, or after administration of a non-naturally occurring melanocortin analog. In some embodiments, paclitaxel is administered at a dose of 5 mg/m^2 to about 500 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0840] In some embodiments, paclitaxel is administered at a dose of at least 5 mg/m^2 to at least 500 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0841] In some embodiments, paclitaxel is administered at a dose of at least about 5 mg/m^2 to at least about 500 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0842] In some embodiments, paclitaxel is administered at a dose of about 5 mg/m^2, 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 20 mg/m^2, 30 mg/m^2, 40 mg/m^2, 50 mg/m^2, 75 mg/m^2, 100 mg/m^2, 125 mg/m^2, 150 mg/m^2, 175 mg/m^2, 200 mg/m^2, 225 mg/m^2, 250 mg/m^2, 275 mg/m^2, 300 mg/m^2, 350 mg/m^2, 400 mg/m^2, 450 mg/m^2, or 500 mg/m^2 or more per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0843] In some embodiments, paclitaxel is administered at a dose of 5 mg/m^2, 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 20 mg/m^2, 30 mg/m^2, 40 mg/m^2, 50 mg/m^2, 75 mg/m^2, 100 mg/m^2, 125 mg/m^2, 150 mg/m^2, 175 mg/m^2, 200 mg/m^2, 225 mg/m^2, 250 mg/m^2, 275 mg/m^2, 300 mg/m^2, 350 mg/m^2, 400 mg/m^2, 450 mg/m^2, or 500 mg/m^2 or more per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0844] In some embodiments, paclitaxel is administered at a dose of at least about 5 mg/m^2, 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 20 mg/m^2, 30 mg/m^2, 40 mg/m^2, 50 mg/m^2, 75 mg/m^2, 100 mg/m^2, 125 mg/m^2, 150 mg/m^2, 175 mg/m^2, 200

mg/m^2, 225 mg/m^2, 250 mg/m^2, 275 mg/m^2, 300 mg/m^2, 350 mg/m^2, 400 mg/m^2, 450 mg/m^2, 500 mg/m^2, or more per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0845] In some embodiments, the paclitaxel is administered hourly, twice daily, once daily, once every 2 days, once every 3 days, once every 4 days, once every 5 days, or once a week.

[0846] In some embodiments, the paclitaxel is administered by continuous 1-hour, 2-hour, 3-hour, 4-hour, 5-hour, 6-hour, 7-hour, 8-hour, 9-hour, 10-hour, 12-hour, 14-hour, 16-hour, 18-hour, 20-hour, 22-hour, 24-hour, 36-hour, or 72-hour infusion. In some embodiments, paclitaxel is administered by daily pulse doses. In some embodiments, the subject has received one or more of a nutritive therapy, a nutritional supplement, an antiemetic, or a therapeutic for preventing cancer associated wasting before during, or after administration of paclitaxel or the non-naturally occurring melanocortin analog.

[0847] In some embodiments, the subject administered the non-naturally occurring melanocortin analog before, during, or after administration of the paclitaxel exhibits one or more of a reduction in vomiting or nausea compared to baseline or control, a reduction in gastrointestinal side effects that are not vomiting or nausea compared to baseline or control, a reduction in asthenia compared to baseline or control, a reduction in anorexia compared to baseline or control, an increase in appetite compared to baseline or control, a reduction in fatigue compared to baseline or control, a reduction in diarrhea compared to baseline or control, an increase in body weight compared to baseline or control, a reduced rate of weight loss compared to baseline or control, an increase in skeletal muscle mass compared to baseline or control, a reduced rate of loss of skeletal muscle mass compared to baseline or control, an increase in cardiac muscle mass compared to baseline or control, a reduced rate of loss of cardiac muscle mass compared to baseline or control, an increase in fat mass compared to baseline or control, a reduced rate of loss of fat mass compared to baseline or control, an increase in bone density compared to baseline or control, a reduction in rate of loss of bone density compared to baseline or control, a reduction in general weakness compared to baseline or control, a reduction of ECOG performance score compared to baseline or control, a maintenance in ECOG performance score, an increase in KPS score

compared to baseline or control, a maintenance in KPS score, no titration of paclitaxel treatment, a reduced titration of paclitaxel treatment compared to baseline or control, a reduction in iatrogenic injury, an increase in cumulative mass compared to baseline or control, a reduction in rate of loss of cumulative mass compared to baseline or control, an increase in net weight gain compared to baseline or control, an increase in cumulative food intake compared to baseline or control, an increase in BMI compared to baseline or control, a reduced BMI decline compared to baseline or control, or a reduced proinflammatory transcript/protein level compared to baseline or control.

[0848] In some embodiments, the subject administered the non-naturally occurring melanocortin analog before, during, or after administration of paclitaxel exhibits one or more of

(a) a reduction in the onset of vomiting or nausea compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after paclitaxel administration;

(b) a reduction in the duration of vomiting or nausea compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 24 hours, 48 hours, 72 hours, 96 hours, 5 days, 6 days, or 7 days after paclitaxel administration;

(c) a reduction in the onset of abdominal discomfort or pain compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after paclitaxel administration;

(d) a reduction in the duration of abdominal discomfort or pain compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 24 hours, 48 hours, 72 hours, 96 hours, 5 days, 6 days, or 7 days after paclitaxel administration;

(e) a reduction in the onset of hemorrhagic colitis compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after paclitaxel administration;

(f) a reduction in the duration of hemorrhagic colitis compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after paclitaxel administration;

(g) a reduction in asthenia compared to baseline or control compared to control within about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after paclitaxel administration;

(h) a reduction in general physical deterioration to baseline or control compared to control measured by an increase in body mass index by about 0.25, 0.5, 1.0, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 5.75, 6, 6.26, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 9.25, 9.5, 9.75, or 10 or more;

(i) a reduction in the onset of influenza-like illness or chills about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after paclitaxel administration;

(j) a reduction in the duration of influenza-like illness or chills about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after paclitaxel administration;

(k) a reduction in anorexia compared to baseline or control measured by an increase in body mass index by about 0.25, 0.5, 1.0, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 5.75, 6, 6.26, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 9.25, 9.5, 9.75, or 10 or more;

(l) an increase in appetite compared to baseline or control, which may be measured by an increase in calorie consumption by about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 125%, 150%, 175%, 200%, 250%, 300%, 350%, 400%, 450%, or 500% or more;

(m) an reduction in fatigue compared to baseline or control, which may be measured by an increase in perceived energy or reduced energy expenditure about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after paclitaxel administration;

(n) a reduction in diarrhea compared to baseline or control about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after paclitaxel administration;

(o) an increase in body weight compared to baseline or control measured by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 225%, 250%, 275%, 300%, 350%, 400%, 450%, or 500%;

(p) a reduced rate of weight loss compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(q) an increase in skeletal mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(r) a reduction in rate of loss of skeletal mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(s) an increase in cardiac mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(t) a reduction in rate of loss of cardiac mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(u) an increase in fat mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(v) a reduction in rate of loss of fat mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(w) an increase in bone density compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(x) a reduction in rate of loss of bone density compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(y) a reduction in general weakness compared to baseline or control as measured by an increase perceived or exerted force without increased energy expenditure about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after administration of paclitaxel;

(z) a maintenance in ECOG performance score or a reduction in ECOG performance score compared to baseline or control by about 1, 2, or 3;

(aa) a maintenance in KPS score or an increase in KPS score compared to baseline or control by about 100, 90, 80, 70, 60, 50, 40, or 30;

(bb) a reduction in titration of paclitaxel treatment by about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% compared to baseline or control;

(cc) an increase in tolerance of administered dose of paclitaxel treatment compared to baseline or control by about 5 mg/m^2, 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 20 mg/m^2, 30 mg/m^2, 40 mg/m^2, 50 mg/m^2, 75 mg/m^2, 100 mg/m^2, 125 mg/m^2, 150 mg/m^2, 175 mg/m^2, 200 mg/m^2, 225 mg/m^2, 250 mg/m^2, 275 mg/m^2, 300 mg/m^2, 350 mg/m^2, 400 mg/m^2, 450 mg/m^2, or 500 mg/m^2 or more;

(dd) an increase in frequency of administration of paclitaxel treatment compared to baseline or control by about 1 hour, 12 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 2 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, or 6 months;

(ee) a reduction iatrogenic injury by about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% compared to baseline or control;

(ff) an increase in cumulative mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(gg) a reduction in rate of loss of cumulative mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(hh) an increase in net weight gain compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(ii) an increase in cumulative food intake compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(jj) an increase in BMI compared to baseline or control by at least about 0.5 kg/m^2, 1.0 kg/m^2, 1.5 kg/m^2, 2.0 kg/m^2, 2.5 kg/m^2, 3.0 kg/m^2, 3.5 kg/m^2, 4.0 kg/m^2, 4.5 kg/m^2, 5.0 kg/m^2, 5.5 kg/m^2, 6.0 kg/m^2, 6.5 kg/m^2, 7.0 kg/m^2, 7.5 kg/m^2, 8.0 kg/m^2, 8.5 kg/m^2, 9.0 kg/m^2, 9.5 kg/m^2, 10.0 kg/m^2, 10.5 kg/m^2, 11.0 kg/m^2, 11.5 kg/m^2, or 12.0 kg/m^2;

(kk) a reduction in an inflammatory transcript level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(ll) a reduction in an inflammatory protein level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(mm) an increase in FAACT score compared to baseline or control by at least 1, 2, 3, 4, or 5 points;

(nn) an increase in OS compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(oo) an increase in PFS compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(pp) an increase in BMI durability compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(qq) a reduction in time to cancer treatment failure compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%; and

(rr) a reduction in ctDNA levels compared to baseline or control by at least about 10%, 20%, 30%m 40%, 50%, 60%, 70%, 80%, 90%, or 100%.

Docetaxel

[0849] In some embodiments, the anti-cancer agent is a plant alkaloid. In some embodiments, the plant alkaloid is docetaxel. In some embodiments, the docetaxel is docetaxel anhydrous.

[0850] In some embodiments, docetaxel is administered hourly, daily, weekly, biweekly, monthly, or bimonthly. In some embodiments, docetaxel is administered through continuous infusion. In some embodiments, docetaxel is administered per day or per cycle at a dose of about 10 mg/m^2 to about 1000 mg/m^2. In some embodiments, docetaxel is administered per cycle at a dose of at least 10 mg/m^2 to at least 1000 mg/m^2. In some embodiments docetaxel is administered per cycle at a dose of at least about 10 mg/m^2 to at least about 1000 mg/m^2.

[0851] In some embodiments, docetaxel is administered a dose of about 10 mg/m^2, 20 mg/m^2, 30 mg/m^2, 40 mg/m^2, 50 mg/m^2, 60 mg/m^2, 70 mg/m^2, 80 mg/m^2, 90 mg/m^2, 100 mg/m^2, 150 mg/m^2, 200 mg/m^2, 250 mg/m^2, 300 mg/m^2, 400 mg/m^2, 500 mg/m^2, 600 mg/m^2, 700 mg/m^2, 800mg/m^2, 900 mg/m^2, or 1000 mg/m^2, or more per day or per cycle. In some embodiments, the docetaxel is administered once daily. In some embodiments, the docetaxel is administered once daily for 1 day to 4 weeks.

[0852] In some embodiments, docetaxel is administered at a dose of 60 mg/m^2 to 100 mg/m^2. In some embodiments, docetaxel is administered in doses of 75 mg/m^2.

[0853] In some embodiments, administration of the docetaxel is associated with one or more symptoms selected from the group consisting of vomiting, nausea, abdominal discomfort or pain, anorexia, fatigue, diarrhea, weight loss, fat mass loss, muscle mass loss, cardiac muscle loss, and general weakness. In some embodiments, nausea or vomiting may begin within 1 minute to 24 hours after administration of docetaxel. In some embodiments, nausea or vomiting lasts up to 1 hour to one week after administration of docetaxel. In some embodiments, nausea or vomiting begins or persists 1 minute to one week after administration of docetaxel. In some embodiments, the administration of docetaxel and a non-naturally occurring melanocortin analog reduces or prevents one or more of these symptoms.

[0854] In some embodiments, nausea or vomiting may begin within 1 to 24 hours after administration of docetaxel. In some embodiments, nausea or vomiting lasts up to 1 hour to 24 hours after administration of docetaxel. In some embodiments, nausea or vomiting begins or persists 24 hours or more after administration docetaxel. In some embodiments, the administration of docetaxel and a non-naturally occurring melanocortin analog reduces or prevents one or more of these symptoms.

[0855] In some embodiments, docetaxel is administered before, during, or after administration of a non-naturally occurring melanocortin analog. In some embodiments, docetaxel is administered at a dose of 10 mg/m^2 to about 1000 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0856] In some embodiments, docetaxel is administered at a dose of at least 10 mg/m^2 to at least 1000 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0857] In some embodiments, docetaxel is administered at a dose of at least about 10 mg/m^2 to at least about 1000 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0858] In some embodiments, docetaxel is administered at a dose of about 10 mg/m^2, 20 mg/m^2, 30 mg/m^2, 40 mg/m^2, 50 mg/m^2, 60 mg/m^2, 70 mg/m^2, 80 mg/m^2, 90 mg/m^2, 100 mg/m^2, 150 mg/m^2, 200 mg/m^2, 250 mg/m^2, 300 mg/m^2, 400 mg/m^2, 500 mg/m^2, 600 mg/m^2, 700 mg/m^2, 800mg/m^2, 900 mg/m^2, or 1000 mg/m^2 or more per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0859] In some embodiments, docetaxel is administered at a dose of 10 mg/m^2, 20 mg/m^2, 30 mg/m^2, 40 mg/m^2, 50 mg/m^2, 60 mg/m^2, 70 mg/m^2, 80 mg/m^2, 90 mg/m^2, 100 mg/m^2, 150 mg/m^2, 200 mg/m^2, 250 mg/m^2, 300 mg/m^2, 400 mg/m^2, 500 mg/m^2, 600 mg/m^2, 700 mg/m^2, 800mg/m^2, 900 mg/m^2, or 1000 mg/m^2 or more per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0860] In some embodiments, docetaxel is administered at a dose of at least about 10 mg/m^2, 20 mg/m^2, 30 mg/m^2, 40 mg/m^2, 50 mg/m^2, 60 mg/m^2, 70 mg/m^2, 80 mg/m^2, 90 mg/m^2, 100 mg/m^2, 150 mg/m^2, 200 mg/m^2, 250 mg/m^2, 300 mg/m^2, 400 mg/m^2, 500 mg/m^2, 600 mg/m^2, 700 mg/m^2, 800mg/m^2, 900 mg/m^2, or 1000 mg/m^2, or more per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0861] In some embodiments, the docetaxel is administered hourly, twice daily, once daily, once every 2 days, once every 3 days, once every 4 days, once every 5 days, or once a week.

[0862] In some embodiments, the docetaxel is administered by continuous 1-hour, 2-hour, 3-hour, 4-hour, 5-hour, 6-hour, 7-hour, 8-hour, 9-hour, 10-hour, 12-hour, 14-hour, 16-hour, 18-hour, 20-hour, 22-hour, 24-hour, 36-hour, or 72-hour infusion. In some embodiments, docetaxel is administered by daily pulse doses. In some embodiments, the subject has received one or more of a nutritive therapy, a nutritional supplement, an antiemetic, or a therapeutic for preventing cancer associated wasting before during, or after administration of docetaxel or the non-naturally occurring melanocortin analog.

[0863] In some embodiments, the subject administered the non-naturally occurring melanocortin analog before, during, or after administration of the docetaxel exhibits one or more of a reduction in vomiting or nausea compared to baseline or control, a reduction in gastrointestinal side effects that are not vomiting or nausea compared to baseline or control, a reduction in asthenia compared to baseline or control, a reduction in anorexia compared to baseline or control, an increase in appetite compared to baseline or control, a reduction in fatigue compared to baseline or control, a reduction in diarrhea compared to baseline or control, an increase in body weight compared to baseline or control, a reduced rate of weight loss compared to baseline or control, an increase in skeletal muscle mass compared to baseline or control, a reduced rate of loss of skeletal muscle mass compared to baseline or control, an increase in cardiac muscle mass compared to baseline or control, a reduced rate of loss of cardiac muscle mass compared to baseline or control, an increase in fat mass compared to baseline or control, a reduced rate of loss of fat mass compared to baseline or control, an increase in bone density compared to baseline or control, a reduction in rate of loss of bone density compared to baseline or control, a reduction in general weakness compared to baseline or control, a reduction of ECOG performance score compared to baseline or control, a maintenance in ECOG performance score, an increase in KPS score compared to baseline or control, a maintenance in KPS score, no titration of docetaxel treatment, a reduced titration of docetaxel treatment compared to baseline or control, a reduction in iatrogenic injury, an increase in cumulative mass compared to baseline or control, a reduction in rate of loss of cumulative mass compared to baseline or control, an increase in net weight gain compared to baseline or control, an increase in cumulative food intake compared to baseline or control, an increase in BMI compared to baseline or control, a reduced BMI decline compared to baseline or control, or a reduced proinflammatory transcript/protein level compared to baseline or control.

[0864] In some embodiments, the subject administered the non-naturally occurring melanocortin analog before, during, or after administration of docetaxel exhibits one or more of

(a) a reduction in the onset of vomiting or nausea compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19

hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after docetaxel administration;

(b) a reduction in the duration of vomiting or nausea compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 24 hours, 48 hours, 72 hours, 96 hours, 5 days, 6 days, or 7 days after docetaxel administration;

(c) a reduction in the onset of abdominal discomfort or pain compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after docetaxel administration;

(d) a reduction in the duration of abdominal discomfort or pain compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 24 hours, 48 hours, 72 hours, 96 hours, 5 days, 6 days, or 7 days after docetaxel administration;

(e) a reduction in the onset of hemorrhagic colitis compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after docetaxel administration;

(f) a reduction in the duration of hemorrhagic colitis compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after docetaxel administration;

(g) a reduction in asthenia compared to baseline or control compared to control within about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours,

about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after docetaxel administration;

(h) a reduction in general physical deterioration to baseline or control compared to control measured by an increase in body mass index by about 0.25, 0.5, 1.0, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 5.75, 6, 6.26, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 9.25, 9.5, 9.75, or 10 or more;

(i) a reduction in the onset of influenza-like illness or chills about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after docetaxel administration;

(j) a reduction in the duration of influenza-like illness or chills about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after docetaxel administration;

(k) a reduction in anorexia compared to baseline or control measured by an increase in body mass index by about 0.25, 0.5, 1.0, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 5.75, 6, 6.26, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 9.25, 9.5, 9.75, or 10 or more;

(l) an increase in appetite compared to baseline or control, which may be measured by an increase in calorie consumption by about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 125%, 150%, 175%, 200%, 250%, 300%, 350%, 400%, 450%, or 500% or more;

(m) an reduction in fatigue compared to baseline or control, which may be measured by an increase in perceived energy or reduced energy expenditure about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after docetaxel administration;

(n) a reduction in diarrhea compared to baseline or control about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8

hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after docetaxel administration;

(o) an increase in body weight compared to baseline or control measured by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 225%, 250%, 275%, 300%, 350%, 400%, 450%, or 500%;

(p) a reduced rate of weight loss compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(q) an increase in skeletal mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(r) a reduction in rate of loss of skeletal mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(s) an increase in cardiac mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(t) a reduction in rate of loss of cardiac mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(u) an increase in fat mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(v) a reduction in rate of loss of fat mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(w) an increase in bone density compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(x) a reduction in rate of loss of bone density compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(y) a reduction in general weakness compared to baseline or control as measured by an increase perceived or exerted force without increased energy expenditure about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after administration of docetaxel;

(z) a maintenance in ECOG performance score or a reduction in ECOG performance score compared to baseline or control by about 1, 2, or 3;

(aa) a maintenance in KPS score or an increase in KPS score compared to baseline or control by about 100, 90, 80, 70, 60, 50, 40, or 30;

(bb) a reduction in titration of docetaxel treatment by about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% compared to baseline or control;

(cc) an increase in tolerance of administered dose of docetaxel treatment compared to baseline or control by about 10 mg/m^2, 20 mg/m^2, 30 mg/m^2, 40 mg/m^2, 50 mg/m^2, 60 mg/m^2, 70 mg/m^2, 80 mg/m^2, 90 mg/m^2, 100 mg/m^2, 150 mg/m^2, 200 mg/m^2, 250 mg/m^2, 300 mg/m^2, 400 mg/m^2, 500 mg/m^2, 600 mg/m^2, 700 mg/m^2, 800mg/m^2, 900 mg/m^2, or 1000 mg/m^2 or more;

(dd) an increase in frequency of administration of docetaxel treatment compared to baseline or control by about 1 hour, 12 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 2 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, or 6 months;

(ee) a reduction IN iatrogenic injury by about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% compared to baseline or control;

(ff) an increase in cumulative mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(gg) a reduction in rate of loss of cumulative mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(hh) an increase in net weight gain compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(ii) an increase in cumulative food intake compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(jj) an increase in BMI compared to baseline or control by at least about 0.5 kg/m^2, 1.0 kg/m^2, 1.5 kg/m^2, 2.0 kg/m^2, 2.5 kg/m^2, 3.0 kg/m^2, 3.5 kg/m^2, 4.0 kg/m^2, 4.5 kg/m^2, 5.0 kg/m^2, 5.5 kg/m^2, 6.0 kg/m^2, 6.5 kg/m^2, 7.0 kg/m^2, 7.5 kg/m^2, 8.0 kg/m^2, 8.5 kg/m^2, 9.0 kg/m^2, 9.5 kg/m^2, 10.0 kg/m^2, 10.5 kg/m^2, 11.0 kg/m^2, 11.5 kg/m^2, or 12.0 kg/m^2;

(kk) a reduction in an inflammatory transcript level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(ll) a reduction in an inflammatory protein level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(mm) an increase in FAACT score compared to baseline or control by at least 1, 2, 3, 4, or 5 points;

(nn) an increase in OS compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(oo) an increase in PFS compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(pp) an increase in BMI durability compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(qq) a reduction in time to cancer treatment failure compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%; and

(rr) a reduction in ctDNA levels compared to baseline or control by at least about 10%, 20%, 30%m 40%, 50%, 60%, 70%, 80%, 90%, or 100%.

Doxorubicin

[0865] In some embodiments, the anti-cancer agent is an antibiotic. In some embodiments the antibiotic is an antitumor antibiotic. In some embodiments, the antitumor antibiotic is doxorubicin. In some embodiments, the doxorubicin is doxorubicin hydrochloride.

[0866] In some embodiments, doxorubicin is administered hourly, daily, weekly, biweekly, monthly, or bimonthly. In some embodiments, doxorubicin is administered through continuous infusion. In some embodiments, doxorubicin is administered per day or per cycle at a dose of about 5 mg/m^2 to about 500 mg/m^2.

[0867] In some embodiments, doxorubicin is administered per cycle at a dose of at least 5 mg/m^2 to at least 500 mg/m^2.

[0868] In some embodiments doxorubicin is administered per cycle at a dose of at least about 5 mg/m^2 to at least about 500 mg/m^2.

[0869] In some embodiments, doxorubicin is administered a dose of about 5 mg/m^2,10 mg/m^2, 20 mg/m^2, 30 mg/m^2, 40 mg/m^2, 50 mg/m^2, 60 mg/m^2, 70 mg/m^2, 80 mg/m^2, 90 mg/m^2, 100 mg/m^2, 150 mg/m^2, 200 mg/m^2, 250 mg/m^2, 300 mg/m^2, 400 mg/m^2, or 500 mg/m^2 or more per day or per cycle. In some embodiments, the doxorubicin is administered once daily. In some embodiments, the doxorubicin is administered once daily for 1 day to 4 weeks.

[0870] In some embodiments, doxorubicin is administered as a single agent at a dose of about 60 to 75 mg/m^2 as a single intravenous injection administered at 21-day intervals. In some embodiments, doxorubicin is administered at a dose of 40 to 60 mg/m^{2}every 21 to 28 days. In some embodiments, doxorubicin is administered at a

dose of about 15 to about 37.5 mg/m^2. In some embodiments, doxorubicin is administered once every 21 to 28 days.

[0871] In some embodiments, administration of the doxorubicin is associated with one or more symptoms selected from the group consisting of vomiting, nausea, abdominal discomfort or pain, anorexia, fatigue, diarrhea, weight loss, fat mass loss, muscle mass loss, cardiac muscle loss, and general weakness. In some embodiments, nausea or vomiting may begin within 1 minute to 24 hours after administration of doxorubicin. In some embodiments, nausea or vomiting lasts up to 1 hour to one week after administration of doxorubicin. In some embodiments, nausea or vomiting beings or persists 1 minute to one week after administration of doxorubicin. In some embodiments, the administration of doxorubicin and a non-naturally occurring melanocortin analog reduces or prevents one or more of these symptoms.

[0872] In some embodiments, nausea or vomiting may begin within 1 to 24 hours after administration of doxorubicin. In some embodiments, nausea or vomiting lasts up to 1 hour to 24 hours after administration of doxorubicin. In some embodiments, nausea or vomiting begins or persists 24 hours or more after administration doxorubicin. In some embodiments, the administration of doxorubicin and a non-naturally occurring melanocortin analog reduces or prevents one or more of these symptoms.

[0873] In some embodiments, doxorubicin is administered before, during, or after administration of a non-naturally occurring melanocortin analog. In some embodiments, doxorubicin is administered at a dose of 10 mg/m^2 to about 1000 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0874] In some embodiments, doxorubicin is administered at a dose of at least 10 mg/m^2 to at least 1000 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0875] In some embodiments, doxorubicin is administered at a dose of at least about 5 mg/m^2 to at least about 500 mg/m^2 per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0876] In some embodiments, doxorubicin is administered at a dose of about 5 mg/m^2,10 mg/m^2, 20 mg/m^2, 30 mg/m^2, 40 mg/m^2, 50 mg/m^2, 60 mg/m^2, 70 mg/m^2, 80 mg/m^2, 90 mg/m^2, 100 mg/m^2, 150 mg/m^2, 200 mg/m^2, 250 mg/m^2, 300 mg/m^2, 400

mg/m^2, or 500 mg/m^2 or more per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0877] In some embodiments, doxorubicin is administered at a dose of 5 mg/m^2,10 mg/m^2, 20 mg/m^2, 30 mg/m^2, 40 mg/m^2, 50 mg/m^2, 60 mg/m^2, 70 mg/m^2, 80 mg/m^2, 90 mg/m^2, 100 mg/m^2, 150 mg/m^2, 200 mg/m^2, 250 mg/m^2, 300 mg/m^2, 400 mg/m^2, or 500 mg/m^2 or more per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0878] In some embodiments, doxorubicin is administered at a dose of at least 5 mg/m^2,10 mg/m^2, 20 mg/m^2, 30 mg/m^2, 40 mg/m^2, 50 mg/m^2, 60 mg/m^2, 70 mg/m^2, 80 mg/m^2, 90 mg/m^2, 100 mg/m^2, 150 mg/m^2, 200 mg/m^2, 250 mg/m^2, 300 mg/m^2, 400 mg/m^2, or 500 mg/m^2 or more per day before, during, or after administration of the non-naturally occurring melanocortin analog.

[0879] In some embodiments, the doxorubicin is administered hourly, twice daily, once daily, once every 2 days, once every 3 days, once every 4 days, once every 5 days, or once a week.

[0880] In some embodiments, the doxorubicin is administered by continuous 1-hour, 2-hour, 3-hour, 4-hour, 5-hour, 6-hour, 7-hour, 8-hour, 9-hour, 10-hour, 12-hour, 14-hour, 16-hour, 18-hour, 20-hour, 22-hour, 24-hour, 36-hour, or 72-hour infusion.

[0881] In some embodiments, doxorubicin is administered by daily pulse doses. In some embodiments, the subject has received one or more of a nutritive therapy, a nutritional supplement, an antiemetic, or a therapeutic for preventing cancer associated wasting before during, or after administration of doxorubicin or the non-naturally occurring melanocortin analog.

[0882] In some embodiments, the subject administered the non-naturally occurring melanocortin analog before, during, or after administration of the doxorubicin exhibits one or more of a reduction in vomiting or nausea compared to baseline or control, a reduction in gastrointestinal side effects that are not vomiting or nausea compared to baseline or control, a reduction in asthenia compared to baseline or control, a reduction in anorexia compared to baseline or control, an increase in appetite compared to baseline or control, a reduction in fatigue compared to baseline or control, a reduction in diarrhea compared to baseline or control, an increase in body weight compared to

baseline or control, a reduced rate of weight loss compared to baseline or control, an increase in skeletal muscle mass compared to baseline or control, a reduced rate of loss of skeletal muscle mass compared to baseline or control, an increase in cardiac muscle mass compared to baseline or control, a reduced rate of loss of cardiac muscle mass compared to baseline or control, an increase in fat mass compared to baseline or control, a reduced rate of loss of fat mass compared to baseline or control, an increase in bone density compared to baseline or control, a reduction in rate of loss of bone density compared to baseline or control, a reduction in general weakness compared to baseline or control, a reduction of ECOG performance score compared to baseline or control, a maintenance in ECOG performance score, an increase in KPS score compared to baseline or control, a maintenance in KPS score, no titration of doxorubicin treatment, reduced titration of doxorubicin treatment compared to baseline or control, reduction in Iatrogenic injury, an increase in cumulative mass compared to baseline or control, a reduction in rate of loss of cumulative mass compared to baseline or control, an increase in net weight gain compared to baseline or control, an increase in cumulative food intake compared to baseline or control, an increase in BMI compared to baseline or control, a reduced BMI decline compared to baseline or control, or a reduced proinflammatory transcript/protein level compared to baseline or control.

[0883] In some embodiments, the subject administered the non-naturally occurring melanocortin analog before, during, or after administration of doxorubicin exhibits one or more of

(a) a reduction in the onset of vomiting or nausea compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after doxorubicin administration;

(b) a reduction in the duration of vomiting or nausea compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 24 hours, 48 hours, 72 hours, 96 hours, 5 days, 6 days, or 7 days after doxorubicin administration;

(c) a reduction in the onset of abdominal discomfort or pain compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after doxorubicin administration;

(d) a reduction in the duration of abdominal discomfort or pain compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 24 hours, 48 hours, 72 hours, 96 hours, 5 days, 6 days, or 7 days after doxorubicin administration;

(e) a reduction in the onset of hemorrhagic colitis compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after doxorubicin administration;

(f) a reduction in the duration of hemorrhagic colitis compared to baseline or control about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after doxorubicin administration;

(g) a reduction in asthenia compared to baseline or control compared to control within about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after doxorubicin administration;

(h) a reduction in general physical deterioration to baseline or control compared to control measured by an increase in body mass index by about 0.25, 0.5, 1.0, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 5.75, 6, 6.26, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 9.25, 9.5, 9.75, or 10 or more;

(i) a reduction in the onset of influenza-like illness or chills about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after doxorubicin administration;

(j) a reduction in the duration of influenza-like illness or chills about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours after doxorubicin administration;

(k) a reduction in anorexia compared to baseline or control measured by an increase in body mass index by about 0.25, 0.5, 1.0, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 5.75, 6, 6.26, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 9.25, 9.5, 9.75, or 10 or more;

(l) an increase in appetite compared to baseline or control, which may be measured by an increase in calorie consumption by about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 125%, 150%, 175%, 200%, 250%, 300%, 350%, 400%, 450%, or 500% or more;

(m) a reduction in fatigue compared to baseline or control, which may be measured by an increase in perceived energy or reduced energy expenditure about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after doxorubicin administration;

(n) a reduction in diarrhea compared to baseline or control about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after doxorubicin administration;

(o) an increase in body weight compared to baseline or control measured by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%,

30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 225%, 250%, 275%, 300%, 350%, 400%, 450%, or 500%;

(p) a reduced rate of weight loss compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(q) an increase in skeletal mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(r) a reduction in rate of loss of skeletal mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(s) an increase in cardiac mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(t) a reduction in rate of loss of cardiac mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(u) an increase in fat mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(v) a reduction in rate of loss of fat mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(w) an increase in bone density compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(x) a reduction in rate of loss of bone density compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(y) a reduction in general weakness compared to baseline or control as measured by an increase perceived or exerted force without increased energy expenditure about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, or about 2 weeks after administration of doxorubicin;

(z) a maintenance in ECOG performance score or a reduction in ECOG performance score compared to baseline or control by about 1, 2, or 3;

(aa) a maintenance in KPS score or an increase in KPS score compared to baseline or control by about 100, 90, 80, 70, 60, 50, 40, or 30;

(bb) a reduction in titration of doxorubicin treatment by about1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% compared to baseline or control;

(cc) an increase in tolerance of administered dose of doxorubicin treatment compared to baseline or control by about 5 mg/m^2,10 mg/m^2, 20 mg/m^2, 30 mg/m^2, 40 mg/m^2, 50 mg/m^2, 60 mg/m^2, 70 mg/m^2, 80 mg/m^2, 90 mg/m^2, 100 mg/m^2, 150 mg/m^2, 200 mg/m^2, 250 mg/m^2, 300 mg/m^2, 400 mg/m^2, or 500 mg/m^2 or more;

(dd) an increase in frequency of administration of doxorubicin treatment compared to baseline or control by about 1 hour, 12 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 2 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, or 6 months;

(ee) a reduction IN iatrogenic injury by about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% compared to baseline or control;

(ff) an increase in cumulative mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(gg) a reduction in rate of loss of cumulative mass compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(hh) an increase in net weight gain compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(ii) an increase in cumulative food intake compared to baseline or control by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 2%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%;

(jj) an increase in BMI compared to baseline or control by at least about 0.5 kg/m^2, 1.0 kg/m^2, 1.5 kg/m^2, 2.0 kg/m^2, 2.5 kg/m^2, 3.0 kg/m^2, 3.5 kg/m^2, 4.0 kg/m^2, 4.5 kg/m^2, 5.0 kg/m^2, 5.5 kg/m^2, 6.0 kg/m^2, 6.5 kg/m^2, 7.0 kg/m^2, 7.5 kg/m^2, 8.0 kg/m^2, 8.5 kg/m^2, 9.0 kg/m^2, 9.5 kg/m^2, 10.0 kg/m^2, 10.5 kg/m^2, 11.0 kg/m^2, 11.5 kg/m^2, or 12.0 kg/m^2;

(kk) a reduction in an inflammatory transcript level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(ll) a reduction in an inflammatory protein level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(mm) an increase in FAACT score compared to baseline or control by at least 1, 2, 3, 4, or 5 points;

(nn) an increase in OS compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(oo) an increase in PFS compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(pp) an increase in BMI durability compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%;

(qq) a reduction in time to cancer treatment failure compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%; and

(rr) a reduction in ctDNA levels compared to baseline or control by at least about 10%, 20%, 30%m 40%, 50%, 60%, 70%, 80%, 90%, or 100%.

Additional Embodiments of Non-Naturally Occurring Melanocortin Analogs

[0884] Additional aspects of melanocortin analogs that may be used in the methods of the present technology are described below.

[0885] Cyclized melanocortin analogs have shown improved efficacy and stability. See Balse-Srinivasan et al., *J. Med. Chem.* 46(17): 3728-3733 (2003) and Bednarek et al., *Biochem. Biophys. Res. Com.* 286(3): 641-645 (2001); Kavarana, et al., *J. Med. Chem.* 45(12): 2644-2650 (2002). In one aspect, the non-naturally occurring melanocortin analog represented by Formula I is cyclized. The following represents a non-limiting list of examples of how the non-naturally occurring melanocortin analog represented by Formula I may be cyclized:

[0886] In Formula I, disulfide bond between R^1 or R^2 and R^7 or Y^1, when R^1 or R^2 is cysteine and R^7 or Y^1 is cysteine as described in Balse-Srinivasan et al., *J. Med. Chem.*, 2003, 46(23): 4965-4973. When Y^1 is cysteine, Y^2 is not absent, but is selected from the group consisting of D-threonine, L-threonine, D-proline, L-proline and a piperazin-2-one ring.

[0887] A lactam bridge between R^1 and R^7, when R^1 is norleucine and R^7 is glutamic acid, as described in Mayorov et al. *J. Med. Chem.* 49: 1946-1952 (2006) and Bednarek et al., *Biochem. Biophys. Res. Com.* 286(3): 641-645 (2001).

[0888] A side-chain lactam bridge between R^2 and R^7, when R^2 is glutamic acid or aspartic acid and R^7 is lysine, as described in Bednarek et al., *Biochem. Biophys. Res. Com.* 286(3): 641-645 (2001).

[0889] A lactam bridge between R^1 and R^7, when R^1 is succinic acid or o-pthalic acid and R^7 is lysine, as described in Bednarek et al., *Biochem. Biophys. Res. Com.* 286(3): 641-645 (2001) and Kavarana et al., *J. Med. Chem.* 45(12): 2644-2650 (2002).

[0890] A lactam bridge between R^2 or R^3 and R^7, when R^2 or R^3 is succinic acid and R^7 is 2,3-diamino-propionic acid as described in Bednarek et al., *Biochem. Biophys. Res. Com.* 286(3): 641-645 (2001).

[0891] A "backbone" cyclized peptide is formed by covalent bond formation between the C- and/or N-terminus of a linear peptide of interest. An example of this is described in the bonding of two amide nitrogens via a bridge consisting of alkyl groups and an amide, as described by Hess et al., *J. Med. Chem.* 50: 6201-6211 (2007).

Peptide Synthesis

[0892] The non-naturally occurring melanocortin analogs described herein may be readily synthesized by any known conventional procedure for the formation of a peptide linkage between amino acids. Such conventional procedures include, for example, any solution phase procedure permitting a condensation between the free alpha amino group of an amino acid or residue thereof having the carboxyl group or other reactive groups protected and the free primary carboxyl group of another amino acid or residue thereof having the amino group or other reactive groups protected. In an exemplary procedure, the peptides described herein may be synthesized by solid-phase synthesis and purified according to methods known in the art. Any of a number of well-known procedures utilizing a variety of resins and reagents may be used to prepare the peptides described herein.

[0893] The process for synthesizing the peptides may be carried out by a procedure whereby each amino acid in the desired sequence is added one at a time in succession to another amino acid or residue thereof or by a procedure whereby peptide fragments with the desired amino acid sequence are first synthesized conventionally and then condensed to provide the desired peptide. The resulting peptide is then cyclized to yield a cyclic peptide.

[0894] Solid phase peptide synthesis methods are well known and practiced in the art. In such methods, the synthesis of peptides may be carried out by sequentially incorporating the desired amino acid residues one at a time into the growing peptide chain according to the general principles of solid phase methods. These methods are described in numerous references, including Merrifield, *Angew Chem.* 24:799-810 (1985) and Barany et al., *The Peptides, Analysis, Synthesis and Biology*, Vol. 2, Gross E. and Meienhofer J., Eds. Academic Press 1-284 (1980).

[0895] In chemical syntheses of peptides, reactive side chain groups of the various amino acid residues are protected with suitable protecting groups, which prevent a chemical reaction from occurring at that site until the protecting group is removed. Also common is the protection of the alpha amino group of an amino acid residue or fragment while that entity reacts at the carboxyl group, followed by the selective removal of the alpha amino protecting group to allow a subsequent reaction to take place at that site.

Specific protecting for solid phase synthesis methods and solution phase synthesis methods groups are known to those having ordinary skill in the art.

[0896] Alpha amino groups may be protected by a suitable protecting group, including a urethane-type protecting group, such as benzyloxycarbonyl (Z) and substituted benzyloxycarbonyl, such as p-chlorobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, p-biphenyl-isopropoxycarbonyl, 9-fluorenylmethoxycarbonyl (Fmoc) and p-methoxybenzyloxycarbonyl (Moz); aliphatic urethane-type protecting groups, such as t-butyloxycarbonyl (Boc), diisopropylmethoxycarbonyl, isopropoxycarbonyl, and allyloxycarbonyl. Fmoc is useful for alpha amino protection.

[0897] Guanidino groups may be protected by a suitable protecting group, such as nitro, p-toluenesulfonyl (Tos), Z, pentamethylchromanesulfonyl (Pmc), adamantyloxycarbonyl, pentamethyldihydrobenzofuran-5-sulfonyl (Pbf) and Boc. Pmc is a useful protecting group for Arg.

[0898] Solid phase synthesis is commenced from the C-terminal end of the peptide by coupling a protected alpha amino acid to a suitable resin. Such starting material is prepared by attaching an alpha amino-protected amino acid by an ester linkage to a p-benzyloxybenzyl alcohol (Wang) resin or a 2-chlorotrityl chloride resin, by an amide bond between an Fmoc-Linker, such as p-((R,S)-α-(1-(9H-fluor-en-9-yl)-methoxyformamido)-2,4-dimethyloxybenzyl)-phenoxyacetic acid (Rink linker) to a benzhydrylamine (BHA) resin, or by other means well known in the art. Fmoc-Linker-BHA resin supports are commercially available and generally used when feasible. The resins are carried through repetitive cycles as necessary to add amino acids sequentially. The alpha amino Fmoc protecting groups are removed under basic conditions. Piperidine, piperazine, diethylamine, or morpholine (20-40% v/v) in N,N-dimethylformamide (DMF) may be used for this purpose.

[0899] Following removal of the alpha amino protecting group, the subsequent protected amino acids are coupled stepwise in the desired order to obtain an intermediate, protected peptide-resin. The activating reagents used for coupling of the amino acids in the solid phase synthesis of the peptides are well known in the art. After the peptide is synthesized, if desired, the orthogonally protected side chain protecting

groups may be removed using methods well known in the art for further derivatization of the peptide.

[0900] Reactive groups in a peptide may be selectively modified, either during solid phase synthesis or after removal from the resin. For example, peptides may be modified to obtain N-terminus modifications, such as acetylation, while on resin, or may be removed from the resin by use of a cleaving reagent and then modified. Methods for N-terminus modification, such as acetylation, and for C-terminus modification, such as amidation, are known in the art. Similarly, methods for modifying side chains of amino acids are well known to those skilled in the art of peptide synthesis. The choice of modifications made to reactive groups present on the peptide will be determined, in part, by the characteristics that are desired in the peptide.

[0901] The peptide may be cyclized prior to cleavage from the peptide resin. For cyclization through reactive side chain moieties, the desired side chains are deprotected, and the peptide suspended in a suitable solvent and a cyclic coupling agent added. Suitable solvents include, for example DMF, dichloromethane (DCM) or 1-methyl-2-pyrrolidone (NMP). Suitable cyclic coupling reagents include, for example, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), benzotriazole-1-yl-oxy-tris(dimethylamino)phosphoniumhexafluorophosphate (BOP), benzotriazole-1-yl-oxy-tris(pyrrolidino)phosphoniumhexafluorophosphate (PyBOP), 2-(7-aza-1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TATU), 2-(2-oxo-1 (2H)-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU) or N,N′-dicyclohexylcarbodiimide/1-hydroxybenzotriazole (DCCI/HOBt). Coupling is convention initiated by use of a suitable base, such as N,N-diispropylethylamine (DIPEA), sym-collidine or N-methylmorpholine (NMM).

[0902] Following cleavage of peptides from the solid phase following their synthesis, the peptide may be purified by any number of methods, such as reverse phase high performance liquid chromatography (RP-HPLC), using a suitable column, such as a C_{18} column. Other methods of separation or purification, such as methods based on the size or charge of the peptide, may also be employed. Once purified, the peptide may be characterized by any number of methods, such as high-performance liquid chromatography (HPLC), amino acid analysis, mass spectrometry, and the like.

Salt Forms of Peptides

[0903] The non-naturally occurring melanocortin analog peptides described herein may be in the form of any salt. The term "pharmaceutically acceptable salts" refers to salts prepared from non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Exemplary salts are the ammonium, calcium, lithium, magnesium, potassium, and sodium salts. Salts derived from organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N′-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

[0904] When the peptides described herein are basic, acid addition salts may be prepared from non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, carboxylic, citric, ethanesulfonic, formic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, malonic, mucic, nitric, pamoic, pantothenic, phosphoric, propionic, succinic, sulfuric, tartaric, p-toluenesulfonic acid, trifluoroacetic acid, and the like. Acid addition salts of the peptides described herein are prepared in a suitable solvent from the peptide and an excess of an acid, such as hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, trifluoroacetic, citric, tartaric, maleic, succinic or methanesulfonic acid. The acetate salt form is especially useful. Where the peptides described herein include an acidic moiety, suitable salts may include alkali metal salts, such as sodium or potassium salts, or alkaline earth metal salts, such as calcium or magnesium salts.

Methods of Administration

[0905] In any of the foregoing aspects, the non-naturally occurring melanocortin analog is administered via intraperitoneal, intravenous, parenteral, subcutaneous, intramuscular, intracerebroventricular, intranasal, or oral administration.

[0906] In some embodiments, the pharmaceutical composition comprising the non-naturally occurring melanocortin analog is administered to the subject parenterally.

[0907] In some embodiments, the pharmaceutical composition comprising the non-naturally occurring melanocortin analog is administered to the subject subcutaneously.

[0908] In any of the foregoing aspects, the non-naturally occurring melanocortin analog may be present in a pharmaceutical composition. In some embodiments, the pharmaceutical composition further comprises a pharmaceutical salt. In some embodiments, the pharmaceutical composition further comprises a pharmaceutical carrier. In some embodiments, the pharmaceutical carrier comprises water.

[0909] In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of 0.1 mg/mL to 500 mg/mL, relative to a total volume of the pharmaceutical composition.

[0910] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3), and the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of 5 mg/mL to 100 mg/mL, relative to a total volume of the pharmaceutical composition. In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of about 10 mg/mL, about 20 mg/mL, about 30 mg/mL, about 40 mg/mL, about 50 mg/mL, or about 60 mg/mL, relative to a total volume of the pharmaceutical composition. In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of about 50 mg/mL, relative to a total volume of the pharmaceutical composition.

[0911] In any of the foregoing aspects, the non-naturally occurring melanocortin analog may cross the blood-brain-barrier of the subject.

[0912] In any of the foregoing aspects, the non-naturally occurring melanocortin analog is administered to a subject prior to or after a meal.

[0913] In any of the foregoing aspects, the non-naturally occurring melanocortin analog is administered to a subject with a meal.

[0914] In any of the foregoing aspects, a therapeutically effective amount of the non-naturally occurring melanocortin analog is administered, and the therapeutically effective amount of the non-naturally occurring melanocortin analog is from 0.001 mg/kg to 25 mg/kg per body weight of the subject. In some embodiments, the therapeutically effective amount of the non-naturally occurring melanocortin analog is from 0.5 mg/kg to 10 mg/kg per body weight of the subject.

[0915] In any of the foregoing aspects, the non-naturally occurring melanocortin analog may be administered at least once daily in an amount ranging from 0.001 mg/kg to 25 mg/kg per body weight of the subject. In some embodiments, the non-naturally occurring melanocortin analog is administered at least once daily in an amount ranging from about 0.5 mg/kg to about 10 mg/kg per body weight of the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3), and the non-naturally occurring melanocortin analog is administered at least once daily in an amount ranging from 0.001 mg/kg to 25 mg/kg per body weight of the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3), and the non-naturally occurring melanocortin analog is administered at least once daily in an amount ranging from 0.5 mg/kg to 10 mg/kg per body weight of the subject.

[0916] In any of the foregoing aspects, the non-naturally occurring melanocortin analog may be administered to the subject for at least 1 day, 1 week, 1 month, 3 months, 6 months, 1 year, or 5 years.

[0917] In any of the foregoing aspects, wherein the non-naturally occurring melanocortin analog may be administered to the subject for 1 day, 5 days, 7 days, 14 days, 21 days, 28 days, 35 days, 40 days, 45 days, 50 days, 60 days, 75 days, 90 days, 100 days, 110 days, or 120 days.

[0918] The anti-cancer agent and the non-naturally occurring melanocortin analog of the present technology may be formulated as a single composition with a single dose or multiple doses. Alternatively, the anti-cancer agent and the non-naturally occurring melanocortin analog may be formulated independently as separate compositions each containing the anti-cancer agent and the non-naturally occurring melanocortin analog, which are co-administered or separately administered.

[0919] In some embodiments, the anti-cancer agent and the non-naturally occurring melanocortin analog are present in a single pharmaceutical composition.

[0920] In some embodiments, the single pharmaceutical composition is formulated for intraperitoneal, intravenous, parenteral, subcutaneous, intramuscular, intracerebroventricular, or oral administration. In some embodiments, the single pharmaceutical composition is formulated for subcutaneous administration. In some embodiments, the single pharmaceutical composition further comprises a pharmaceutically acceptable carrier and/or excipient. In some embodiments, the pharmaceutically acceptable carrier and/or excipient comprises water.

[0921] In any of the foregoing aspects, the anti-cancer agent and the non-naturally occurring melanocortin analog may be administered simultaneously as a single composition. In some embodiments, the non-naturally occurring melanocortin analog is present in the single composition in a concentration of 0.1 mg/mL to 500 mg/mL, relative to a total volume of the single composition.

[0922] In some embodiments, the anti-cancer agent is present in the single pharmaceutical composition in a concentration of 0.001 mg/mL to 1,000 mg/mL, and the non-naturally occurring melanocortin analog is present in the single pharmaceutical composition in a concentration of 0.1 mg/mL to 50 mg/mL, each relative to a total volume of the single pharmaceutical composition.

[0923] In some embodiments, the anti-cancer agent is present in the single pharmaceutical composition in a concentration of 0.001 mg/mL to 1,000 mg/mL, 0.01 mg/mL to 900 mg/mL, 0.05 mg/mL to 800 mg/mL, 0.1 mg/mL to 700 mg/mL, 0.5 mg/mL to 600 mg/mL, 1 mg/mL to 500 mg/mL, 2.5 mg/mL to 400 mg/mL, 5 mg/mL to 300 mg/mL, 7.5 mg/mL to 200 mg/mL, 10 mg/mL to 100 mg/mL, 25 mg/mL to 90 mg/mL, or 50 mg/mL to 75 mg/mL, relative to a total volume of the single pharmaceutical composition.

[0924] In some embodiments, the non-naturally occurring melanocortin analog is present in the single pharmaceutical composition in a concentration of 0.1 mg/mL to 50 mg/mL, 0.5 mg/mL to 40 mg/mL, 1 mg/mL to 30 mg/mL, 2.5 mg/mL to 20 mg/mL, or 5 mg/mL to 10 mg/mL, relative to a total volume of the single pharmaceutical composition.

[0925] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3), and wherein the non-naturally occurring melanocortin analog is present in the single composition in a concentration of 5 mg/mL to 100 mg/mL, relative to a total volume of the single composition. In some embodiments, the non-naturally occurring melanocortin analog is present in the single composition in a concentration of about 10 mg/mL, about 20 mg/mL, about 30 mg/mL, about 40 mg/mL, about 50 mg/mL, or about 60 mg/mL, relative to a total volume of the single composition. In some embodiments, the non-naturally occurring melanocortin analog is present in the single composition in a concentration of about 50 mg/mL, relative to a total volume of the single composition.

[0926] In some embodiments, the non-naturally occurring melanocortin analog is present in the single composition at a dose of about 5 mg to about 500 mg in a dose volume of about 1 mL to 20 mL, and wherein the administration is performed once, twice, 3 times, 4 times, 5 times, or 10 times per day. In some embodiments, the non-naturally occurring melanocortin analog is present in the single composition at a dose of about 50 mg to about 100 mg in a dose volume of about 2 mL to 10 mL, and wherein the administration is performed once, twice, 3 times, 4 times, 5 times, or 10 times per day. In some embodiments, the non-naturally occurring melanocortin analog is present in the single composition at a dose of about 75 mg in a dose volume of about 5 mL, and wherein the administration is performed once, twice, 3 times, 4 times, 5 times, or 10 times per day. In some embodiments, the administration is performed once per day.

[0927] In any of the foregoing aspects, the anti-cancer agent may be present in a first pharmaceutical composition; and the non-naturally occurring melanocortin analog may be present in a second pharmaceutical composition.

[0928] In some embodiments, the first and the second pharmaceutical compositions are different and are administered sequentially.

[0929] In some embodiments, the first and the second pharmaceutical compositions are different and are administered simultaneously but separately.

[0930] In some embodiments, the second pharmaceutical composition is administered subcutaneously.

[0931] In some embodiments, the anti-cancer agent is present in a first pharmaceutical composition. The anti-cancer agent may be formulated with an optionally present pharmaceutically acceptable carrier and/or excipient to form the first pharmaceutical composition. In some embodiments, the non-naturally occurring melanocortin analog is present in a second pharmaceutical composition. The non-naturally occurring melanocortin analog may be formulated with an optionally present pharmaceutically acceptable carrier and/or excipient to form the second pharmaceutical composition. In some embodiments, the first and the second pharmaceutical compositions are different.

[0932] In some embodiments, the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition in a concentration of 0.1 mg/mL to 50 mg/mL, relative to a total volume of the second pharmaceutical composition. In some embodiments, the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition in a concentration of 0.1 mg/mL to 50 mg/mL, 0.5 mg/mL to 40 mg/mL, 1 mg/mL to 30 mg/mL, 2.5 mg/mL to 20 mg/mL, or 5 mg/mL to 10 mg/mL, relative to a total volume of the second pharmaceutical composition.

[0933] In some embodiments, the anti-cancer agent comprises a chemotherapy, and the chemotherapy is present in the first pharmaceutical composition in a concentration of 0.001 mg/mL to 1,000 mg/mL, relative to a total volume of the first pharmaceutical composition.

[0934] In some embodiments, the anti-cancer agent is present in the first pharmaceutical composition in a concentration of 0.001 mg/mL to 1,000 mg/mL, relative to a total volume of the first pharmaceutical composition. In some embodiments, the anti-cancer agent is present in the first pharmaceutical composition in a concentration of 0.001 mg/mL to 1,000 mg/mL, 0.01 mg/mL to 900 mg/mL, 0.05 mg/mL to 800 mg/mL, 0.1 mg/mL to 700 mg/mL, 0.5 mg/mL to 600 mg/mL, 1 mg/mL to 500 mg/mL, 2.5 mg/mL to 400 mg/mL, 5 mg/mL to 300 mg/mL, 7.5 mg/mL to 200 mg/mL, 10 mg/mL to 100 mg/mL, 25 mg/mL to 90 mg/mL, or 50 mg/mL to 75 mg/mL, relative to a total volume of the first pharmaceutical composition.

[0935] In some embodiments, the anti-cancer agent is cisplatin, and cisplatin is present in the first pharmaceutical composition in a concentration of 0.01 mg/mL to 50 mg/mL, relative to a total volume of the first pharmaceutical composition. In some embodiments, cisplatin is present in the first pharmaceutical composition in a concentration of 0.01 mg/mL to 50 mg/mL, 0.05 mg/mL to 45 mg/mL, 0.1 mg/mL to 40 mg/mL, 0.5 mg/mL to 35 mg/mL, 1 mg/mL to 30 mg/mL, 2.5 mg/mL to 25 mg/mL, 5 mg/mL to 20 mg/mL, 7.5 mg/mL to 15 mg/mL, or 10 mg/mL to 12.5 mg/mL, relative to a total volume of the first pharmaceutical composition.

[0936] In some embodiments, the anti-cancer agent is 5-FU, and 5-FU is present in the first pharmaceutical composition in a concentration of 0.1 mg/mL to 500 mg/mL, relative to a total volume of the first pharmaceutical composition. In some embodiments, 5-FU is present in the first pharmaceutical composition in a concentration of 0.1 mg/mL to 500 mg/mL, 0.5 mg/mL to 450 mg/mL, 1 mg/mL to 400 mg/mL, 2.5 mg/mL to 350 mg/mL, 5 mg/mL to 300 mg/mL, 7.5 mg/mL to 250 mg/mL, 10 mg/mL to 200 mg/mL, 25 mg/mL to 150 mg/mL, or 50 mg/mL to 100 mg/mL, relative to a total volume of the first pharmaceutical composition.

[0937] In some embodiments, the anti-cancer agent is doxorubicin, and doxorubicin is present in the first pharmaceutical composition in a concentration of 0.01 mg/mL to 50 mg/mL, relative to a total volume of the first pharmaceutical composition. In some embodiments, doxorubicin is present in the first pharmaceutical composition in a concentration of 0.01 mg/mL to 50 mg/mL, 0.05 mg/mL to 25 mg/mL, 0.1 mg/mL to 10 mg/mL, 0.5 mg/mL to 5 mg/mL, or 1 mg/mL to 2 mg/mL relative to a total volume of the first pharmaceutical composition.

[0938] The non-naturally occurring melanocortin analog of the combination therapy may be administered using any means known in the art, including orally, rectally, vaginally, ocularly, intranasally, topically, parenterally, or by injection. If administered by injection, the peptide injection may be intravenous (IV), subcutaneous (SC), intramuscular (IM), intraperitoneal (IP), intracerebroventricular (ICV), or other means known in the art. The non-naturally occurring melanocortin analog of the combination therapy may be formulated by any means known in the art, including but not limited to formulation as tablets, capsules, caplets, suspensions, powders, lyophilized preparations, suppositories, pessaries, ocular drops, skin patches, orally

soluble formulations, enteric formulations, solutions sprays, aerosols and the like, and may be mixed and formulated with buffers, binders, excipients, stabilizers, lubricants, oils, adjuvants, anti-oxidants and other agents known in the art. In general, any route of administration by which the peptides are introduced across an epidermal layer of cells may be employed. Administration includes topical delivery. Administration includes delivery across the blood brain barrier. Administration includes delivery through mucous membranes, buccal administration, ophthalmic administration, oral administration, dermal administration, inhalation administration, nasal administration, urethral administration, vaginal administration, rectal administration, and the like.

[0939] In some embodiments, the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition in a concentration of 0.1 mg/mL to 500 mg/mL, relative to a total volume of the second pharmaceutical composition.

[0940] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3), and the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition in a concentration of 5 mg/mL to 100 mg/mL, relative to a total volume of the second pharmaceutical composition. In some embodiments, the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition in a concentration of about 10 mg/mL, about 20 mg/mL, about 30 mg/mL, about 40 mg/mL, about 50 mg/mL, or about 60 mg/mL, relative to a total volume of the second pharmaceutical composition. In some embodiments, the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition in a concentration of about 50 mg/mL, relative to a total volume of the second pharmaceutical composition.

[0941] In some embodiments, the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition at a dose of about 5 mg to about 500 mg in a dose volume of about 1 mL to 20 mL, and wherein the administration is performed once, twice, 3 times, 4 times, 5 times, or 10 times per day. In some embodiments, the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition at a dose of about 50 mg to about 100 mg in a dose volume of about 2 mL to 10 mL, and wherein the administration is performed once, twice, 3 times, 4 times, 5 times, or 10 times per day. In some embodiments, the non-naturally

occurring melanocortin analog is present in the second pharmaceutical composition at a dose of about 75 mg in a dose volume of about 5 mL, and wherein the administration is performed once, twice, 3 times, 4 times, 5 times, or 10 times per day. In some embodiments, the administration is performed once per day.

[0942] In some embodiments, the second pharmaceutical composition comprising the non-naturally occurring melanocortin analog is formulated for intraperitoneal, intravenous, parenteral, subcutaneous, intramuscular, intracerebroventricular, or oral administration. In some embodiments, the second pharmaceutical composition comprising the non-naturally occurring melanocortin analog is formulated for subcutaneous administration.

[0943] In some embodiments, the second pharmaceutical composition further comprises a pharmaceutically acceptable carrier and/or excipient. In related embodiments, the second pharmaceutical composition contains 0.1 to 99.9999 wt.%, preferably 1 to 99.999 wt.%, preferably 5 to 99.99 wt.%, preferably 10 to 99.9 wt.%, preferably 15 to 99 wt.%, preferably 20 to 90 wt.%, preferably 30 to 85 wt.%, preferably 40 to 80 wt.%, preferably 50 to 75 wt.%, preferably 60 to 70 wt.% of the pharmaceutically acceptable carrier and/or excipient relative to a total weight of the second pharmaceutical composition.

[0944] In some embodiments, the first pharmaceutical composition further comprises a pharmaceutically acceptable carrier and/or excipient. In related embodiments, the first pharmaceutical composition contains 0.1 to 99.9999 wt.%, preferably 1 to 99.999 wt.%, preferably 5 to 99.99 wt.%, preferably 10 to 99.9 wt.%, preferably 15 to 99 wt.%, preferably 20 to 90 wt.%, preferably 30 to 85 wt.%, preferably 40 to 80 wt.%, preferably 50 to 75 wt.%, preferably 60 to 70 wt.% of the pharmaceutically acceptable carrier and/or excipient relative to a total weight of the first pharmaceutical composition.

[0945] In some embodiments, the pharmaceutically acceptable carrier and/or excipient of the first pharmaceutical composition is at least one selected from the group consisting of water, a buffer, an inorganic salt, a fatty acid, a vegetable oil, a synthetic fatty ester, a surfactant, and a polymer.

[0946] In some embodiments, the pharmaceutically acceptable carrier and/or excipient of the second pharmaceutical composition is water. In some embodiments,

the pharmaceutically acceptable carrier and/or excipient of the second pharmaceutical composition is a buffer.

[0947] In some embodiments, the anti-cancer agent comprises cisplatin, and cisplatin is administered orally and/or intraperitoneally.

[0948] In some embodiments, the anti-cancer agent comprises 5-FU, and 5-FU is administered orally and/or intraperitoneally.

[0949] In some embodiments, the anti-cancer agent comprises doxorubicin, and doxorubicin is administered orally and/or intraperitoneally.

[0950] In some embodiments, the anti-cancer agent comprises cyclophosphamide, and cyclophosphamide is administered orally and/or intraperitoneally.

[0951] In some embodiments, the anti-cancer agent comprises vincristine, and vincristine is administered orally and/or intraperitoneally.

[0952] In some embodiments, the anti-cancer agent comprises cisplatin ponsegromab, and cisplatin ponsegromab is administered orally and/or intraperitoneally.

[0953] In some embodiments, the subject is administered two or more different anti-cancer agents. In some embodiments, the two or more different anticancer agents are selected from the group consisting of cisplatin, 5-FU, doxorubicin, cyclophosphamide, vincristine, cisplatin ponsegromab, carboplatin, temozolomide, capecitabine, fludarabine, gemcitabine, methotrexate, paclitaxel, and docetaxel.

[0954] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3).

[0955] In any of the foregoing aspects, the non-naturally occurring melanocortin analog and the anti-cancer agent may be administered concurrently.

[0956] In any of the foregoing aspects, the non-naturally occurring melanocortin analog and the anti-cancer agent may be administered sequentially.

[0957] In any of the foregoing aspects, the non-naturally occurring melanocortin analog may be administered before (i.e., pretreatment) and/or after (i.e., post treatment) the anti-cancer agent.

[0958] In any of the foregoing aspects, the non-naturally occurring melanocortin analog may be administered before the anti-cancer agent is administered, wherein the subject has not received an anti-cancer therapy.

[0959] In any of the foregoing aspects, the non-naturally occurring melanocortin analog may be administered after the anti-cancer agent, wherein the subject has received anti-cancer therapy. In some embodiments, the non-naturally occurring melanocortin analog is administered after the subject has received one or more doses of the anti-cancer agent. In some embodiments, the non-naturally occurring melanocortin analog is administered after the subject has received two or more doses of the anti-cancer agent. In some embodiments, the non-naturally occurring melanocortin analog is administered after the subject has received one or more cycles of treatment with the anti-cancer agent. In some embodiments, the non-naturally occurring melanocortin analog is administered after the subject has completed treatment with the anti-cancer agent.

[0960] In any of the foregoing aspects, the non-naturally occurring melanocortin analog may be administered after the final dose of the anti-cancer agent.

[0961] In some embodiments, the non-naturally occurring melanocortin analog is administered before administration of the first dose of the anti-cancer agent.

[0962] In some embodiments, the non-naturally occurring melanocortin analog is administered both before administration of the anti-cancer agent and simultaneously with administration of the anti-cancer agent.

[0963] In some embodiments, the non-naturally occurring melanocortin analog is administered both before and after administration of the anti-cancer agent.

[0964] In some embodiments, the non-naturally occurring melanocortin analog is administered both simultaneously with administration of the anti-cancer agent and after administration of the anti-cancer agent.

[0965] In some embodiments, the non-naturally occurring melanocortin analog is administered before administration of the anti-cancer agent, simultaneously with administration of the anticancer agent, and after administration of the anti-cancer agent.

[0966] In some embodiments, the non-naturally occurring melanocortin analog is administered at least 1 day, at least 2 days, at least 3 days, at least 5 days, at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 6 months, at least 1 year, at least 2 years, or at least 5 years before administration of the anti-cancer agent.

[0967] In some embodiments, the non-naturally occurring melanocortin analog is administered about 1 day, about 2 days, about 3 days, about 5 days, about 1 week, about 2 weeks, about 3 weeks, about 1 month, about 2 months, about 3 months, about 6 months, about 1 year, about 2 years, or about 5 years before administration of the anti-cancer agent.

[0968] In some embodiments, the non-naturally occurring melanocortin analog is administered at least about 1 day, at least about 2 days, at least about 3 days, at least about 5 days, at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 1 month, at least about 2 months, at least about 3 months, at least about 6 months, at least about 1 year, at least about 2 years, or at least about 5 years before administration of the anti-cancer agent.

[0969] In some embodiments, the non-naturally occurring melanocortin analog is administered at least 1 day, at least 2 days, at least 3 days, at least 5 days, at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 6 months, at least 1 year, at least 2 years, or at least 5 years after administration of the anti-cancer agent.

[0970] In some embodiments, the non-naturally occurring melanocortin analog is administered about 1 day, about 2 days, about 3 days, about 5 days, about 1 week, about 2 weeks, about 3 weeks, about 1 month, about 2 months, about 3 months, about 6 months, about 1 year, about 2 years, or about 5 years after administration of the anti-cancer agent.

[0971] In some embodiments, the non-naturally occurring melanocortin analog is administered at least about 1 day, at least about 2 days, at least about 3 days, at least

about 5 days, at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 1 month, at least about 2 months, at least about 3 months, at least about 6 months, at least about 1 year, at least about 2 years, or at least about 5 years after administration of the anti-cancer agent.

[0972] In some embodiments, the first and the second pharmaceutical compositions are different and are administered simultaneously (i.e., concurrently) but separately.

[0973] When the non-naturally occurring melanocortin analog and the anti-cancer agent are administered sequentially, the interval of time between the administration of the anti-cancer agent (e.g., chemotherapeutic agent) and the administration of the non-naturally occurring melanocortin analog may be about 0.5-1 minutes, 2-3 minutes, 4-5 minutes, 6-8 minutes, 9-10 minutes, 12-15 minutes, 20-25 minutes, 30 to 60 minutes, 1 hour, 1-2 hours, 2-6 hours, 2-12 hours, 12-24 hours, 1-2 days, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 15 weeks, 20 weeks, 26 weeks, 52 weeks, 11-15 weeks, 15-20 weeks, 20-30 weeks, 30-40 weeks, 40-50 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, 1 year, 2 years, or any period of time in between. In some embodiments, the first pharmaceutical composition containing the anti-cancer agent and the second pharmaceutical composition containing the non-naturally occurring melanocortin analog are administered less than 15 minutes, less than 30 minutes, less than 45 minutes, less than 1 hour, less than 2 hours, less than 4 hours, less than 8 hours, less than 12 hours, less than 16 hours, less than 20 hours, less than 24 hours, less than 36 hours, or less than 48 hours apart.

[0974] The non-naturally occurring melanocortin analog and the anti-cancer agent of the present technology may also be cyclically administered. For example, the cyclic administration may involve the administration of the first pharmaceutical composition comprising the anti-cancer agent for a period of time, which is followed by the administration of the second pharmaceutical composition comprising the non-naturally occurring melanocortin analog for a period of time and repeating such a sequential administration.

[0975] In some embodiments, a therapeutically effective amount of the anti-cancer agent is administered to a subject with a cancer. In some embodiments, a therapeutically effective amount of the anti-cancer agent is administered at least once per week.

[0976] In some embodiments, the anti-cancer agent is cisplatin. A therapeutically effective amount of cisplatin ranging from 0.01 mg/kg to 25 mg/kg, 0.1 mg/kg to 20 mg/kg, 0.5 mg/kg to 15 mg/kg, 1 mg/kg to 10 mg/kg, or 2 mg/kg to 5 mg/kg may be administered per body weight of the subject. In some embodiments, a therapeutically effective amount of cisplatin of about 2.5 mg/kg may be administered per body weight of the subject.

[0977] In some embodiments, the anti-cancer agent is 5-FU. A therapeutically effective amount of 5-FU ranging from 0.1 mg/kg to 700 mg/kg, 0.5 mg/kg to 600 mg/kg, 1 mg/kg to 500 mg/kg, 5 mg/kg to 400 mg/kg, 10 mg/kg to 300 mg/kg, 25 mg/kg to 200 mg/kg, or 50 mg/kg to 100 mg/kg, is administered per body weight of the subject. In some embodiments, a therapeutically effective amount of 5-FU of about 70 mg/kg per body weight of the subject.

[0978] In some embodiments, the anti-cancer agent is a cytotoxic antibiotic such as doxorubicin. A therapeutically effective amount of a doxorubicin ranging from about 0.005 mg/kg to 50 mg/kg, 0.01 mg/kg to 20 mg/kg, 0.05 mg/kg to 15 mg/kg, 0.1 mg/kg to 10 mg/kg, or 0.4 mg/kg to 5 mg/kg, is administered per body weight of the subject. In some embodiments, a therapeutically effective amount of doxorubicin of about 2 mg/kg per body weight of the subject.

[0979] In some embodiments, the non-naturally occurring melanocortin analog or a pharmaceutical composition thereof (e.g., the second pharmaceutical composition) may be administered hourly (such as every hour, every 2 hours, every 4 hours, every 8 hours, etc.), once a day, or twice a day. In some embodiments, the second pharmaceutical composition containing the non-naturally occurring melanocortin analog may be administered every morning, every evening, or every afternoon. In some embodiments, the non-naturally occurring melanocortin analog or the pharmaceutical composition thereof may be administered before meal, after meal, or with meal.

[0980] In some embodiments, the non-naturally occurring melanocortin analog or the pharmaceutical composition thereof may be administered as a dosing regimen

comprising once, twice, or three times a day administration on a (i) weekly; (ii) every other week; (iii) one week of therapy followed by two, three or four weeks off; (iv) two weeks of therapy followed by one, two, three or four weeks off; (v) three weeks of therapy followed by one, two, three, four or five week off; (vi) four weeks of therapy followed by one, two, three, four or five week off; (vii) five weeks of therapy followed by one, two, three, four or five week off; or (viii) monthly schedule. The (i)-(viii) schedule may be repeated 2, 4, 6, 8, 10, or 12 times or more. In some embodiments, the non-naturally occurring melanocortin analog or pharmaceutical composition thereof is administered at various dosages during the dosing regimen (e.g., a first dose with an effective amount of 10 mg/kg and a second dose with an effective amount of 5 mg/kg).

[0981] In some embodiments, the non-naturally occurring melanocortin analog or the pharmaceutical composition may be administered once every other day, once every 2 or 3 days, once every third day, once per week, once every other week, once every third week, once every month, once every six weeks, once every other month, once every three months, once every six months, or once per year. In some embodiments, administration of the non-naturally occurring melanocortin analog or the pharmaceutical composition at any of the dosing frequencies of the present technology may be repeated for a total of at least 2 dosages, at least 3 dosages, at least 4 dosages, at least 5 dosages, at least 10 dosages, at least 15 dosages, at least 20 dosages, at least 30 dosages, at least 40 dosages, at least 50 dosages or more. In some embodiments, the frequency of dosages of the non-naturally occurring melanocortin analog or the pharmaceutical composition is the same during a treatment regimen. In other embodiments, the frequency of dosages of the non-naturally occurring melanocortin analog or the pharmaceutical composition is different during a treatment regimen. The non-naturally occurring melanocortin analog or the pharmaceutical composition may be administered even less frequently. Alternatively, the dosage regimen may be decreased or increased from an initial dosing regimen for days, weeks, months, or years. In some embodiments, the dosing regimen may be repeated at other intervals.

[0982] In some embodiments, the non-naturally occurring melanocortin analog is administered at least once daily in an amount ranging from about 0.001 mg/kg to 25 mg/kg, 0.01 mg/kg to 20 mg/kg, 0.05 mg/kg to 15 mg/kg, 0.075 mg/kg to 10 mg/kg, 0.1 mg/kg to 8 mg/kg, 0.2 mg/kg to 6 mg/kg, 0.3 mg/kg to 4 mg/kg, 0.4 mg/kg to 2 mg/kg, or 0.5 mg/kg to 1 mg/kg per body weight of the subject.

[0983] In some embodiments, the non-naturally occurring melanocortin analog is administered at least once daily in an amount ranging from about 0.5 mg/kg to about 10 mg/kg, about 1 mg/kg to about 7.5 mg/kg, or about 2.5 mg/kg to about 5 mg/kg per body weight of the subject.

[0984] In some embodiments, the non-naturally occurring melanocortin analog is administered at least once daily in an amount about 0.25 mg/kg, 0.5 mg/kg, 1 mg/kg, 1.5 mg/kg, 2.0 mg/kg, 2.5 mg/kg, 3.0 mg/kg, 3.5 mg/kg, 4.0 mg/kg, 4.5 mg/kg, 5.0 mg/kg, 5.5 mg/kg, 6.0 mg/kg, 6.5 mg/kg, 7.0 mg/kg, 7.5 mg/kg, 8.0 mg/kg, 8.5 mg/kg, 9.0 mg/kg, 9.5 mg/kg, or 10.0 mg/kg per body weight of the subject.

[0985] In some embodiments, the non-naturally occurring melanocortin analog is administered at least once daily in an amount at least 0.25 mg/kg, 0.5 mg/kg, 1 mg/kg, 1.5 mg/kg, 2.0 mg/kg, 2.5 mg/kg, 3.0 mg/kg, 3.5 mg/kg, 4.0 mg/kg, 4.5 mg/kg, 5.0 mg/kg, 5.5 mg/kg, 6.0 mg/kg, 6.5 mg/kg, 7.0 mg/kg, 7.5 mg/kg, 8.0 mg/kg, 8.5 mg/kg, 9.0 mg/kg, 9.5 mg/kg, or 10.0 mg/kg per body weight of the subject.

[0986] In some embodiments, the non-naturally occurring melanocortin analog is administered at least once daily in an amount at least about 0.25 mg/kg, 0.5 mg/kg, 1 mg/kg, 1.5 mg/kg, 2.0 mg/kg, 2.5 mg/kg, 3.0 mg/kg, 3.5 mg/kg, 4.0 mg/kg, 4.5 mg/kg, 5.0 mg/kg, 5.5 mg/kg, 6.0 mg/kg, 6.5 mg/kg, 7.0 mg/kg, 7.5 mg/kg, 8.0 mg/kg, 8.5 mg/kg, 9.0 mg/kg, 9.5 mg/kg, or 10.0 mg/kg per body weight of the subject.

[0987] In some embodiments, the non-naturally occurring melanocortin analog is administered at least once daily in an amount at least about 1.5 mg/kg, 2.0 mg/kg, 2.5 mg/kg, 3.0 mg/kg, 3.5 mg/kg, 4.0 mg/kg, 4.5 mg/kg, 5.0 mg/kg, 5.5 mg/kg, 6.0 mg/kg, 6.5 mg/kg, 7.0 mg/kg, 7.5 mg/kg, 8.0 mg/kg, 8.5 mg/kg, 9.0 mg/kg, 9.5 mg/kg, or 10.0 mg/kg per body weight of the subject, for the entire treatment period. In some embodiments, the non-naturally occurring melanocortin analog is administered after a dosing equivalence point is reached.

[0988] In some embodiments, the non-naturally occurring melanocortin analog is administered at least once daily in a first amount at least about 1.5 mg/kg, 2.0 mg/kg, 2.5 mg/kg, 3.0 mg/kg, 3.5 mg/kg, 4.0 mg/kg, 4.5 mg/kg, 5.0 mg/kg, 5.5 mg/kg, 6.0 mg/kg, 6.5 mg/kg, 7.0 mg/kg, 7.5 mg/kg, 8.0 mg/kg, 8.5 mg/kg, 9.0 mg/kg, 9.5 mg/kg, or 10.0 mg/kg per body weight of the subject, and in a second amount at least about 0.01 mg/kg, 0.1 mg/kg, 0.25 mg/kg, 0.5 mg/kg, 0.75 mg/kg, 1.0 mg/kg, 1.25 mg/kg, 1.5

mg/kg, 1.75 mg/kg, 2.0 mg/kg, 2.25 mg/kg, 2.5 mg/kg, 2.75 mg/kg, or 3 mg/kg per body weight of the subject, wherein the second amount is less than the first amount. In some embodiments, the first amount is administered until a dosing equivalence point is reached. In some embodiments, the second amount is administered after the dosing equivalence is reached.

[0989] In some embodiments, the non-naturally occurring melanocortin analog is administered about once daily in an amount about 3.0 mg/kg per body weight of the subject for the entire treatment period.

[0990] In some embodiments, the non-naturally occurring melanocortin analog is administered at least once daily in an amount about 3.0 mg/kg per body weight of the subject for the entire treatment period.

[0991] In some embodiments, the non-naturally occurring melanocortin analog is administered at least about once daily in an amount about 3.0 mg/kg per body weight of the subject for the entire treatment period.

[0992] In some embodiments, the non-naturally occurring melanocortin analog is administered about once daily in an amount about 3.0 mg/kg per body weight of the subject until a dosing equivalence point is reached.

[0993] In some embodiments, the non-naturally occurring melanocortin analog is administered at least once daily in an amount about 3.0 mg/kg per body weight of the subject until a dosing equivalence point is reached.

[0994] In some embodiments, the non-naturally occurring melanocortin analog is administered at least about once daily in an amount about 3.0 mg/kg per body weight of the subject until a dosing equivalence point is reached.

[0995] In some embodiments, the non-naturally occurring melanocortin analog is administered about once daily in a first amount about 3.0 mg/kg per body weight of the subject, and in a second amount of about 1.0 mg/kg per body weight of the subject. In some embodiments, the first amount is administered until a dosing equivalence point is reached. In some embodiments, the second amount is administered after a dosing equivalence point is reached.

[0996] In some embodiments, the non-naturally occurring melanocortin analog is administered about once daily in a first amount at least 3.0 mg/kg per body weight of

the subject, and in a second amount of at least 1.0 mg/kg per body weight of the subject. In some embodiments, the first amount is administered until a dosing equivalence point is reached. In some embodiments, the second amount is administered after a dosing equivalence point is reached.

[0997] In some embodiments, the non-naturally occurring melanocortin analog is administered about once daily in a first amount at least about 3.0 mg/kg per body weight of the subject, and in a second amount of at least about 1.0 mg/kg per body weight of the subject. In some embodiments, the first amount is administered until a dosing equivalence point is reached. In some embodiments, the second amount is administered after a dosing equivalence point is reached.

[0998] In some embodiments, the non-naturally occurring melanocortin analog is administered two or more times to the subject. In some embodiments, administration of the non-naturally occurring melanocortin analog comprises two or more of the same doses. In some embodiments, administration of the non-naturally occurring melanocortin analog two or more times consists of the same dose.

[0999] In some embodiments, administration of the non-naturally occurring melanocortin analog comprises two or more different doses. In some embodiments, the two or more doses comprise a second dose that is about two times, three times, four times, five times, six times, seven times, eight times, nine times, or ten times greater than a first dose. In some embodiments, the two or more doses comprise a second dose that is at least two times, three times, four times, five times, six times, seven times, eight times, nine times, or ten times greater than a first dose. In some embodiments, the two or more doses comprise a second dose that is at least about two times, three times, four times, five times, six times, seven times, eight times, nine times, or ten times greater than a first dose.

[1000] In some embodiments, the methods of the present technology are performed on the subject for at least 1 day, 1 week, 1 month, 3 months, 6 months, 1 year, or 5 years. In some embodiments, the combination therapy is administered to the subject for at least 1 day, at least 2 days, at least 5 days, at least 6 days, at least 1 week, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 9 months, at least 1 year, at least 2 years, at least 3 years, at least 4 years, or at least 5 years.

[1001] In some embodiments, the methods of the present technology are performed on the subject for 1 day, 7 days, 14 days, 21 days, 28 days, 35 days, 40 days, 45 days, 50 days, 60 days, 75 days, 90 days, 100 days, 110 days, or 120 days.

[1002] In some embodiments, at least one active ingredient of the combination therapy is administered to a subject in a continuous doing schedule. As used herein, a "continuous dosing schedule" is an administration or dosing regimen without dose interruptions, e.g., without days off treatment. Repetition of 21-day or 28-day treatment cycles without dose interruptions is an exemplary continuous dosing schedule.

[1003] In some embodiments, the chemotherapeutic agent is cisplatin and may be administered intraperitoneally at a dose of 0.01 mg/kg to 25 mg/kg, 0.1 mg/kg to 20 mg/kg, 0.5 mg/kg to 15 mg/kg, 1 mg/kg to 10 mg/kg, or 2 mg/kg to 5 mg/kg per body weight of the subject at intervals of about 7 days (±2 days), about 14 days (±2 days), about 21 days (±2 days), or about 28 days (±2 days) throughout the course of treatment. In some embodiments, the chemotherapeutic agent is 5-FU and may be administered intraperitoneally at a dose of 0.1 mg/kg to 700 mg/kg, 0.5 mg/kg to 600 mg/kg, 1 mg/kg to 500 mg/kg, 5 mg/kg to 400 mg/kg, 10 mg/kg to 300 mg/kg, 25 mg/kg to 200 mg/kg, or 50 mg/kg to 100 mg/kg per body weight of the subject at intervals of about 7 days (±2 days), about 14 days (±2 days), about 21 days (±2 days), or about 28 days (±2 days) throughout the course of treatment. In some embodiments, the chemotherapeutic agent is doxorubicin and may be administered interperitoneally at a dose of 0.005 mg/kg to 50 mg/kg, 0.01 mg/kg to 20 mg/kg, 0.05 mg/kg to 15 mg/kg, 0.1 mg/kg to 10 mg/kg, or 0.4 mg/kg to 5 mg/kg per body weight of the subject at intervals of about 7 days (±2 days), about 14 days (±2 days), about 21 days (±2 days), or about 28 days (±2 days) throughout the course of treatment.

[1004] In some embodiments, the anti-cancer agent comprises cisplatin, and the therapeutically effective amount of cisplatin is from 0.01 mg/kg to 25 mg/kg per body weight of the subject. In some embodiments, the therapeutically effective amount of cisplatin is about 2.5 mg/kg per body weight of the subject.

[1005] In some embodiments, the anti-cancer agent comprises 5-FU, and the therapeutically effective amount of 5-FU is from 0.1 mg/kg to 700 mg/kg per body weight of the subject. In some embodiments, the therapeutically effective amount of 5-FU is about 70 mg/kg per body weight of the subject.

[1006] In some embodiments, the anti-cancer agent comprises doxorubicin, and the therapeutically effective amount of doxorubicin is from 0.005 mg/kg to 50mg/kg per body weight of the subject. In some embodiments, the therapeutically effective amount of doxorubicin is about 2 mg/kg per body weight of the subject.

[1007] In some embodiments, the non-naturally occurring melanocortin analog is administered at least once daily in an amount ranging from 0.001 mg/kg to 25 mg/kg per body weight of the subject.

[1008] In some embodiments, wherein the non-naturally occurring melanocortin analog is administered at least once daily in an amount ranging from about 0.5 mg/kg to about 10 mg/kg per body weight of the subject.

[1009] In some embodiments, the anti-cancer agent comprises cisplatin, and cisplatin is administered at a dose of 0.01 mg/kg to 25 mg/kg per body weight of the subject at intervals of about 2 days, about 3 days, about 5 days, about 7 days, about 14 days, about 21 days, or about 28 days.

[1010] In some embodiments, the anti-cancer agent comprises 5-FU, and 5-FU is administered at a dose of 0.1 mg/kg to 700 mg/kg per body weight of the subject at intervals of about 2 days, about 3 days, about 5 days, about 7 days, about 14 days, about 21 days, or about 28 days.

[1011] In some embodiments, the anti-cancer agent comprises carboplatin, and carboplatin is administered at a dose of 0.1 mg/kg to 700 mg/kg per body weight of the subject at intervals of about 2 days, about 3 days, about 5 days, about 7 days, about 14 days, about 21 days, or about 28 days.

[1012] In some embodiments, the anti-cancer agent comprises cyclophosphamide, and cyclophosphamide is administered at a dose of 0.1 mg/kg to 700 mg/kg per body weight of the subject at intervals of about 2 days, about 3 days, about 5 days, about 7 days, about 14 days, about 21 days, or about 28 days.

[1013] In some embodiments, the anti-cancer agent comprises doxorubicin, and doxorubicin is administered at a dose of 0.1 mg/kg to 700 mg/kg per body weight of the subject at intervals of about 2 days, about 3 days, about 5 days, about 7 days, about 14 days, about 21 days, or about 28 days.

[1014] In some embodiments, the anti-cancer agent comprises vincristine, and vincristine is administered at a dose of 0.1 mg/kg to 700 mg/kg per body weight of the subject at intervals of about 2 days, about 3 days, about 5 days, about 7 days, about 14 days, about 21 days, or about 28 days.

[1015] In some embodiments, the anti-cancer agent comprises cisplatin and/or ponsegromab, and cisplatin and/or ponsegromab is administered at a dose of 0.1 mg/kg to 700 mg/kg per body weight of the subject at intervals of about 2 days, about 3 days, about 5 days, about 7 days, about 14 days, about 21 days, or about 28 days.

[1016] In some embodiments, the anti-cancer agent comprises temozolomide, and temozolomide is administered at a dose of 0.1 mg/kg to 700 mg/kg per body weight of the subject at intervals of about 2 days, about 3 days, about 5 days, about 7 days, about 14 days, about 21 days, or about 28 days.

[1017] In some embodiments, the anti-cancer agent comprises capecitabine, and capecitabine is administered at a dose of 0.1 mg/kg to 700 mg/kg per body weight of the subject at intervals of about 2 days, about 3 days, about 5 days, about 7 days, about 14 days, about 21 days, or about 28 days.

[1018] In some embodiments, the anti-cancer agent comprises fludarabine, and fludarabine is administered at a dose of 0.1 mg/kg to 700 mg/kg per body weight of the subject at intervals of about 2 days, about 3 days, about 5 days, about 7 days, about 14 days, about 21 days, or about 28 days.

[1019] In some embodiments, the anti-cancer agent comprises gemcitabine, and gemcitabine is administered at a dose of 0.1 mg/kg to 700 mg/kg per body weight of the subject at intervals of about 2 days, about 3 days, about 5 days, about 7 days, about 14 days, about 21 days, or about 28 days.

[1020] In some embodiments, the anti-cancer agent comprises methotrexate, and methotrexate is administered at a dose of 0.1 mg/kg to 700 mg/kg per body weight of the subject at intervals of about 2 days, about 3 days, about 5 days, about 7 days, about 14 days, about 21 days, or about 28 days.

[1021] In some embodiments, the anti-cancer agent comprises paclitaxel, and paclitaxel is administered at a dose of 0.1 mg/kg to 700 mg/kg per body weight of the

subject at intervals of about 2 days, about 3 days, about 5 days, about 7 days, about 14 days, about 21 days, or about 28 days.

[1022] In some embodiments, the anti-cancer agent comprises docetaxel, and docetaxel is administered at a dose of 0.1 mg/kg to 700 mg/kg per body weight of the subject at intervals of about 2 days, about 3 days, about 5 days, about 7 days, about 14 days, about 21 days, or about 28 days.

[1023] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3), and the non-naturally occurring melanocortin analog is administered at a daily dose of 0.001 mg/kg to 25 mg/kg per body weight of the subject.

[1024] In some embodiments, the daily body weight of a subject treated with the combination therapy is at least 1% to 15% greater than that treated with the corresponding anti-cancer agent alone. In some embodiments, the daily body weight of a subject treated with the combination therapy (e.g., cisplatin and TCMCB07, 5-FU and TCMCB7, doxorubicin and TCMCB07) is at least about 1% greater, at least about 2% greater, at least about 3% greater, at least about 4% greater, at least about 5% greater, at least about 6% greater, at least about 7% greater, at least about 8% greater, at least about 9% greater, at least about 10% greater, at least about 12% greater, at least about 15% greater, at least about 20% greater, at least about 25% greater, at least about 28% greater, or at least about 30% greater than that treated with the corresponding anti-cancer agent alone (e.g., cisplatin and saline, 5-FU and saline, doxorubicin and saline).

[1025] In some embodiments, the method prevents or reduces fat mass loss associated with the anti-cancer agent. In some embodiments, the fat mass of a subject treated with the combination therapy is at least 10% to 100% greater than that treated with the corresponding anti-cancer agent alone. In some embodiments, the fat mass of a subject treated with the combination therapy (e.g., cisplatin and TCMCB07, 5-FU and TCMCB7, doxorubicin and TCMCB07) is at least about 10% greater, at least about 15% greater, at least about 20% greater, at least about 25% greater, at least about 30% greater, at least about 35% greater, at least about 40% greater, at least about 45% greater, at least about 50% greater, at least about 60% greater, at least about 70% greater, at least about 80% greater, at least about 90% greater, at least about 95%

greater, at least about 100% greater, at least about 125% greater, at least about 150% greater, or at least about 200% greater than that treated with the corresponding anti-cancer agent alone (e.g., cisplatin and saline, 5-FU and saline, doxorubicin and TCMCB07).

[1026] In some embodiments, the method prevents or reduces muscle mass loss (i.e., lean mass loss) associated with the anti-cancer agent. In some embodiments, the muscle mass loss is cardiac muscle mass loss, skeletal muscle mass loss, or both. In some embodiments, the cardiac muscle mass loss is determined by measuring change in heart weight. In some embodiments, the skeletal muscle mass loss is determined by measuring change in gastrocnemius tissue weight. In related embodiments, the muscle mass loss is cardiac muscle mass loss, skeletal muscle mass loss, or both. In some embodiments, cardiac muscle loss is determined by heart weight. In some embodiments, skeletal muscle mass loss is determined by gastrocnemius tissue weight.

[1027] In some embodiments, the heart weight of a subject treated with the combination therapy is at least 0.1% to 10% greater than that treated with the corresponding anti-cancer agent alone. In some embodiments, the heart weight of a subject treated with the combination therapy (e.g., cisplatin and TCMCB07, 5-FU and TCMCB7, doxorubicin and TCMCB07) is at least about 0.1% greater, at least about 0.2% greater, at least about 0.5% greater, at least about 1% greater, at least about 2% greater, at least about 3% greater, at least about 4% greater, at least about 5% greater, at least about 6% greater, at least about 7% greater, at least about 8% greater, at least about 9% greater, at least about 10% greater, at least about 12% greater, at least about 15% greater, at least about 20% greater, at least about 25% greater, or at least about 40% greater than that treated with the corresponding anti-cancer agent alone (e.g., cisplatin and saline, 5-FU and saline, doxorubicin and saline).

[1028] In some embodiments, the gastrocnemius tissue weight of a subject treated with the combination therapy is at least 0.1% to 10% greater than that treated with the corresponding anti-cancer agent alone. In some embodiments, the gastrocnemius tissue weight of a subject treated with the combination therapy (e.g., cisplatin and TCMCB07, 5-FU and TCMCB07, doxorubicin and TCMCB07) is at least about 0.1% greater, at least about 0.2% greater, at least about 0.5% greater, at least about 1% greater, at least about 2% greater, at least about 3% greater, at least about 4% greater,

at least about 5% greater, at least about 6% greater, at least about 7% greater, at least about 8% greater, at least about 9% greater, at least about 10% greater, at least about 12% greater, at least about 15% greater, at least about 20% greater, at least about 25% greater, or at least about 40% greater than that treated with the corresponding anti-cancer agent alone (e.g., cisplatin and saline, 5-FU and saline, doxorubicin and saline).

[1029] In some embodiments, the method prevents or reduces fatigue associated with the anti-cancer agent. In some embodiments, fatigue is determined by monitoring locomotor activity. In some embodiments, the locomotor activity of a subject treated with the combination therapy (e.g., cisplatin and TCMCB07, 5-FU and TCMCB7, doxorubicin and TCMCB07) is at least about 1% greater, at least about 2% greater, at least about 3% greater, at least about 4% greater, at least about 5% greater, at least about 6% greater, at least about 7% greater, at least about 8% greater, at least about 9% greater, at least about 10% greater, at least about 12% greater, at least about 15% greater, at least about 20% greater, at least about 25% greater, at least about 28% greater, at least about 30% greater, at least about 40% greater, or at least about 50% greater than that treated with the corresponding anti-cancer agent alone (e.g., cisplatin and saline, 5-FU and saline, doxorubicin and saline).

EXAMPLES

[1030] The following examples are intended to illustrate various embodiments of the present technology. As such, the specific embodiments discussed are not to be construed as limitations on the scope of the present technology. It will be apparent to one skilled in the art that various equivalents, changes, and modifications may be made without departing from the scope of present technology, and it is understood that such equivalent embodiments, are to be included herein. Further, all references cited herein are hereby incorporated by reference in their entirety, as if fully set forth herein.

Example 1: Peptide Synthesis-Generic

[1031] The non-naturally occurring melanocortin analogs described herein were synthesized by conventional procedures (e.g., solution-phase procedure, solid-phase synthesis) for the formation of a peptide linkage between amino acids. The solution-phase procedure involved a condensation between the free alpha amino group of an amino acid or derivative thereof having the carboxyl group or other reactive groups

protected and the free primary carboxyl group of another amino acid or derivative thereof having the amino group or other reactive groups protected. The solid-phase synthesis utilized a variety of resins and reagents and may involve additional purification steps.

[1032] The process for synthesizing the non-naturally occurring melanocortin analogs was generally performed by a procedure as follows. Each amino acid in the desired sequence of the non-naturally occurring melanocortin analogs was added one at a time in succession to another amino acid or derivative thereof or by a procedure whereby peptide fragments with the desired amino acid sequence were first synthesized conventionally and then condensed to provide the desired peptide. In most cases, the resulting peptide was then cyclized to yield a cyclic peptide.

[1033] Solid-phase peptide synthesis was carried out by sequentially incorporating the desired amino acid residues one at a time into the growing peptide chain coupled to a solid-phase support according to the general principles of solid phase methods (*see* Merrifield, *Angew Chem.* 24:799-810 (1985) and Barany et al., *The Peptides, Analysis, Synthesis and Biology*, Vol. 2, Gross E. and Meienhofer J., Eds. Academic Press 1-284 (1980)). An exemplary solid-phase synthesis of non-naturally occurring melanocortin analogs is provided below.

[1034] Initially, the C-terminal amino acid residue of the non-naturally occurring melanocortin analog was coupled to a solid-phase support, *e.g.*, a solid-phase resin. Coupling of the C-terminal amino acid residue and the solid-phase support may be carried out according to any method know in the art. Depending on the coupling method, the alpha-amine of the C-terminal amino acid residue may or may not be protected with an amine protecting group, as described below. Likewise, the carboxyl group of the amino acid residue may or may not be activated prior to coupling to the solid-phase support in order to increase its electrophilicity. Some methods of coupling rely on the formation of an ester bond between the carboxyl group of the amino acid and a reactive handle on the solid-phase resin. For example, an amino acid residue may be coupled to a p-benzyloxybenzyl alcohol resin (Wang) or a 2-chlorotrityl chloride resin via an ester linkage. Some methods of coupling rely on the formation of an aminde bond between the carboxyl group of the amino acid and a reactive handle on the solid-phase resin For example, an amino acid residue may be coupled to a benzhydrylamine

(BHA) resin through an Fmoc-linker such as, for example, p-((R,S)-α-(1-(9H-fluor-en-9-yl)-methoxyformamido)-2,4-dimethyloxybenzyl)-phenoxyacetic acid (Rink linker) via an amide linkage.

[1035] The non-naturally occurring melanocortin analog was then synthesized by sequential amino acid addition or combination of peptide fragments. Subsequently, the peptide was cleaved from the solid-phase support and purified by methods known in the art, such as, for example, reverse phase high performance liquid chromatography (RP-HPLC) using a suitable column, such as a C_{18} column. Additionally, or alternatively, other methods of separation or purification were employed, including, but not limited to, methods based on the size or charge of the peptide. Once purified, the peptide was characterized by methods such as high-performance liquid chromatograph (HPLC), amino acid analysis, mass spectrometry, and the like.

Example 2: Peptide Synthesis-Protecting Groups

[1036] During synthesis of the non-naturally occurring melanocortin analogs, reactive side chain groups of the various amino acid residues were protected with suitable protecting groups, which prevented undesirable chemical reaction from occurring at that site until the protecting group was removed.

[1037] Additionally, protection of the alpha amino group of an amino acid residue or fragment was performed while that entity reacting with the carboxyl group, followed by the selective removal of the alpha amino protecting group to allow a subsequent reaction to take place at that site. Specific protecting groups for solid phase synthesis methods and solution phase synthesis methods are known to those having ordinary skill in the art. Alpha amino groups were protected by a suitable protecting group, including a urethane-type protecting group, such as benzyloxycarbonyl (Z) and substituted benzyloxycarbonyl, such as p-chlorobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, p-biphenyl-isopropoxycarbonyl, 9-fluorenylmethoxycarbonyl (Fmoc) and p-methoxybenzyloxycarbonyl (Moz); aliphatic urethane-type protecting groups, such as t-butyloxycarbonyl (Boc), diisopropylmethoxycarbonyl, isopropoxycarbonyl, and allyloxycarbonyl. Fmoc was also used for alpha amino protection. Guanidino groups, if present, were protected by a suitable protecting group, such as nitro, p-toluenesulfonyl (Tos), Z, pentamethylchromanesulfonyl (Pmc),

adamantyloxycarbonyl, pentamethyldihydrobenzofuran-5-sulfonyl (Pbf) and Boc. Pmc was used as a protecting group for Arg.

[1038] Alpha aminoprotecting groups may be removed under basic conditions, such as, for example, using a solution of piperidine, piperazine, diethylamine, or morpholine (20-40% v/v) in N,N-dimethylformamide (DMF). In synthesis methods in which alpha amino protecting groups were used, protecting groups were removed after synthesis of the peptide and before or after cleavage of the solid-phase support.

Example 3: Peptide Synthesis-Additional Modifications

[1039] If necessary, the peptides were further modified to obtain N-terminus modifications, such as acetylation, while on resin, or were removed from the resin by use of a cleaving reagent and then modified. Likewise, C-terminus modification (e.g., amidation), was performed if needed.

[1040] Additionally, the cyclized peptide structures were obtained prior to cleavage from the peptide resin. For cyclization through reactive side chain moieties, the desired side chains were deprotected, and the peptide suspended in a suitable solvent and a cyclic coupling agent added. Suitable solvents, for example DMF, dichloromethane (DCM) or 1-methyl-2-pyrrolidone (NMP), were used for the cyclization. Suitable cyclic coupling reagents (e.g., 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), benzotriazole-1-yl-oxy-tris(dimethylamino)phosphoniumhexafluorophosphate (BOP), benzotriazole-1-yl-oxy-tris(pyrrolidino)phosphoniumhexafluorophosphate (PyBOP), 2-(7-aza-1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TATU), 2-(2-oxo-1 (2H)-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU), N,N′-dicyclohexylcarbodiimide/1-hydroxybenzotriazole (DCCI/HOBt)) were also used for the cyclization. Coupling was initiated by a suitable base, such as N,N-diispropylethylamine (DIPEA), sym-collidine or N-methylmorpholine (NMM).

Example 4: Peptide Synthesis-Generic

[1041] The non-naturally occurring melanocortin analogs described herein were synthesized by conventional procedures (e.g., solution-phase procedure, solid-phase synthesis) for the formation of a peptide linkage between amino acids. The solution-

phase procedure involved a condensation between the free alpha amino group of an amino acid or residue thereof having the carboxyl group or other reactive groups protected and the free primary carboxyl group of another amino acid or residue thereof having the amino group or other reactive groups protected. The solid-phase synthesis utilized a variety of resins and reagents and could involve additional purification steps.

[1042] The process for synthesizing the non-naturally occurring melanocortin analogs was generally performed by a procedure as follows. Each amino acid in the desired sequence of the non-naturally occurring melanocortin analogs was added one at a time in succession to another amino acid or residue thereof or by a procedure whereby peptide fragments with the desired amino acid sequence were first synthesized conventionally and then condensed to provide the desired peptide. The resulting peptide was then cyclized to yield a cyclic peptide.

[1043] Solid phase peptide synthesis was carried out by sequentially incorporating the desired amino acid residues one at a time into the growing peptide chain according to the general principles of solid phase methods (*see* Merrifield, *Angew Chem.* 24:799-810 (1985) and Barany et al., *The Peptides, Analysis, Synthesis and Biology*, Vol. 2, Gross E. and Meienhofer J., Eds. Academic Press 1-284 (1980)).

[1044] Following cleavage of peptides from the solid phase following their synthesis, the peptide was purified by methods, such as reverse phase high performance liquid chromatography (RP-HPLC), using a suitable column, such as a C_{18} column. Additionally or alternatively, other methods of separation or purification were employed, such as methods based on the size or charge of the peptide. Once purified, the peptide was characterized by methods such as high-performance liquid chromatograph (HPLC), amino acid analysis, mass spectrometry, and the like.

Example 5: Peptide Synthesis-Protecting Groups

[1045] During synthesis of the non-naturally occurring melanocortin analogs, reactive side chain groups of the various amino acid residues were protected with suitable protecting groups, which prevented undesirable chemical reaction from occurring at that site until the protecting group was removed.

[1046] Additionally, protection of the alpha amino group of an amino acid residue or fragment was performed while that entity reacting with the carboxyl group, followed

by the selective removal of the alpha amino protecting group to allow a subsequent reaction to take place at that site. Specific protecting for solid phase synthesis methods and solution phase synthesis methods groups are known to those having ordinary skill in the art. Alpha amino groups were protected by a suitable protecting group, including a urethane-type protecting group, such as benzyloxycarbonyl (Z) and substituted benzyloxycarbonyl, such as p-chlorobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, p-biphenyl-isopropoxycarbonyl, 9-fluorenylmethoxycarbonyl (Fmoc) and p-methoxybenzyloxycarbonyl (Moz); aliphatic urethane-type protecting groups, such as t-butyloxycarbonyl (Boc), diisopropylmethoxycarbonyl, isopropoxycarbonyl, and allyloxycarbonyl. Fmoc was also used for alpha amino protection. Guanidino groups, if present, were protected by a suitable protecting group, such as nitro, p-toluenesulfonyl (Tos), Z, pentamethylchromanesulfonyl (Pmc), adamantyloxycarbonyl, pentamethyldihydrobenzofuran-5-sulfonyl (Pbf) and Boc. Pmc was used as a protecting group for Arg.

[1047] Solid-phase synthesis was commenced from the C-terminal end of the non-naturally occurring melanocortin analog by coupling a protected alpha amino acid to a suitable resin. Such starting material was prepared by attaching an alpha amino-protected amino acid by an ester linkage to a p-benzyloxybenzyl alcohol (Wang) resin or a 2-chlorotrityl chloride resin, by an amide bond between an Fmoc-Linker, such as p-((R,S)-α-(1-(9H-fluor-en-9-yl)-methoxyformamido)-2,4-dimethyloxybenzyl)-phenoxyacetic acid (Rink linker) to a benzhydrylamine (BHA) resin. Fmoc-Linker-BHA resin supports were commercially available. The resins were carried through repetitive cycles as necessary to add amino acids sequentially. The alpha amino Fmoc protecting groups were removed under basic conditions. Piperidine, piperazine, diethylamine, or morpholine (20-40% v/v) in N,N-dimethylformamide (DMF) may be used for this purpose.

[1048] Following removal of the alpha amino protecting group, the subsequent protected amino acids were coupled stepwise in a desired order to obtain a protected peptide-resin intermediate. Activating reagents were used for coupling of the amino acids in the solid phase synthesis of the peptides. After the peptide was synthesized, if desired, the orthogonally protected side chain protecting groups were removed using methods well known in the art for further derivatization of the peptide.

Example 6: Peptide Synthesis-Additional Modifications

[1049] If necessary, the peptides were further modified to obtain N-terminus modifications, such as acetylation, while on resin, or were removed from the resin by use of a cleaving reagent and then modified. Likewise, C-terminus modification (e.g., amidation), was performed if needed.

[1050] Additionally, the cyclized peptide structures were obtained prior to cleavage from the peptide resin. For cyclization through reactive side chain moieties, the desired side chains were deprotected, and the peptide suspended in a suitable solvent and a cyclic coupling agent added. Suitable solvents, for example DMF, dichloromethane (DCM) or 1-methyl-2-pyrrolidone (NMP), were used for the cyclization. Suitable cyclic coupling reagents (e.g., 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), benzotriazole-1-yl-oxy-tris(dimethylamino)phosphoniumhexafluorophosphate (BOP), benzotriazole-1-yl-oxy-tris(pyrrolidino)phosphoniumhexafluorophosphate (PyBOP), 2-(7-aza-1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TATU), 2-(2-oxo-1 (2H)-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU), N,N′-dicyclohexylcarbodiimide/1-hydroxybenzotriazole (DCCI/HOBt)) were also used for the cyclization. Coupling was initiated by a suitable base, such as N,N-diispropylethylamine (DIPEA), sym-collidine or N-methylmorpholine (NMM).

Example 7. Treatment with TCMCB07 and Cisplatin/5-FU in Rat Model: General Materials and Methods

[1051] Unless otherwise specified, the following materials and methods, dosing, and measurements of Examples 7-11 were used to generate the results and discussion of Examples 12-14.

[1052] **Animals:** *Species*: rat; *Strain*: SAS Sprague Dawley; *Sex*: Male; *Age*: 9-10 weeks at the beginning of TCMCB07 administration; *Body weight*: 280 $\pm$ 5 g at the beginning of TCMCB07 administration; *Vendor*: Charles River Laboratory (Wilmington, MA, USA)

[1053] **Husbandry**: Rats were individually housed in a ventilated caging system (IVC) in standard polycarbonate cages with bedding and enrichment provided by OHSU

animal facility. Rat room temperature 21 ± 1°C and Light cycle: 6 AM to 6 PM. Diet (Purina rodent diet 5001, Purina, St. Louis, MO, USA) and tap water were provided by OHSU animal facility, *Ad libitum*.

[1054] *General humane endpoint criteria*: If the animal had mild or moderate impairment of general condition (welfare scoring: activity, posture, piloerection, orbital tightening, breathing problems, diarrhea; dehydration, worsened body condition; other signs of pain, other abnormal behavior, inability to feed, drink, urinate, defecate or groom itself) it was followed and treated according to Veterinary Care SOP for maximum of 2 days, within what time the overall body condition should have returned to normal, otherwise the animals were euthanized. If the overall body condition was impaired to a severe extent, the animals were euthanized immediately. Other criteria included: delay more than 5 seconds in righting reflex, body temperature cannot be maintained within 24 hours, hydrocephalus, unsolvable malocclusion, severe injury or chronic wound, and automutilation.

[1055] *Model-related humane endpoint criteria*: 20% weight loss when compared to the maximum weight during the study, body condition score reached 2.

[1056] *Procedure-specific humane endpoint criteria*: Behavioral tests: Animals were unable to perform the behavioral tests in the experiment. Dosing: If the test substance administration caused impairment in the general condition or signs of pain (such as mentioned in "general and model-related humane endpoint criteria"), the dosing was stopped. If the overall body condition did not improve (estimation with welfare scoring) for supportive treatment, the animals were euthanized.

[1057] *Additional criteria:* Detectable skin reaction (ulceration, swelling, discharge) including subcutaneous space. If parenteral dosing lasts long: abnormally strong response to injection, excessive scratching or biting of injection site.

Example 8. Treatment with TCMCB07 and Cisplatin, 5-FU, Cyclophosphamide, Vincristine, Doxorubicin, or Cisplatin Ponsegromab in Rat Model: Chemotherapy Dose-Response Study

[1058] Mortality was observed in rats treated with high dose of cisplatin (5 mg/kg/week), 5-FU (125 mg/kg/week), cyclophosphamide, vincristine, doxorubicin, or cisplatin plus an anti-GDF-15 mAb comprising a human ponsegromab Fab region and

a murine Fc region after the second cycle of chemotherapy. Therefore, the third cycle of chemotherapy was discontinued to ensure survival of both high dose groups. Data not shown.

[1059] Based on the results of dose-response study, doses of cisplatin 2.5 mg/kg/week (ip), 5-FU 70 mg/kg/week (ip), cyclophosphamide 65 mg/kg/week (ip), vincristine 0.27 mg/kg/week (ip), doxorubicin 2 mg/kg/week (ip), and cisplatin and the anti-GDF-15 mAb were chosen for the TCMCB07/chemotherapy study. Data not shown.

Example 9. Treatment with TCMCB07 and Anticancer Agents in Rat Model: Dosing

[1060] Cisplatin dosing: Chemotherapy agent cisplatin (Teva, North Wales, PA, USA) was purchased from the Pharmacy of Oregon Health & Science University. The concentration of cisplatin was 1 mg/mL. Based on the results of previous rat dose-response studies, the dose of 2.5 mg/kg cisplatin, 70 mg/kg 5-FU, 65 mg/kg cyclophosphamide, 0.27 mg/kg vincristine, 2 mg/kg doxorubicin, and cisplatin and anti-GDF-15 mAb (see Example 8) or administration once per week through intraperitoneal injection (ip) were chosen. Two group rats (chemotherapeutic agent/saline and chemotherapeutic agent/TCMCB07) were treated with a chemotherapeutic agent selected from cisplatin, 5-FU, cyclophosphamide, vincristine, doxorubicin, and cisplatin and anti-GDF-15 on day 0, 7, 14 for total three cycles. The chemotherapeutic agent injection volume was calculated according to individual body weights measured on the day of administration (2.5 µL/g body weight). The injection volume for each animal was carefully checked prior to ip injection.

[1061] TCMCB07 dosing: TCMCB07 (Lot #: AJF84 //473-26, provided by Endevica Bio) was freshly prepared every 1-2 days by dissolving in sterile water at 3 mg/mL in a glass bottle and then stored in 4^0C until dosing. The sc injection volume was 0.5 µL/g (body weight). TCMCB07 dosing was started on day 0 until the endpoint day (day 21). Each dose of TCMCB07 (3 mg/kg/day) was spilt to two sc injections that were performed in early morning and evening: 9:30-10:30 AM after measurement of food intake and body weight and 4:50-5:50 PM before the dark phase onset. Total dosing duration was 21 days. On the endpoint day, rats were only dosed with morning injections. An example experimental scheme is shown in FIG. 5.

Example 10. Therapy with TCMCB07 and Cisplatin, 5-FU, Cyclophosphamide, Vincristine, Doxorubicin, or Cisplatin and Ponsegromab in Rat Model: Measurements

[1062] *Daily food intake*: food intake was measured each day at 8:30 AM – 9:30 AM for total 21-day dosing period (day 0 – 21). Food spillage in the cage bedding was carefully checked, weighed and subtracted from food weight change. Food consumption (daily food intake normalized to daily body weight), cumulative food intake, and weekly food intake were calculated.

[1063] *Daily body weight*: body weight was measured each day at 8:30 AM – 9:30 AM for total 21-day dosing period (days 0 – 21). Daily and weekly body weight gain were calculated.

[1064] *Overall body condition*: overall body condition was observed at daily basis, including morbidity and mortality.

[1065] *Locomotor activity*: voluntary home cage locomotor activity was measured throughout the entire experimental period using a MiniMitter system (MiniMitter, Bend, OR, USA) before and after dosing. Under isoflurane anesthesia, MiniMitter transponders for sensing movement and body temperature were implanted subcutaneously into interscapular area, and the animals were returned to their home cages. Body temperature and movement in a-axis, y-axis and z-axis were automatically recorded in 5-minute intervals. Total movement counts in 12-hour dark phase (active phase) and in 12-hour light phase (inactive phase) were calculated. Movement baseline of each animal was calculated by averaging movement counts of 4 days prior to dosing. Locomotor activity change (%) after dosing was normalized to the baseline.

[1066] *Body composition*: Initial fat mass and lean mass of each animal were measured by a Magnetic Resonance Imaging (MRI) scanner (EchoMRI 4-in-1 Live Animal Composition Analyser; Echo Medical System, Houston, TX, USA) on the day of but prior to MiniMitter implantation, due to MiniMitters' interruption to the MR scans. On the endpoint day, terminal fat mass and lean mass were measured after MiniMitter removal but prior to tissue collection. Net gain (%) of fat mass, lean Mass and water were calculated.

[1067] *Muscle mass*: Cardiac muscle mass and skeletal muscle mass were measurand in the endpoint. After blood collection, heart was dissected and weighed.

Left and right gastrocnemii were dissected and weighed. The average weight of gastrocnemii was calculated. Both cardiac and skeletal muscle mass was normalized to initial body weight. The tissues were snap frozen with dry ice and then stored in -80 ºC.

[1068] *Spleen weight*: Spleen was dissected and weighed, and the weight was normalized to initial body weight.

[1069] *Hematology assay*: On the endpoint day, blood was collected via cardiac puncture and placed into a 1 mL EDTA tube. Hematological parameters were analyzed using a hematology analyzer (HemaVet, 950FS, Drew Scientific, Oxford CT, USA), including total leucocyte counts, leucocyte differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), leucocyte ratio, erythrocytes, and thrombocytes.

[1070] *Serum sample*: Prior to blood collection, the last sc TCMCB07 injection was performed. The time between the last TCMCB07 injection and blood collection was recorded in each animal for further circulating TCMCB07 levels and correlation analysis. Blood was collected through cardiac puncture and placed in a 10-mL tube. Serum was isolated after centrifugation at 1500 x g for 10 minutes. Serum aliquots were stored in -80 ºC.

[1071] Data are shown in FIGS. 1A-4.

Example 11. Treatment with TCMCB07 and Cisplatin, 5-FU, Cyclophosphamide, Vincristine, Doxorubicin, or Cisplatin and Ponsegromab in Rat Model: Results and Discussion

[1072] As shown in FIGS. 6A-6D, 7A-7D, 8A-B, 9A-B, and 10A-D peripheral treatment of the non-naturally occurring melanocortin analog (e.g., TCMCB07) increased food intake in rats with multiple cycles of cisplatin or 5-FU chemotherapy, reversing anorexia induced by platinum-based (e.g., cisplatin) or non-platinum-based (e.g., 5-FU) chemotherapy.

[1073] As shown in FIGS. 11A-E, 12A-B, 13A-B, 14A-B, 15A-D, and 16A-D, peripheral treatment of the non-naturally occurring melanocortin analog (e.g., TCMCB07) attenuated body weight loss in rats with multiple cycles of cisplatin, 5-FU

therapy, cyclophosphamide, vincristine, or cisplatin and ponsegromab maintaining normal body weight during the platinum-based or non-platinum-based chemotherapy.

[1074] As shown in FIGS. 17A-F, 18A-B, and 19A-B, the non-naturally occurring melanocortin analog (e.g., TCMCB07) treatment protected cardiac muscle mass and modestly reduced skeletal muscle wasting during the platinum-based or non-platinum-based chemotherapy.

[1075] As shown in FIGS. 20A-D, 21A-D, and 22A-D the non-naturally occurring melanocortin analog (e.g., TCMCB07) treatment increased fat mass and modestly improved lean mass during the platinum-based or non-platinum-based chemotherapy.

[1076] As shown in FIGS. 23A-D and 24A-D, the non-naturally occurring melanocortin analog (e.g., TCMCB07) treatment had no significant effects on chemotherapy-induced fatigue.

[1077] As shown in FIGS. 25A-D and 26A-D, the non-naturally occurring melanocortin analog (e.g., TCMCB07) treatment exhibited no adverse effects and had no toxicity in hematology when given in combination with a platinum-based (e.g., cisplatin) or non-platinum-based (e.g., 5-FU) chemotherapy.

Example 12. Treatment with TCMCB07 and Doxorubicin in Rat Model

[1078] As shown in FIGs. 27A-D and 28A-B, rats treated with a combination therapy of TCMCB07 ("B07") and doxorubicin increased body weight significantly more than CHF rats treated with doxorubicin alone during the first two weeks of treatment. In the first seven days, CHF rats treated with the combination therapy showed a significantly greater change in bodyweight compared to initial weight than CHF rats treated with doxorubicin alone (FIG. 27A). At two weeks, both rats treated with the combination therapy and rats treated with the vehicle control showed a significantly greater change in bodyweight than rats treated with doxorubicin alone (FIG. 27B). At three weeks, there was no difference in bodyweight change between the three groups (FIG. 27C). At four weeks, rats treated with the vehicle control showed a significantly greater change in bodyweight than rats treated with doxorubicin alone (FIG. 27D). As shown in FIG. 28A, rats treated with doxorubicin and TCMCB07 generally had a higher body weight than CHF rats treated with vehicle and rats treated with doxorubicin alone during the first week, but during the second week of treatment rats treated with

doxorubicin and TCMCB07 only had a higher body weight than rats treated with doxorubicin alone. As shown in FIG. 28B, during the third and fourth weeks of treatment, rats treated with doxorubicin and TCMCB07 generally had a higher bodyweight than rats treated with doxorubicin alone, but a lower body weight than rats treated with vehicle control. These results suggest that TCMCB07 reduces the side effects (i.e., weight loss) caused by doxorubicin treatment.

Example 13: Post treatment with TCMCB07 After Cisplatin Administration in a Rat Model

[1079] Rats (n=10 per condition) were treated with cisplatin alone or cisplatin plus TCMCB07 for 3 weeks total. Cisplatin was intraperitoneally administered at 2.5 mg/kg on days 1 and 8, and at 5.0 mg/kg on day 15. Starting on day 22, rats were then administered TCMCB07 at 3 mg/kg daily by subcutaneous injection or were administered saline. Rats were assessed for body weight (g), body weight gain (percent of initial), and food intake each day. As shown in FIG. 28A and 28B, post treatment with TCMCB07 resulted in increased body weight and body weight gain in both rats administered cisplatin and rats administered cisplatin plus TCMCB07 relative to rats administered saline post treatment. Additionally, post treatment with TCMCB07 resulted in increased cumulative food intake relative to rates administered saline post treatment. These results suggest that post treatment with TCMCB07 may improve negative outcomes associated with cisplatin administration.

[1080] These experiments will be repeated, and body mass index (BMI) of rats will be recorded before any doses of TCMCB07 and/or cisplatin are administered, between TCMCB07 and/or cisplatin doses, and after all doses of TCMCB07 and/or cisplatin are administered. It is expected that post treatment with TCMCB07 will increase BMI in rats relative to those that do not receive TCMCB07 post treatment.

Example 14: Pretreatment with TCMCB07 Before Cisplatin Administration in a Rat Model

[1081] Rats (n=10 per condition) will be pretreated with either TCMCB07 or saline for 14 days. On days 15, 22, and 29, TCMCB07 and saline pretreated rats will be administered a first dose of cisplatin or cisplatin plus TCMCB07. Cisplatin will be

interperitoneally administered and TCMCB07 will be administered by subcutaneous injection.

[1082] It is expected that rats pretreated with TCMCB07 will have improved outcomes like body weight, body weight gain, BMI, and cumulative food intake relative to rats pretreated with saline. Additionally, it is expected that the rats administered cisplatin plus TCMCB07 will display better outcomes relative to rats administered cisplatin alone. In other words, it is expected that body weight, body weight gain, BMI, and cumulative food intake will be highest in rats administered TCMCB07 pretreatment and cisplatin plus TCMCB07. It is expected that these measurements will be lowest in the rats administered saline pretreatment followed by cisplatin treatment alone.

Example 15: cAMP Biological Data

[1083] The antagonist and/or agonist activity of exemplary non-naturally occurring melanocortin analogs (e.g., SEQ ID NOs: 3-5, 8-10, 13, 14, and 290-308) at the MC1R, MC3R, MC4R, and/or MC5R was measured via cAMP accumulation assay, according to the following procedure.

[1084] Recombinant cell lines shown in Table 1 were first stimulated with a melanocortin receptor agonist (e.g., a-MSH), followed by addition of melanocortin receptor antagonists to the cells, in order to evaluate inhibition of cyclic adenosine monophosphate (cAMP) levels. cAMP levels were quantified using Homogeneous Time-Resolved Fluorescence (HTRF). The stimulation and cAMP measurement were performed sequentially. First, the compound stimulated the GPCR which then induced downstream signaling, which was measured soon after. Cell lines used comprised human embryonic kidney (HEK) 293 cells engineered to overexpress MC3R (HEK293/CRE-luc/MC3R) or MC4R (HEK293/MC4R/CRE-GFP). Exemplary cell lines and stimulated receptors used are detailed in Table 1.

Table 1. Cell lines

Cell Line	**Receptor**
HEK293/CRE-luc/MC3R	MC3R
HEK293/MC4R/CRE-GFP	MC4R

[1085] Exemplary non-naturally occurring melanocortin analogs were tested for antagonist and/or activity at the human melanocortin 3 receptor and melanocortin 4 receptor at concentrations ranging from 0.1 nM to 1,000 nM. After stimulation, the level of cyclic adenosine monophosphate (cAMP) in each well was quantified via Homogenous Time-Resolved Fluorescence (HTRF) as a measurement of receptor activity. Dose-response curves and estimated EC_{50} and/or IC_{50} values were then obtained for each antagonist peptide against the MC1R. MC3R, MC4R, and/or MC5R. HS024(TFA) (Ac-c(Cys-Nle-Arg-His-dNal(2')-Arg-Trp-Gly-Cys)-NH2; SEQ ID NO: 525) and was used as a positive control for the antagonist activity of MC3R (FIG. 30A) and MC4R (FIG. 30B).

Non-naturally occurring melanocortin analog grouping

[1086] Non-naturally occurring melanocortin analogs were grouped based on structural similarities. Group A included non-naturally occurring melanocortin analogs A1 and A2, which are linear peptides comprising the motif Pro-dNal(2')-Arg-Trp. Without intending to be limited by any particular theory, the Pro-dNal(2')-Arg-Trp motif is thought to be a pharmacophore on the MC3 and MC4 receptors. Group A peptides are provided in Table 2.

Table 2. Group A non-naturally occurring melanocortin analogs

SEQ ID NO	**Non-naturally occurring melanocortin analog**	**Formula**
13	A1	Ac-Nle-Asp-Pro-dNal(2')-Arg-Trp-Lys-dVal-dPro-NH_2
14	A2	Ac-Nle-Pro-dNal(2')-Arg-Trp-dVal-dPro-NH_2

[1087] Group B included non-naturally occurring melanocortin analogs B1 to B9, which are cyclic and linear peptides comprising the motif Pro-Phe-Phe-Arg-Trp-Lys (SEQ ID NO: 528). Without intending to be limited by any particular theory, the Pro-Phe-Phe-dNal(2')-Arg-Trp motif is thought to be a pharmacophore on the MC3 and MC4 receptors. In particular, the cyclic peptides, B1-B3, comprise the cyclic motif c(Asp-Pro-

Phe-Phe-Arg-Trp-Lys) (SEQ ID NO: 529). Linear peptides B4-B9 differ from each other by N-terminal and/or C-terminal groups. Group B peptides are provided in Table 3.

Table 3. Group B non-naturally occurring melanocortin analogs

SEQ ID NO	Non-naturally occurring melanocortin analog	Formula
504	B1	Ac-Nle-c(Asp-Pro-Phe-Phe-Arg-Trp-Lys)-dVal-dPro-NH_2
505	B2	Ac-Leu-c(Asp-Pro-Phe-Phe-Arg-Trp-Lys)-Val-Pro-NH_2
506	B3	Leu-c(Asp-Pro-Phe-Phe-Arg-Trp-Lys)-Val-Pro
507	B4	Leu-Pro-Phe-Phe-Arg-Trp-Val-Pro
508	B5	Ile-Pro-Phe-Phe-Arg-Trp-Val-Pro
509	B6	Val-Pro-Phe-Phe-Arg-Trp-Val-Pro
510	B7	Leu-Asp-Pro-Phe-Phe-Arg-Trp-Lys-Val-Pro
511	B8	Ile-Asp-Pro-Phe-Phe-Arg-Trp-Lys-Val-Pro
512	B9	Val-Asp-Pro-Phe-Phe-Arg-Trp-Lys-Val-Pro

[1088] Group C included non-naturally occurring melanocortin analogs C1 to C9, which are cyclic and linear peptides comprising the motif Pro-Trp-Arg-Trp-Lys (SEQ ID NO: 530) or a derivative thereof. Without intending to be limited by any particular theory, the Pro-Trp-Arg-Trp-Lys motif is thought to be a pharmacophore on the MC3 and MC4 receptors. In particular, the cyclic peptides, C1-C3, comprise the cyclic motif c(Asp-Pro-Trp-Arg-Trp-Lys) (SEQ ID NO: 531). Linear peptides C4-C9 comprise the motif Pro-Trp-Arg-Trp-Lys or Pro-Trp-Arg-Trp-Val (SEQ ID NO: 532). Group C peptides are provided in Table 4.

Table 4. Group C non-naturally occurring melanocortin analogs

SEQ ID NO	Non-naturally occurring melanocortin analog	Formula

513	C1	Ac-Nle-c(Asp-Pro-Trp-Arg-Trp-Lys)-dVal-dPro-NH_2
514	C2	Ac-Leu-c(Asp-Pro-Trp-Arg-Trp-Lys)-Val-Pro-NH_2
515	C3	Leu-c(Asp-Pro-Trp-Arg-Trp-Lys)-Val-Pro
516	C4	Leu-Pro-Trp-Arg-Trp-Val-Pro
517	C5	Ile-Pro-Trp-Arg-Trp-Val-Pro
518	C6	Val-Pro-Trp-Arg-Trp-Val-Pro
519	C7	Leu-Asp-Pro-Trp-Arg-Trp-Lys-Val-Pro
520	C8	Ile-Asp-Pro-Trp-Arg-Trp-Lys-Val-Pro
521	C9	Val-Asp-Pro-Trp-Arg-Trp-Lys-Val-Pro

[1089] Group D included non-naturally occurring melanocortin analogs D1 to D14 and known MC3R/MC4R antagonists TCMCB02 and TCMCB07, all of which are cyclic peptides comprising the motif Pro-His-dNal(2')-Arg-Trp or a derivative thereof. Without intending to be limited by any particular theory, the Pro-His-dNal(2')-Arg-Trp motif is thought to be a pharmacophore on the MC3 and MC4 receptors. Group D non-naturally occurring melanocortin analogs are provided in Table 5.

Table 5. Group D non-naturally occurring melanocortin analogs

SEQ ID NO	**Non-naturally occurring melanocortin analog**	**Formula**
5	D1	Ac-Nle-$_c$(Asp-Pro-His-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
8	D2	Ac-Nle-$_c$(Asp-His-dNal(2')-Arg-Trp-Pro-Lys)-dVal-dPro-NH_2
4	D3	Ac-Nle-$_c$(Asp-Hyp-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
9	D4	Ac-Nle-$_c$(Asp-Hyp-dNal(2')-Arg-Trp-Pro-Lys)-dVal-dPro-NH_2
10	D5	Ac-Nle-$_c$(Asp-Pro-His-dNal(2')-Arg-Trp-Lys)-dPro-dVal-NH_2

11	D1α	Ac-Nle-c(Asp-Phe-Phe-Pro-His-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
12	D1β	Ac-Nle-Phe-Phe-c(Asp-Phe-His-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
6	D1γ	Ac-Nle-c(Asp-Phe-His-dNal(2')-Arg-Trp-Lys)-dLeu-dPro-NH_2
7	D1δ	Ac-Nle-c(Asp-Phe-His-dNal(2')-Arg-Trp-Lys)-dTle-dPro-NH_2
282	D6	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dThr-dPro-dThr-NH_2
423	D7	Ac-Nle-c(Asp-His-dNal(2')-Arg-Trp-Lys)-dPro-dVal-NH_2
291	D8	Ac-Nle-c(Asp-His-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
288	D9	Ac-Nle-c(dAsp-Pro-dNal(2')-Arg-Trp-dLys)-dPro-dVal-NH_2
295	D10	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-β^3Pro-β^2Val-NH_2
296	D11	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-β^3Pro-β^3Val-NH_2
301	D12	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-β^2Val-β^3Pro-NH_2
302	D13	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-β^3Val-β^3Pro-NH_2
307	D14	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-β^3Pro-β^3Pro-NH_2
286	TCMCB02	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dPro-dVal-NH_2
3	TCMCB07	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
522	Control A: NDP-Alpha-MSH	Ac-Ser-Tyr-Ser-Nle-Glu-His-dPhe-Arg-Trp-Gly-Lys-Pro-Val-NH_2

523	Control B: SHU9119	Ac-Nle-c(Asp-His-d-Nal(2')-Arg-Trp-Lys)-NH_2
524	Control C: PG932	Ac-Nle-c(Asp-Pro-d-Nal(2')-Arg-Trp-Lys)-Pro-Val-NH_2

[1090] Group E included non-naturally occurring melanocortin analogs E1 through E24, all of which are cyclic peptides comprising the motif X-c(Asp-Pro-dNal(2')-Arg-Trp-Lys) (SEQ ID NO: 533), wherein X is an amino acid other than Ac-Nle. Without intending to be limited by any particular theory, the Pro-dNal(2')-Arg-Trp motif in Group E peptides is thought to be a pharmacophore on the MC3 and MC4 receptors. Group E non-naturally occurring melanocortin analogs are provided in Table 6.

Table 6. Group E non-naturally occurring melanocortin analogs

SEQ ID NO	**Non-naturally occurring melanocortin analog**	**Formula**
15	E1	Ac-dArg-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
16	E2	Ac-dMet-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
17	E3	Ac-dIle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
18	E4	Ac-dLeu-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
19	E5	Ac-dVal-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
20	E6	Ac-dAla-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
21	E7	Ac-Ala-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
22	E8	Ac-Tle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
23	E9	Ac-dTle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
24	E10	Ac-dNle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
25	E11	Ac-Nva-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
26	E12	Ac-Gly-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
27	E13	Ac-dPro-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
28	E14	Ac-dCys-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
29	E15	Ac-dPhe-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2

30	E16	Ac-dTyr-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
31	E17	Ac-dGln-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
32	E18	Ac-dAsn-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
35	E19	dTyr-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
36	E20	Tyr-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
37	E21	Dmt-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
195	E22	Ac-Nle-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
196	E23	Ac-Nle-Nle-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
197	E24	Ac-Nle-Nle-Nle-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2

[1091] Group F included non-naturally occurring melanocortin analogs F1 through F32, all of which are peptides cyclized through a bridge other than a bridge between Asp and Lys. Without intending to be limited by any particular theory, the various cyclization forms of the Group F peptides are thought to alter the binding ability of the peptides at the MC3 and MC4 receptors. Group F non-naturally occurring melanocortin analogs are provided in Table 7.

Table 7. Group F non-naturally occurring melanocortin analogs

SEQ ID NO	**Non-naturally occurring melanocortin analog**	**Formula**
40	F1	Ac-Nle-c(dAsp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
41	F2	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-dLys)-dVal-dPro-NH_2
42	F3	Ac-Nle-c(Cys-Pro-dNal(2')-Arg-Trp-Cys)-dVal-dPro-NH_2
43	F4	Ac-Nle-c(dCys-Pro-dNal(2')-Arg-Trp-Cys)-dVal-dPro-NH_2
44	F5	Ac-Nle-c(Cys-Pro-dNal(2')-Arg-Trp-dCys)-dVal-dPro-NH_2
50	F6	Ac-Nle-c(Cys-Pro-dNal(2')-Arg-Trp-Pen)-dVal-dPro-NH_2
51	F7	Ac-Nle-c(dCys-Pro-dNal(2')-Arg-Trp-Pen)-dVal-dPro-NH_2

52	F8	Ac-Nle-c(Pen-Pro-dNal(2')-Arg-Trp-Cys)-dVal-dPro-NH_2
53	F9	Ac-Nle-c(Pen-Pro-dNal(2')-Arg-Trp-dCys)-dVal-dPro-NH_2
54	F10	Ac-Nle-c(Pen-Pro-dNal(2')-Arg-Trp-Pen)-dVal-dPro-NH_2
55	F11	Ac-Nle-c(dPen-Pro-dNal(2')-Arg-Trp-Pen)-dVal-dPro-NH_2
56	F12	Ac-Nle-c(dPen-Pro-dNal(2')-Arg-Trp-dPen)-dVal-dPro-NH_2
57	F13	Ac-Nle-c(Pen-Pro-dNal(2')-Arg-Trp-dPen)-dVal-dPro-NH_2
58	F14	Ac-Nle-c(Cys-dNal(2')-Arg-Trp-Pen)-dVal-dPro-NH_2
59	F15	Ac-Nle-c(dCys-dNal(2')-Arg-Trp-Pen)-dVal-dPro-NH_2
60	F16	Ac-Nle-c(Pen-dNal(2')-Arg-Trp-Cys)-dVal-dPro-NH_2
61	F17	Ac-Nle-c(Pen-dNal(2')-Arg-Trp-dCys)-dVal-dPro-NH_2
62	F18	Ac-Nle-c(Pen-dNal(2')-Arg-Trp-Pen)-dVal-dPro-NH_2
63	F19	Ac-Nle-c(dPen-dNal(2')-Arg-Trp-Pen)-dVal-dPro-NH_2
64	F20	Ac-Nle-c(dPen-dNal(2')-Arg-Trp-dPen)-dVal-dPro-NH_2
65	F21	Ac-Nle-c(Pen-dNal(2')-Arg-Trp-dPen)-dVal-dPro-NH_2
45	F22	Ac-Nle-c(dCys-Pro-dNal(2')-Arg-Trp-dCys)-dVal-dPro-NH_2
46	F23	Ac-Nle-c(Cys-dNal(2')-Arg-Trp-Cys)-dVal-dPro-NH_2
47	F24	Ac-Nle-c(dCys-dNal(2')-Arg-Trp-Cys)-dVal-dPro-NH_2
48	F25	Ac-Nle-c(Cys-dNal(2')-Arg-Trp-dCys)-dVal-dPro-NH_2
49	F26	Ac-Nle-c(dCys-dNal(2')-Arg-Trp-dCys)-dVal-dPro-NH_2
66	F27	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Orn)-dVal-dPro-NH_2
67	F28	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-dOrn)-dVal-dPro-NH_2
68	F29	Ac-Nle-c(Glu-Pro-dNal(2')-Arg-Trp-Orn)-dVal-dPro-NH_2
69	F30	Ac-Nle-c(Glu-Pro-dNal(2')-Arg-Trp-dOrn)-dVal-dPro-NH_2
201	F31	c(CO-cis-CH=CH-CO-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
205	F32	Ac-c(Cys-Arg-dPhe-Cys)-Trp-dVal-dPro-NH_2

[1092] Group G included non-naturally occurring melanocortin analogs G1 through G24, all of which are cyclic peptides comprising the motif Asp-X-dNal(2')-Arg-Trp-Lys (SEQ ID NO: 534), where X is an amino acid other than Pro. Without intending to be limited by any particular theory, the X-dNal(2')-Arg-Trp motif in Group G peptides is

thought to be a pharmacophore on the MC3 and MC4 receptors. Group G non-naturally occurring melanocortin analogs are provided in Table 8.

Table 8. Group G non-naturally occurring melanocortin analogs

SEQ ID NO	Non-naturally occurring melanocortin analog	Formula
71	G1	Ac-Nle-c(Asp-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
72	G2	Ac-Nle-c(Asp-Ala-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
73	G3	Ac-Nle-c(Asp-dPro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
76	G4	Ac-Nle-c(Asp-Pro-Gly-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
77	G5	Ac-Nle-c(Asp-Gly-Gly-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
78	G6	Ac-Nle-c(Asp-Gly-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
75	G7	Ac-Nle-c(Asp-dMet-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
74	G8	Ac-Nle-c(Asp-dAla-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
79	G9	Ac-Nle-c(Asp-Leu-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
80	G10	Ac-Nle-c(Asp-Ile-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
81	G11	Ac-Nle-c(Asp-Val-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
82	G12	Ac-Nle-c(Asp-dLeu-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
83	G13	Ac-Nle-c(Asp-dIle-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
84	G14	Ac-Nle-c(Asp-dVal-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
85	G15	Ac-Nle-c(Asp-Trp-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
86	G16	Ac-Nle-c(Asp-dTrp-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
211	G17	Ac-Nle-c(Asp-Cpe-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
212	G18	Ac-Nle-c(Asp-Che-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
213	G19	Ac-Nle-c(Asp-Oic-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
214	G20	Ac-Nle-c(Asp-Ioc-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
215	G21	Ac-Nle-c(Asp-Tic-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
202	G22	Ac-Nle-c(Asp-β-Ala-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2

203	G23	Ac-Nle-c(Asp-Mamb-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
204	G24	Ac-Nle-c(Asp-Acpc-dNal(2') Arg-Trp-Lys)-dVal-dPro-NH_2

[1093] Group H included non-naturally occurring melanocortin analogs H1 through H15, all of which are cyclic peptides comprising the motif Asp-Pro-dNal(2')-X-Trp-Lys (SEQ ID NO: 535), where X is an amino acid other than Arg. Without intending to be limited by any particular theory, the Pro-dNal(2')-X-Trp motif in Group H peptides is thought to be a pharmacophore on the MC3 and MC4 receptors. Group H non-naturally occurring melanocortin analogs are provided in Table 9.

Table 9. Group H non-naturally occurring melanocortin analogs

SEQ ID NO	**Non-naturally occurring melanocortin analog**	**Formula**
97	H1	Ac-Nle-c(Asp-Pro-dNal(2')-Trp-Lys)-dVal-dPro-NH_2
98	H2	Ac-Nle-c(Asp-Pro-dNal(2')-Lys-Trp-Lys)-dVal-dPro-NH_2
99	H3	Ac-Nle-c(Asp-Pro-dNal(2')-dLys-Trp-Lys)-dVal-dPro-NH_2
100	H4	Ac-Nle-c(Asp-Pro-dNal(2')-dArg-Trp-Lys)-dVal-dPro-NH_2
101	H5	Ac-Nle-c(Asp-Pro-dNal(2')-Orn-Trp-Lys)-dVal-dPro-NH_2
102	H6	Ac-Nle-c(Asp-Pro-dNal(2')-dOrn-Trp-Lys)-dVal-dPro-NH_2
103	H7	Ac-Nle-c(Asp-Pro-dNal(2')-His-Trp-Lys)-dVal-dPro-NH_2
104	H8	Ac-Nle-c(Asp-Pro-dNal(2')-Ala-Trp-Lys)-dVal-dPro-NH_2
105	H9	Ac-Nle-c(Asp-Pro-dNal(2')-Gly-Trp-Lys)-dVal-dPro-NH_2
106	H10	Ac-Nle-c(Asp-Pro-dNal(2')-Asp-Trp-Lys)-dVal-dPro-NH_2
107	H11	Ac-Nle-c(Asp-Pro-dNal(2')-Glu-Trp-Lys)-dVal-dPro-NH_2
108	H12	Ac-Nle-c(Asp-Pro-dNal(2')-dHis-Trp-Lys)-dVal-dPro-NH_2
109	H13	Ac-Nle-c(Asp-Pro-dNal(2')-dAla-Trp-Lys)-dVal-dPro-NH_2
110	H14	Ac-Nle-c(Asp-Pro-dNal(2')-dAsp-Trp-Lys)-dVal-dPro-NH_2
111	H15	Ac-Nle-c(Asp-Pro-dNal(2')-dGlu-Trp-Lys)-dVal-dPro-NH_2

[1094] Group I included non-naturally occurring melanocortin analogs I1 through I13, all of which are cyclic peptides comprising the motif Asp-Pro-dNal(2')-Arg-X-Lys (SEQ ID NO: 536), where X is an amino acid other than Trp. Without intending to be

limited by any particular theory, the Pro-dNal(2')-Arg-X motif in Group I peptides is thought to be a pharmacophore on the MC3 and MC4 receptors. Group I non-naturally occurring melanocortin analogs are provided in Table 10.

Table 10. Group I non-naturally occurring melanocortin analogs

SEQ ID NO	**Non-naturally occurring melanocortin analog**	**Formula**
112	I1	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Lys)-dVal-dPro-NH_2
113	I2	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Nal(1')-Lys)-dVal-dPro-NH_2
119	I3	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-dNal(1')-Lys)-dVal-dPro-NH_2
115	I4	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Phe-Lys)-dVal-dPro-NH_2
120	I5	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-dPhe-Lys)-dVal-dPro-NH_2
121	I6	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-dNal(2')-Lys)-dVal-dPro-NH_2
116	I7	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Tyr-Lys)-dVal-dPro-NH_2
117	I8	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-His-Lys)-dVal-dPro-NH_2
122	I9	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-dTyr-Lys)-dVal-dPro-NH_2
123	I10	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-dHis-Lys)-dVal-dPro-NH_2
118	I11	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Ala-Lys)-dVal-dPro-NH_2
124	I12	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-dAla-Lys)-dVal-dPro-NH_2
200	I13	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-dTrp-Lys)-dVal-dPro-NH_2

[1095] Group J included non-naturally occurring melanocortin analogs J1 through J69, all of which are cyclic peptides comprising the motif Asp-Pro-dNal(2')-Arg-Trp-Lys (SEQ ID NO: 526) and a C-terminus other than dVal-dPro-NH_2. Without intending to be bound by any particular theory, variations to the C-terminus is thought to alter the transport of the Group J peptides through the intestinal tract and/or the blood-brain-barrier. Group J non-naturally occurring melanocortin analogs are provided in Table 11.

Table 11. Group J non-naturally occurring melanocortin analogs

SEQ ID NO	Non-naturally occurring melanocortin analog	Formula
126	J1	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Val-Pro-NH_2
127	J2	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-OH
128	J3	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dPro-dVal-OH
129	J4	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-Hyp-NH_2
130	J5	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dHyp-NH_2
131	J6	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Val-Hyp-NH_2
132	J7	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Val-dHyp-NH_2
133	J8	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Hyp-dVal-NH_2
134	J9	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dHyp-dVal-NH_2
135	J10	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Hyp-Val-NH_2
136	J11	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dHyp-Val-NH_2
137	J12	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dVal-NH_2
138	J13	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dPro-dPro-NH_2
139	J14	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-NH_2
140	J15	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dPro-NH_2
141	J16	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Val-NH_2
142	J17	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Pro-NH_2
143	J18	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Ala-NH_2
144	J19	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dAla-NH_2
145	J20	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dHyp-NH_2
146	J21	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Hyp-NH_2
147	J22	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dAla-dAla-NH_2
148	J23	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Ala-Ala-NH_2
149	J24	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Gly-Gly-NH_2
150	J25	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-Asp-NH_2
151	J26	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-Arg-NH_2

152	J27	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-Asn-NH_2
153	J28	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dAsp-NH_2
154	J29	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dArg-NH_2
155	J30	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dAsn-NH_2
156	J31	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Asp-dPro-NH_2
157	J32	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Arg-dPro-NH_2
158	J33	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Asn-dPro-NH_2
159	J34	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dAsp-dPro-NH_2
160	J35	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dArg-dPro-NH_2
161	J36	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dAsn-dPro-NH_2
162	J37	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Asp-NH_2
163	J38	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Arg-NH_2
164	J39	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Asn-NH_2
165	J40	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dAsp-NH_2
166	J41	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dArg-NH_2
167	J42	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dAsn-NH_2
168	J43	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Lys-Pro-Val-NH_2
169	J44	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Lys-dPro-dVal-NH_2
170	J45	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dLys-dPro-dVal-NH_2
171	J46	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Lys-dPro-NH_2
172	J47	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dLys-dPro-NH_2
173	J48	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Lys-Val-Pro-NH_2
174	J49	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Lys-dVal-dPro-NH_2
175	J50	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dLys-dVal-dPro-NH_2
176	J51	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Arg-Pro-Val-NH_2
177	J52	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Arg-dPro-dVal-NH_2

178	J53	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dArg-dPro-dVal-NH_2
179	J54	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Arg-Val-Pro-NH_2
180	J55	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Arg-dVal-dPro-NH_2
181	J56	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dArg-dVal-dPro-NH_2
182	J57	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dTle-dVal-dPro-NH_2
183	J58	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dTle-dPro-NH_2
184	J59	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dTle-dVal-NH_2
185	J60	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dTle-dTle-NH_2
186	J61	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dTle-dTle-dPro-NH_2
187	J62	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dTle-dTle-dVal-NH_2
188	J63	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dPro-dTle-NH_2
189	J64	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dTle-NH_2
190	J65	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dVal-dPro-NH_2
191	J66	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dPro-dVal-dPro-NH_2
192	J67	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dVal-dVal-dPro-NH_2
193	J68	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-dVal-dPro-NH_2
194	J69	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dVal-dVal-dVal-dVal-dVal-dPro-NH_2
206	J70	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-Trp-NH_2

[1096] Group K included non-naturally occurring melanocortin analogs K1 through K23, all of which are cyclic peptides comprising the motif Asp-Pro-dPhe-Arg-Trp-Lys (SEQ ID NO: 537), or a derivative thereof. Without intending to be limited by any

particular theory, the Pro-dPhe-Arg-Trp motif in Group K peptides is thought to be a pharmacophore on the MC3 and MC4 receptors. Group K non-naturally occurring melanocortin analogs are provided in Table 12.

Table 12. Group K non-naturally occurring melanocortin analogs

SEQ ID NO	**Non-naturally occurring melanocortin analog**	**Formula**
391	K1	Ac-Nle-c(Asp-Pro-p(Cl)dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2
394	K2	Ac-Nle-c(Asp-Pro-p(F)dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2
396	K3	Ac-Nle-c(Asp-His-p(Cl)dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2
398	K4	Ac-Nle-c(Asp-His-p(Br)dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2
399	K5	Ac-Nle-c(Asp-His-p(F)dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2
392	K6	Ac-Nle-c(Asp-Pro-p(I)dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2
393	K7	Ac-Nle-c(Asp-Pro-p(Br)dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2
395	K8	Ac-Nle-c(Asp-Pro-p(CF3)dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2
397	K9	Ac-Nle-c(Asp-His-p(I)dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2
400	K10	Ac-Nle-c(Asp-His-p(CF3)dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2
401	K11	Ac-Nle-c(Asp-Pro-Pro-dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2
402	K12	Ac-Nle-c(Asp-Trp-Pro-dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2
403	K13	Ac-Nle-c(Asp-His-dPhe-Pro-Trp-Lys)-dVal-dPro-NH_2
406	K14	Ac-Nle-c(Asp-Pro-dPhe-Pro-Trp-Lys)-dVal-dPro-NH_2
375	K15	Ac-Nle-c(Asp-Pro-dPhe-Arg-dTrp-Lys)-dVal-dPro-NH_2
376	K16	Ac-Nle-c(Asp-His-Arg-p(I)dPhe-Arg-Tic-Lys)-dVal-dPro-NH_2
377	K17	Ac-Nle-c(Asp-His-Arg-dBip-Arg-Tic-Lys)-dVal-dPro-NH_2
378	K18	Ac-Nle-c(Asp-Pro-Arg-p(I)dPhe-Arg-Tic-Lys)-dVal-dPro-NH_2
379	K19	Ac-Nle-c(Asp-Pro-Arg-dBip-Arg-Tic-Lys)-dVal-dPro-NH_2

380	K20	Ac-Nle-c(Asp-Arg-Pro-p(I)dPhe-Arg-Tic-Lys)-dVal-dPro-NH_2
381	K21	Ac-Nle-c(Asp-Arg-Pro-dBip-Arg-Tic-Lys)-dVal-dPro-NH_2
125	K22	Ac-Nle-c(Asp-Pro-Bip-Arg-Trp-Lys)-dVal-dPro-NH_2
388	K23	Ac-Nle-c(Asp-Atc-dPhe-Arg-Trp-Lys)-dVal-dPro-NH_2

[1097] Group L included non-naturally occurring melanocortin analogs L1 through L22, all of which are cyclic peptides comprising the Pro at one or more of R^2, R^3, R^5, and R^7. Without intending to be bound by any particular theory, inclusion of a Pro residue at one or more of R^2, R^3, R^5, and R^7 positions is thought to promote and stabilize the formation of β-turns in the peptides. Group L non-naturally occurring melanocortin analogs are provided in Table 13.

Table 13. Group L non-naturally occurring melanocortin analogs

SEQ ID NO	**Non-naturally occurring melanocortin analog**	**Formula**
198	L1	Ac-Nle-c(Asp-Pro-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
199	L2	Ac-Nle-c(Asp-Trp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
216	L3	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Pro-Lys)-dVal-dPro-NH_2
217	L4	Ac-Nle-c(Asp-His-dNal(2')-Pro-Trp-Lys)-dVal-dPro-NH_2
220	L5	Ac-Nle-c(Asp-Pro-dNal(2')-Pro-Trp-Lys)-dVal-dPro-NH_2

[1098] Group M included non-naturally occurring melanocortin analogs M1 through M11, all of which are cyclic peptides comprising the motif Glu-dNal(2')-Arg-Trp or a derivative thereof. Without intending to be limited by any particular theory, the Glu-dNal(2')-Arg-Trp motif in Group M peptides is thought to be a pharmacophore on the MC3 and MC4 receptors. Group M non-naturally occurring melanocortin analogs are provided in Table 14.

Table 14. Group M non-naturally occurring melanocortin analogs

SEQ ID NO	Non-naturally occurring melanocortin analog	Formula
225	M1	Ac-Nle-c(Asp-Glu-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
234	M2	Ac-Nle-c(Asp-Glu-His-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
226	M3	Ac-Nle-c(Asp-Glu-dNal(2')-Arg-Trp-Gly-Lys)-dVal-dPro-NH_2
235	M4	Ac-Nle-c(Asp-Glu-His-dNal(2')-Arg-Trp-Gly-Lys)-dVal-dPro-NH_2
227	M5	Ac-Nle-c(Asp-Pro-Glu-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
228	M6	Ac-Nle-c(Asp-Pro-Glu-dNal(2')-Arg-Trp-Gly-Lys)-dVal-dPro-NH_2
229	M7	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Gly-Lys)-dVal-dPro-NH_2
230	M8	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Gly-Lys)-dPro-dPro-Lys-Asp-NH_2
231	M9	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Gly-Lys)-dPro-dPro-dLys-dAsp-NH_2
232	M10	Ac-Glu-c(Asp-Pro-dNal(2')-Arg-Trp-Gly-Lys)-dPro-dPro-Lys-Asp-NH_2
233	M11	Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dPro-dPro-dLys-dAsp-NH_2

[1099] Group N included non-naturally occurring melanocortin analogs N1 through N8, all of which are cyclic peptides comprising the motif dAla-His-dNal(2')-Arg-Trp or a derivative thereof. Without intending to be limited by any particular theory, the dAla-His-dNal(2')-Arg-Trp motif in Group N peptides is thought to be a pharmacophore on the MC3 and MC4 receptors. Further, the inclusion of dAla in Group N is thought to

promote and stabilize b-turns in the Group N peptides. Group N non-naturally occurring melanocortin analogs are provided in Table 14.

Table 14. Group N non-naturally occurring melanocortin analogs

SEQ ID NO	Non-naturally occurring melanocortin analog	Formula
236	N1	Ac-Nle-c(Asp-dAla-His-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
237	N2	Ac-Arg-c(Asp-dAla-His-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
240	N3	Ac-dArg-c(Asp-dAla-His-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
241	N4	Ac-Arg-c(Asp-dAla-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
242	N5	Ac-dArg-c(Asp-dAla-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
243	N6	Ac-Nle-c(Asp-Ala-His-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
244	N7	Ac-Arg-c(Asp-Ala-His-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2
245	N8	Ac-dArg-c(Asp-Ala-His-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2

[1100] Group O included non-naturally occurring melanocortin analogs O1 through O8, all of which are cyclic peptides comprising the motif Trp-Arg-dNal(2')-Pro, or a derivative thereof. Without intending to be limited by any particular theory, the Trp-Arg-dNal(2')-Pro motif in Group O peptides is thought to be a pharmacophore on the MC3 and MC4 receptors. Group O non-naturally occurring melanocortin analogs are provided in Table 14.

Table 14. Group O non-naturally occurring melanocortin analogs

SEQ ID NO	Non-naturally occurring	Formula

	melanocortin analog	
246	O1	Ac-Nle-c(Asp-Trp-Arg-dNal(2')-Pro-Lys)-dVal-dPro-NH_2
247	O2	Ac-Nle-c(Asp-Pro-Trp-dNal(2')-Lys)-dVal-dPro-NH_2
248	O3	Ac-Nle-c(Asp-Pro-Trp-Arg-dNal(2')-Pro-Lys)-dVal-dPro-NH_2
249	O4	Ac-Nle-c(Asp-Pro-Trp-Arg-dNal(2')-Lys)-dVal-dPro-NH_2
250	O5	Ac-Nle-c(Lys-Trp-Arg-dNal(2')-Pro-Asp)-dVal-dPro-NH_2
255	O6	Ac-dVal-dPro-c(Asp-Trp-Arg-dNal(2')-Pro-Lys)-Nle-NH_2
256	O7	Ac-dVal-dPro-c(Lys-Trp-Arg-dNal(2')-Pro-Asp)-Nle-NH_2
257	O8	Ac-dVal-dPro-c(Asp-Trp-Arg-dNal(2')-Pro-Lys)-Nle-Nle-NH_2
258	O9	Ac-dVal-dPro-c(Lys-Trp-Arg-dNal(2')-Pro-Asp)-Nle-Nle-NH_2
259	O10	Ac-dVal-dPro-c(Asp-Trp-Arg-dNal(2')-Pro-Lys)-dVal-dPro-NH_2
260	O11	Ac-dVal-dPro-c(Lys-Trp-Arg-dNal(2')-Pro-Asp)-dVal-dPro-NH_2

Agonist activity of melanocortin analogs on melanocortin 1 receptor

[1101] Administration of some non-naturally occurring melanocortin analogs agonized MC1R activity, as measured by cAMP levels. Among the non-naturally occurring melanocortin analogs, K1-K5 and D1-D14 each had EC_{50} values under 10000 nM, with K5 having the lowest EC_{50} at 0.0083 (Table 15).

Table 15. Dose-response results of melanocortin analogs and control against the melanocortin 1 receptor (MC1R)

Non-naturally occurring melanocortin analog	Max Activation %	EC_{50} (nM)*	Hill Coefficient	Top (%)
K1	104.04	0.0221	0.96	101.86
K2	100.00	0.0138	1.67	98.07

K3	103.20	0.0010	0.52	102.24
K4	102.18	0.0060	1.19	98.22
K5	103.65	0.0083	1.23	99.65
D6	97.21	0.31	0.89	96.26
TCMCB02	97.07	3.63	1.08	95.85
D7	101.87	0.016	1.53	100.54
D8	101.39	0.011	1.18	100.08
D9	96.60	51.1	1.37	98.26
D10	93.38	9.07	0.91	97.43
D11	98.22	6.31	1.12	97.61
TCMCB07	99.19	0.33	1.23	97.94
A1	93.67	5.79	0.91	95.46
J2	97.86	0.73	1.24	96.31
D12	99.11	0.12	1.26	97.23
D13	97.40	0.87	1.22	95.36
D14	94.15	5.01	1.30	93.46
D1	98.39	22.3	1.19	100.65
D1α	98.91	29.0	2.04	99.10
D1β	99.05	30.3	1.79	99.27
D1γ	99.60	0.86	1.07	99.70
D1δ	101.79	1.43	1.33	100.99
D2	101.79	0.38	1.12	101.26
D3	99.39	0.19	1.09	97.87
D4	92.97	85.9	1.21	97.89
E1	65.60	>1000	-	-
E2	88.22	450.00	-	-
E3	91.66	36.00	-	-
E4	95.13	12.00	-	-
E5	88.80	430.00	-	-
E6	71.56	>1000	-	-
E7	82.51	>1000	-	-
E8	90.10	12.00	-	-

E9	76.15	>1000	-	-
E10	92.83	49.00	-	-
E11	89.45	100.00	-	-
E12	73.89	>1000	-	-
E13	74.08	>1000	-	-
E14	85.00	420.00	-	-
E15	87.38	640.00	-	-
E16	69.87	>1000	-	-
E17	65.49	>1000	-	-
E18	67.41	>1000	-	-
E19	59.17	>1000	-	-
E20	59.47	>1000	-	-
E21	60.87	>1000	-	-
E22	91.19	110.00	-	-
E23	91.61	73.00	-	-
E24	92.75	200.00	-	-
F1	92.35	4.20	-	-
F2	80.66	970.00	-	-
F3	90.95	13.00	-	-
F4	86.57	0.59	-	-
F5	73.15	110.00	-	-
F6	78.56	27.00	-	-
F7	83.37	3.50	-	-
F8	76.73	76.00	-	-
F9	69.53	>1000	-	-
F10	73.55	33.00	-	-
F11	88.05	4.60	-	-
F12	57.26	>1000	-	-
F13	74.38	>1000	-	-
F14	36.66	0.00	-	-
F15	39.67	0.00	-	-
F16	38.93	0.00	-	-

F17	35.33	0.00	-	-
F18	30.12	0.00	-	-
F19	9.59	0.00	-	-
F20	22.79	0.00	-	-
F21	17.69	0.00	-	-
F22	97.37	4.10	-	-
F23	53.76	>1000	-	-
F24	33.58	0.00	-	-
F25	56.58	>1000	-	-
F26	53.03	>1000	-	-
F27	88.72	13.00	-	-
F28	74.21	430.00	-	-
F29	84.82	3.30	-	-
F30	78.33	510.00	-	-
F31	56.13	>1000	-	-
F32	7.45	nd	-	-
G1	78.73	930.00	-	-
G2	94.84	34.00	-	-
G3	74.41	510.00	-	-
G4	51.26	>1000	-	-
G5	52.80	>1000	-	-
G6	89.34	27.00	-	-
G7	70.91	130.00	-	-
G8	64.75	220.00	-	-
G9	83.79	47.00	-	-
G10	89.21	28.00	-	-
G11	90.99	54.00	-	-
G12	86.84	19.00	-	-
G13	75.84	32.00	-	-
G14	86.09	100.00	-	-
G15	87.22	86.00	-	-
G16	59.36	>1000	-	-

G17	54.22	150.00	-	-
G18	84.37	6.20	-	-
G19	70.97	140.00	-	-
G20	86.58	57.00	-	-
G21	92.22	18.00	-	-
G22	69.15	>1000	-	-
G23	53.94	>1000	-	-
G24	20.68	nd	-	-
H1	21.33	0.00	-	-
H2	86.46	140.00	-	-
H3	28.05	0.00	-	-
H4	40.64	0.00	-	-
H5	68.34	430.00	-	-
H6	-4.73	0.00	-	-
H7	84.03	430.00	-	-
H8	67.49	>1000	-	-
H9	1.92	0.00	-	-
H10	-1.67	0.00	-	-
H11	6.23	0.00	-	-
H12	2.59	0.00	-	-
H13	-6.48	0.00	-	-
H14	-3.24	0.00	-	-
H15	-14.16	0.00	-	-
I1	83.56	300.00	-	-
I2	84.70	9.30	-	-
I3	82.38	280.00	-	-
I4	68.45	16.00	-	-
I5	81.02	210.00	-	-
I6	69.44	100.00	-	-
I7	81.98	780.00	-	-
I8	68.30	>1000	-	-
I9	69.17	>1000	-	-

I10	31.92	0.00	-	-
I11	27.68	0.00	-	-
I12	38.05	0.00	-	-
I13	87.25	35.00	-	-
J1	83.66	0.15	-	-
J2	89.25	32.00	-	-
J3	82.73	290.00	-	-
J4	88.38	25.00	-	-
J5	92.01	17.00	-	-
J6	87.13	29.00	-	-
J7	90.61	36.00	-	-
J8	82.37	480.00	-	-
J9	85.63	96.00	-	-
J10	87.15	470.00	-	-
J11	85.82	110.00	-	-
J12	87.40	70.00	-	-
J13	86.16	86.00	-	-
J14	89.19	120.00	-	-
J15	84.59	150.00	-	-
J16	81.77	3.00	-	-
J17	81.56	64.00	-	-
J18	75.74	4.10	-	-
J19	84.64	4.80	-	-
J20	71.48	28.00	-	-
J21	77.99	120.00	-	-
J22	87.13	25.00	-	-
J23	87.47	3.30	-	-
J24	75.66	2.20	-	-
J25	83.46	110.00	-	-
J26	79.94	1.10	-	-
J27	77.97	10.00	-	-
J28	77.88	58.00	-	-

J29	78.89	3.80	-	-
J30	78.66	11.00	-	-
J31	82.41	100.00	-	-
J32	80.60	0.82	-	-
J33	80.59	4.70	-	-
J34	80.50	27.00	-	-
J35	76.55	0.19	-	-
J36	81.11	4.00	-	-
J37	82.41	190.00	-	-
J38	87.49	0.33	-	-
J39	89.75	3.80	-	-
J40	70.55	82.00	-	-
J41	59.09	8.30	-	-
J42	76.49	10.00	-	-
J43	82.38	0.15	-	-
J44	76.11	1.30	-	-
J45	85.56	0.00	-	-
J46	65.11	3.50	-	-
J47	75.45	0.13	-	-
J48	78.54	0.82	-	-
J49	78.73	1.70	-	-
J50	88.28	35.00	-	-
J51	91.85	0.28	-	-
J52	86.87	7.60	-	-
J53	89.29	4.70	-	-
J54	93.24	16.00	-	-
J55	89.79	7.40	-	-
J56	86.48	7.00	-	-
J57	87.52	40.00	-	-
J58	90.23	40.00	-	-
J59	85.83	28.00	-	-
J60	88.10	56.00	-	-

J61	91.86	35.00	-	-
J62	74.52	110.00	-	-
J63	86.28	76.00	-	-
J64	90.04	63.00	-	-
J65	84.97	82.00	-	-
J66	79.87	130.00	-	-
J67	90.70	110.00	-	-
J68	89.42	11.00	-	-
J69	62.70	840.00	-	-
J70	87.90	63.00	-	-
K6	74.08	0.17	-	-
K7	87.17	0.00	-	-
K8	74.92	3.20	-	-
K9	91.44	0.14	-	-
K10	90.44	0.00	-	-
K11	60.91	>1000	-	-
K12	97.65	160.00	-	-
K13	97.69	300.00	-	-
K14	-7.97	0.00	-	-
K15	97.84	46.00	-	-
K16	79.68	35.00	-	-
K17	70.67	220.00	-	-
K18	83.65	190.00	-	-
K19	68.43	150.00	-	-
K20	61.03	450.00	-	-
K21	73.08	43.00	-	-
K22	97.84	380.00	-	-
K23	84.67	740.00	-	-
L1	59.14	>1000	-	-
L2	68.24	>1000	-	-
L3	73.64	>1000	-	-
L4	94.63	17.00	-	-

L5	27.72	nd	-	-
M1	71.01	>1000	-	-
M2	87.97	>1000	-	-
M3	81.67	530.00	-	-
M4	75.18	1.80	-	-
M5	26.21	0.00	-	-
M6	44.74	0.00	-	-
M7	95.36	0.19	-	-
M8	90.31	12.00	-	-
M9	92.25	12.00	-	-
M10	23.32	0.00	-	-
M11	81.34	53.00	-	-
N1	87.05	2.80	-	-
N2	97.18	6.80	-	-
N3	98.30	4.50	-	-
N4	36.23	0.00	-	-
N5	57.38	>1000	-	-
N6	86.54	0.00	-	-
N7	94.68	82.00	-	-
N8	91.94	29.00	-	-
O1	56.44	>1000	-	-
O2	1.65	0.00	-	-
O3	55.40	>1000	-	-
O4	72.50	>1000	-	-
O5	56.82	>1000	-	-
O6	31.27	0.00	-	-
O7	54.34	>1000	-	-
O8	77.22	>1000	-	-
O9	71.95	>1000	-	-
O10	58.49	>1000	-	-
O11	38.68	0.00	-	-

Control A replicate 1	98.13	0.13	1.03	95.25
Control A replicate 2	101.43	0.018	1.28	100.86
Control B	101.65	0.012	1.03	99.88
Control C	92.95	6.58	0.94	93.95

Antagonist activity of melanocortin analogs on melanocortin 3 receptor

[1102] Administration of some non-naturally occurring melanocortin analogs inhibited MC3R activity, as measured by cAMP levels. Among the non-naturally occurring melanocortin analogs (FIGS. 30A-YY; 31A-OO; 32A-ZZ; 33A-SS), A1 (B07L), D1-D4, D6-D8, D10-D14 TCMCB02,TCMCB07, E1-E24, F1-F8, F10, F11, F22, F27-F30, G1, G2, G6, G9-G11, G15, G17-G19, G21, H1, H2, H5, H7, H8, I2-I7, I9, I13, J1-J70, K1-K4, K6-K10, L2, M1-M3, M7-M11, N1-N3, and N6-N8 all had IC_{50} values under 10000 nM (Table 16).

Table 16. Dose-response results of melanocortin analogs and control against the melanocortin 3 receptor (MC3R)

Non-naturally occurring melanocortin analog	**Max Activation %**	**IC_{50} (nM)***	**Hill Coefficient**	**Top (%)**
HS024(TFA)	102.29	867.28	0.93	117.07
A1	92.89	17.2	0.83	94.81
A2	7.92	nd	0.82	9.73
B1	6.86	nd	1.05	-
B2	10.28	nd	0.34	20.30
B3	0.83	nd	1.00	100.00
B4	7.81	nd	0.36	29.62
B5	0.14	nd	-0.76	736.17
B6	5.00	nd	1.62	4.27
B7	1.43	nd	-0.84	7754.77

B8	4.86	nd	12.04	4.40
B9	1.08	nd	2.26	1.22
C1	4.55	nd	0.23	6.49
C2	0.27	nd	-0.48	0.42
C3	3.32	nd	49.34	3.18
C4	-0.32	nd	-5.34	-
C5	-0.49	nd	13.82	-0.10
C6	-0.80	nd	1.00	100.00
C7	0.16	nd	-0.13	1.86
C8	0.47	nd	-57.42	0.80
C9	1.24	nd	2.95	-64.92
D1	86.86	26.2	0.97	89.34
D1α	82.54	201	1.33	92.55
D1β	86.69	252	1.58	100.22
D1γ	87.50	20.4	1.08	89.22
D1δ	91.12	52.7	0.78	100.58
D2	72.61	407	1.10	100
D3	103.11	2.18	1.18	102.08
D4	89.30	132	0.75	109.40
D5	24.60	>10000	1.04	472.61
D6	91.96	3.11	1.16	92.14
D7	91.34	4.66	0.98	90.73
D8	91.90	3.82	0.94	96.59
D9	25.29	>1000	-	-
D10	102.19	7.07	0.95	98.78
D11	101.88	8.43	0.96	104.20
D12	109.62	2.97	1.06	101.14
D13	101.11	7.73	1.01	105.58
D14	97.44	6.25	1.06	94.89
TCMCB02	101.79	25.9	0.88	105.34
TCMCB07	105.85	2.43	0.94	100.29
E1	89.36	2.98	-	-

E2	88.44	2.64	-	-
E3	99.69	5.92	-	-
E4	100.08	1.15	-	-
E5	93.27	2.97	-	-
E6	92.11	4.79	-	-
E7	103.77	37.00	-	-
E8	95.38	2.10	-	-
E9	99.83	12.40	-	-
E10	94.70	1.71	-	-
E11	97.82	2.44	-	-
E12	96.70	12.71	-	-
E13	96.79	19.21	-	-
E14	94.10	20.37	-	-
E15	97.57	4.79	-	-
E16	101.58	13.04	-	-
E17	99.57	460.00	-	-
E18	87.32	720.00	-	-
E19	91.21	7.00	-	-
E20	100.16	15.00	-	-
E21	97.88	2.99	-	-
E22	101.03	10.36	-	-
E23	99.92	24.05	-	-
E24	114.41	250.62	-	-
F1	99.18	680.00	-	-
F2	95.30	57.58	-	-
F3	116.46	8.50	-	-
F4	97.69	1.20	-	-
F5	113.88	480.00	-	-
F6	92.13	9.31	-	-
F7	102.32	2.75	-	-
F8	99.39	8.66	-	-
F9	85.83	>1000	-	-

F10	103.05	27.51	-	-
F11	102.64	2.82	-	-
F12	62.20	>1000	-	-
F13	79.91	>1000	-	-
F14	23.62	nd	-	-
F15	40.94	nd	-	-
F16	35.39	nd	-	-
F17	51.40	>1000	-	-
F18	47.40	nd	-	-
F19	35.74	nd	-	-
F20	36.75	nd	-	-
F21	42.05	nd	-	-
F22	103.37	2.38	-	-
F23	41.67	nd	-	-
F24	46.59	nd	-	-
F25	48.12	nd	-	-
F26	26.72	nd	-	-
F27	98.39	0.96	-	-
F28	101.36	480.00	-	-
F29	100.79	0.93	-	-
F30	100.09	73.84	-	-
F31	81.92	>1000	-	-
F32	nd	nd	-	-
G1	103.93	200.00	-	-
G2	103.42	3.29	-	-
G3	34.10	>1000	-	-
G4	101.32	>1000	-	-
G5	90.49	>1000	-	-
G6	26.71	91.89	-	-
G7	100.32	>1000	-	-
G8	100.00	665.07	-	-
G9	106.38	17.63	-	-

G10	98.73	9.51	-	-
G11	93.14	4.38	-	-
G12	86.49	>1000	-	-
G13	100.00	768.44	-	-
G14	100.00	>1000	-	-
G15	97.44	9.96	-	-
G16	76.84	>1000	-	-
G17	89.88	830.00	-	-
G18	97.98	180.00	-	-
G19	106.55	20.0	-	-
G20	86.17	>1000	-	-
G21	99.81	12.73	-	-
G22	82.73	>1000	-	-
G23	80.52	>1000	-	-
G24	50.14	>1000	-	-
H1	98.07	680.00	-	-
H2	97.20	4.11	-	-
H3	14.72	nd	-	-
H4	11.41	nd	-	-
H5	108.54	290.00	-	-
H6	16.99	nd	-	-
H7	96.90	7.86	-	-
H8	92.71	580.00	-	-
H9	11.89	nd	-	-
H10	1.67	nd	-	-
H11	26.28	nd	-	-
H12	5.66	nd	-	-
H13	9.49	nd	-	-
H14	1.31	nd	-	-
H15	4.88	nd	-	-
I1	14.70	nd	-	-
I2	93.84	4.90	-	-

I3	104.80	15.31	-	-
I4	118.50	2.50	-	-
I5	101.15	2.66	-	-
I6	95.48	1.72	-	-
I7	96.52	400.00	-	-
I8	26.72	nd	-	-
I9	99.20	14.88	-	-
I10	14.13	nd	-	-
I11	6.55	nd	-	-
I12	11.29	nd	-	-
I13	100.53	2.14	-	-
J1	99.17	2.46	-	-
J2	98.07	5.15	-	-
J3	96.64	49.52	-	-
J4	93.35	1.04	-	-
J5	101.11	1.55	-	-
J6	95.50	5.12	-	-
J7	107.05	9.22	-	-
J8	103.43	7.39	-	-
J9	95.54	4.78	-	-
J10	100.11	5.97	-	-
J11	92.83	1.34	-	-
J12	103.67	3.72	-	-
J13	101.97	11.25	-	-
J14	90.92	14.00	-	-
J15	99.89	9.26	-	-
J16	94.84	1.77	-	-
J17	95.72	6.29	-	-
J18	92.60	2.47	-	-
J19	93.62	2.96	-	-
J20	96.19	13.02	-	-
J21	91.93	9.44	-	-

J22	95.97	3.54	-	-
J23	102.83	2.15	-	-
J24	100.66	2.34	-	-
J25	97.98	5.41	-	-
J26	96.45	0.90	-	-
J27	98.42	1.71	-	-
J28	95.69	7.00	-	-
J29	99.78	1.07	-	-
J30	98.33	2.63	-	-
J31	102.59	12.36	-	-
J32	99.97	1.63	-	-
J33	95.17	1.15	-	-
J34	94.65	3.49	-	-
J35	96.86	0.45	-	-
J36	101.47	1.05	-	-
J37	96.68	3.48	-	-
J38	99.44	0.54	-	-
J39	100.69	0.76	-	-
J40	95.61	25.00	-	-
J41	95.89	0.73	-	-
J42	105.24	3.70	-	-
J43	98.06	0.33	-	-
J44	99.93	1.37	-	-
J45	95.75	0.60	-	-
J46	96.89	1.59	-	-
J47	99.15	0.74	-	-
J48	97.53	0.43	-	-
J49	91.01	1.21	-	-
J50	99.29	3.02	-	-
J51	95.21	0.68	-	-
J52	92.65	2.10	-	-
J53	100.04	1.03	-	-

J54	101.10	2.03	-	-
J55	99.93	1.67	-	-
J56	93.12	2.06	-	-
J57	101.75	5.80	-	-
J58	98.93	5.95	-	-
J59	94.09	5.39	-	-
J60	101.36	13.48	-	-
J61	95.08	6.50	-	-
J62	92.46	28.56	-	-
J63	106.24	21.52	-	-
J64	104.15	7.68	-	-
J65	111.44	23.00	-	-
J66	98.09	130.00	-	-
J67	96.02	7.68	-	-
J68	102.36	6.20	-	-
J69	67.06	45.60	-	-
J70	94.91	9.49	-	-
K1	79.14	0.84	-	-
K2	39.46	1.81	-	-
K3	25.76	0.76	-	-
K4	66.50	1.11	-	-
K5	nd	nd	-	-
K6	105.73	1.65	-	-
K7	98.23	1.02	-	-
K8	100.34	1.60	-	-
K9	98.87	1.81	-	-
K10	92.12	2.82	-	-
K11	2.23	nd	-	-
K12	38.37	>1000	-	-
K13	1.15	nd	-	-
K14	-2.24	nd	-	-
K15	24.16	nd	-	-

K16	93.81	>1000	-	-
K17	102.59	>1000	-	-
K18	89.06	>1000	-	-
K19	103.71	>1000	-	-
K20	95.05	>1000	-	-
K21	77.47	>1000	-	-
K22	39.78	>1000	-	-
K23	nd	nd		
L1	57.26	>1000	-	-
L2	90.52	920.00	-	-
L3	100.17	>1000	-	-
L4	-5.98	nd	-	-
L5	2.33	nd	-	-
M1	100.66	640.00	-	-
M2	63.53	>1000	-	-
M3	97.49	380.00	-	-
M4	95.76	300.00	-	-
M5	35.20	nd	-	-
M6	45.32	nd	-	-
M7	98.57	1.89	-	-
M8	90.76	1.17	-	-
M9	96.17	1.28	-	-
M10	89.56	810.00	-	-
M11	96.76	18.87	-	-
N1	100.62	54.00	-	-
N2	95.40	140.00	-	-
N3	93.98	250.00	-	-
N4	95.44	>1000	-	-
N5	66.39	>1000	-	-
N6	67.88	130.00	-	-
N7	104.04	120.00	-	-
N8	103.55	150.00	-	-

O1	25.85	nd	-	-
O2	8.20	nd	-	-
O3	26.86	nd	-	-
O4	17.30	>1000	-	-
O5	40.14	>1000	-	-
O6	10.53	nd	-	-
O7	1.08	nd	-	-
O8	41.76	>1000	-	-
O9	49.57	>1000	-	-
O10	5.31	>1000	-	-
O11	45.91	nd	-	-
Control A	100.48	0.28	1.30	98.79
Control B replicate 1	106.76	5.00	1.36	103.59
Control B replicate 2	97.17	2.15	1.02	96.90
Control C	100.06	11.1	1.03	102.08

*nd = not determined

Low = low concentration

High = high concentration

Antagonist activity of melanocortin analogs on melanocortin 4 receptor

[1103] Administration of some non-naturally occurring melanocortin analogs inhibited or activated MC4R activity, as measured by cAMP levels. Among the non-naturally occurring melanocortin analogs (FIGS. 34A-DDD; FIGS. 35A-ZZ, FIGS. 36A-RRR, FIGS. 37A-GGG), A1, D1-D4, D6-D14, TCMCB02, TCMCB07, E1-E12,E16, E19-E24, F2-F8, F10, F11, F22, F27-F30, G2, G6, G7, G9-G15, G17-G19, G21, H2, H7, I2, I5, I6, I13, J1-J70, K1, K6, K8, K23, M3, M7-M9, and M11 all had IC_{50} values under 10000 nM respectively (Table 17).

Table 17. Dose-response results of melanocortin analogs and control against the melanocortin 4 receptor (MC4R)

Non-naturally occurring melanocortin analog	**Max Activation %**	**IC_{50} (nM)***	**Hill Coefficient**	**Top (%)**
HS024(TFA)	103.83	153.04	0.61	113.93
A1	93.24	16.4	1.19	94.30
A2	27.41	nd	0.32	652.03
B1	12.65	nd	7.57	12.66
B2	35.52	nd	0.69	729.66
B3	4.41	nd	9.04	-
B4	16.14	nd	1.90	16.60
B5	-0.16	nd	1.22	-0.16
B6	15.38	nd	0.28	37.93
B7	-2.96	nd	-1.76	516.09
B8	13.55	nd	0.49	20.03
B9	-3.71	nd	-19.71	-0.55
C1	11.12	nd	0.08	51.32
C2	-3.30	nd	48.53	-2.85
C3	8.07	nd	0.44	9.36
C4	-6.88	nd	-7.31	-1.97
C5	2.47	nd	1.13	3.02
C6	6.41	nd	2.07	321.26
C7	5.86	nd	1.62	4.61
C8	3.02	nd	10.57	-
C9	5.89	nd	0.64	219.95
D1	72.06	27.2	0.89	74.47
D1α	80.69	54.9	1.49	81.82
D1β	98.98	102	6.69	98.98
D1γ	93.45	24.4	1.46	94.09

D1δ	119.32	45.6	0.95	125.54
D2	66.52	46.7	1.53	67.13
D3	119.53	8.39	0.86	119.67
D4	91.55	175	1.28	100
D5	41.47	nd	0.67	2724.46
D6	100.91	11.3	1.07	103.87
D7	99.74	12.6	1.09	103.44
D8	114.93	32.2	1.17	117.20
D9	59.59	89.3	0.82	68.30
D10	103.36	4.16	1.24	96.52
D11	101.52	4.87	1.22	99.92
D12	98.39	6.08	0.88	97.58
D13	101.98	4.32	0.95	103.64
D14	98.56	6.02	2.31	98.96
TCMCB02	103.65	15.2	1.78	104.32
TCMCB07	93.96	4.11	1.04	93.63
E1	61.27	89.00	-	-
E2	72.11	680.00	-	-
E3	76.11	230.00	-	-
E4	74.20	260.00	-	-
E5	77.43	160.00	-	-
E6	74.37	410.00	-	-
E7	87.69	78.00	-	-
E8	79.13	520.00	-	-
E9	78.50	470.00	-	-
E10	67.89	190.00	-	-
E11	85.98	130.00	-	-
E12	82.52	470.00	-	-
E13	70.44	>1000	-	-
E14	72.10	480.00	-	-
E15	64.36	>1000	-	-
E16	73.11	530.00	-	-

E17	64.78	>1000	-	-
E18	64.89	>1000	-	-
E19	72.60	320.00	-	-
E20	77.23	41.00	-	-
E21	111.88	190.00	-	-
E22	89.71	350.00	-	-
E23	99.71	56.00	-	-
E24	75.30	250.00	-	-
F1	36.49	nd	-	-
F2	78.58	740.00	-	-
F3	115.63	16.00	-	-
F4	77.04	0.79	-	-
F5	95.87	520.00	-	-
F6	123.29	29.00	-	-
F7	63.31	23.00	-	-
F8	78.73	85.00	-	-
F9	30.75	nd	-	-
F10	68.07	100.00	-	-
F11	102.03	4.80	-	-
F12	-12.54	nd	-	-
F13	16.81	nd	-	-
F14	20.88	nd	-	-
F15	22.55	nd	-	-
F16	20.87	nd	-	-
F17	70.32	>1000	-	-
F18	10.67	nd	-	-
F19	17.91	nd	-	-
F20	9.35	nd	-	-
F21	19.86	nd	-	-
F22	114.05	5.20	-	-
F23	19.92	nd	-	-
F24	30.43	nd	-	-

F25	27.83	nd	-	-
F26	8.61	nd	-	-
F27	99.69	41.00	-	-
F28	64.77	920.00	-	-
F29	86.33	45.00	-	-
F30	71.19	950.00	-	-
F31	57.94	>1000	-	-
F32	0.13	nd	-	-
G1	30.44	nd	-	-
G2	98.98	98.00	-	-
G3	58.43	>1000	-	-
G4	38.73	nd	-	-
G5	48.47	nd	-	-
G6	85.33	260.00	-	-
G7	125.69	300.00	-	-
G8	117.66	>1000	-	-
G9	118.99	14.00	-	-
G10	115.33	22.00	-	-
G11	117.99	11.00	-	-
G12	133.56	280.00	-	-
G13	151.00	260.00	-	-
G14	123.73	820.00	-	-
G15	124.03	140.00	-	-
G16	122.08	>1000	-	-
G17	122.07	220.00	-	-
G18	102.43	140.00	-	-
G19	129.26	330.00	-	-
G20	56.14	>1000	-	-
G21	66.18	180.00	-	-
G22	98.05	>1000	-	-
G23	65.41	>1000	-	-
G24	105.45	>1000	-	-

H1	52.87	>1000	-	-
H2	100.12	200.00	-	-
H3	11.90	nd	-	-
H4	6.72	nd	-	-
H5	72.04	>1000	-	-
H6	6.96	nd	-	-
H7	80.63	210.00	-	-
H8	58.02	>1000	-	-
H9	3.04	nd	-	-
H10	-2.81	nd	-	-
H11	20.27	nd	-	-
H12	-3.16	nd	-	-
H13	7.33	nd	-	-
H14	1.36	nd	-	-
H15	4.19	nd	-	-
I1	7.68	nd	-	-
I2	93.41	110.00	-	-
I3	75.80	>1000	-	-
I4	34.38	nd	-	-
I5	71.40	480.00	-	-
I6	98.24	24.00	-	-
I7	42.66	nd	-	-
I8	5.76	nd	-	-
I9	45.30	nd	-	-
I10	1.58	nd	-	-
I11	10.49	nd	-	-
I12	7.63	nd	-	-
I13	73.57	410.00	-	-
J1	88.46	3.00	-	-
J2	89.12	270.00	-	-
J3	75.67	670.00	-	-
J4	111.05	4.50	-	-

J5	88.25	51.00	-	-
J6	76.34	46.00	-	-
J7	99.31	54.00	-	-
J8	71.11	83.00	-	-
J9	91.02	48.00	-	-
J10	67.99	59.00	-	-
J11	74.42	81.00	-	-
J12	90.81	21.00	-	-
J13	100.37	49.00	-	-
J14	90.52	100.00	-	-
J15	77.24	190.00	-	-
J16	85.71	46.00	-	-
J17	63.95	61.00	-	-
J18	85.90	33.00	-	-
J19	87.69	55.00	-	-
J20	90.89	110.00	-	-
J21	79.20	170.00	-	-
J22	94.50	11.00	-	-
J23	85.45	58.00	-	-
J24	84.91	50.00	-	-
J25	81.01	160.00	-	-
J26	93.70	16.00	-	-
J27	91.26	39.00	-	-
J28	86.52	520.00	-	-
J29	78.21	29.00	-	-
J30	103.95	78.00	-	-
J31	69.40	500.00	-	-
J32	94.46	15.00	-	-
J33	71.77	15.00	-	-
J34	97.63	30.00	-	-
J35	90.44	0.95	-	-
J36	82.15	10.00	-	-

J37	85.84	95.00	-	-
J38	90.16	11.00	-	-
J39	72.58	24.00	-	-
J40	83.18	240.00	-	-
J41	93.49	12.00	-	-
J42	92.03	43.00	-	-
J43	81.01	1.60	-	-
J44	100.05	11.00	-	-
J45	89.30	2.80	-	-
J46	99.73	6.00	-	-
J47	85.84	2.10	-	-
J48	104.18	5.90	-	-
J49	87.46	8.20	-	-
J50	94.46	81.00	-	-
J51	93.30	15.00	-	-
J52	95.41	32.00	-	-
J53	94.05	22.00	-	-
J54	92.29	55.00	-	-
J55	83.75	89.00	-	-
J56	93.08	13.00	-	-
J57	98.18	96.00	-	-
J58	92.22	110.00	-	-
J59	94.69	130.00	-	-
J60	101.87	66.00	-	-
J61	96.20	24.00	-	-
J62	100.29	210.00	-	-
J63	94.82	33.00	-	-
J64	84.43	44.00	-	-
J65	92.49	33.00	-	-
J66	80.23	130.00	-	-
J67	73.51	43.00	-	-
J68	103.30	35.00	-	-

J69	51.40	790.00	-	-
J70	95.36	58.00	-	-
K1	34.36	1.63	0.54	32.75
K2	-54.60	>1000	-	-
K3	-40.29	>1000	-	-
K4	11.63	>1000	-	-
K5	-62.89	>1000	-	-
K6	91.29	2.30	-	-
K7	8.87	nd	-	-
K8	83.09	41.00	-	-
K9	38.84	nd	-	-
K10	37.55	nd	-	-
K11	-0.85	nd	-	-
K12	-25.11	nd	-	-
K13	5.49	nd	-	-
K14	0.37	nd	-	-
K15	-24.19	nd	-	-
K16	63.43	>1000	-	-
K17	86.61	>1000	-	-
K18	48.69	nd	-	-
K19	53.49	>1000	-	-
K20	69.67	>1000	-	-
K21	39.46	nd	-	-
K22	4.09	nd	-	-
K23	88.29	720.00		
L1	41.33	nd	-	-
L2	90.63	>1000	-	-
L3	23.05	nd	-	-
L4	1.62	nd	-	-
L5	4.78	nd	-	-
M1	91.88	>1000	-	-
M2	16.65	nd	-	-

M3	75.60	640.00	-	-
M4	6.24	nd	-	-
M5	13.12	nd	-	-
M6	9.83	nd	-	-
M7	79.84	3.20	-	-
M8	78.80	7.30	-	-
M9	92.47	6.30	-	-
M10	44.10	nd	-	-
M11	63.87	60.00	-	-
N1	15.39	nd	-	-
N2	18.69	nd	-	-
N3	17.60	nd	-	-
N4	45.06	>1000	-	-
N5	36.72	nd	-	-
N6	18.50	nd	-	-
N7	19.88	nd	-	-
N8	24.80	nd	-	-
O1	21.21	nd	-	-
O2	-7.16	nd	-	-
O3	13.22	nd	-	-
O4	34.34	nd	-	-
O5	36.68	>1000	-	-
O6	17.84	nd	-	-
O7	13.06	nd	-	-
O8	21.45	nd	-	-
O9	26.46	nd	-	-
O10	12.75	nd	-	-
O11	49.65	nd	-	-
Control B replicate 1	95.46	1.80	1.05	92.31
Control B replicate 2	89.47	0.28	1.10	85.69

Control C	95.65	4.27	1.08	93.42

*nd = not determined

Agonist activity of melanocortin analogs on melanocortin 5 receptor

[1104] Administration of some non-naturally occurring melanocortin analogs inhibited or activated MC5R activity, as measured by cAMP levels. Among the non-naturally occurring melanocortin analogs all peptides had an EC_{50} value under 1000nM (Table 18).

Table 18. Dose-response results of melanocortin analogs and control against the melanocortin 5 receptor (MC5R)

Non-naturally occurring melanocortin analog	**Max Activation %**	**EC_{50} (nM)***	**Hill Coefficient**	**Top (%)**
K1	102.41	0.025	1.38	102.72
K2	103.71	0.030	1.36	102.19
K3	104.37	0.025	1.10	101.51
K4	104.01	0.059	1.26	101.90
K5	105.08	0.053	1.36	101.90
D6	101.74	0.010	1.05	101.56
TCMCB02	102.11	0.047	1.28	100.95
D7	101.50	0.039	1.13	100.58
D8	102.13	0.027	1.38	100.59
D9	99.67	0.81	1.14	97.75
D10	101.16	0.013	1.18	100.87
D11	101.85	0.0065	0.89	101.92
TCMCB07	102.17	0.0066	1.00	101.69
A1	101.75	0.024	1.15	101.47
J2	103.16	0.012	1.00	101.57
D12	102.75	0.0082	1.26	101.12
D13	103.35	0.013	1.05	102.65

D14	102.16	0.010	1.05	101.84
D1	91.63	14.0	1.07	92.62
D1α	100.95	10.5	1.52	100.67
D1β	99.74	85.4	5.39	99.74
D1γ	101.35	2.04	1.05	101.67
D1δ	99.74	2.97	1.13	99.79
D2	101.83	3.22	1.19	101.59
D3	102.59	0.006	1.03	101.94
D4	100.97	1.47	1.08	101.33
E1	99.27	2.60	-	-
E2	102.67	1.80	-	-
E3	97.94	12.00	-	-
E4	101.65	0.51	-	-
E5	100.63	15.00	-	-
E6	101.06	29.00	-	-
E7	103.10	8.80	-	-
E8	95.84	11.00	-	-
E9	101.75	3.90	-	-
E10	101.43	0.17	-	-
E11	102.79	nd	-	-
E12	101.92	30.00	-	-
E13	100.36	95.00	-	-
E14	101.18	0.54	-	-
E15	101.15	4.50	-	-
E16	98.77	16.00	-	-
E17	98.42	45.00	-	-
E18	96.19	63.00	-	-
E19	70.34	650.00	-	-
E20	86.29	110.00	-	-
E21	87.09	47.00	-	-
E22	103.25	0.08	-	-
E23	100.62	0.14	-	-

E24	98.01	0.35	-	-
F1	95.20	100.00	-	-
F2	101.77	330.00	-	-
F3	80.86	1.90	-	-
F4	88.84	0.00	-	-
F5	91.72	26.00	-	-
F6	85.72	15.00	-	-
F7	85.24	0.35	-	-
F8	91.50	7.60	-	-
F9	86.20	47.00	-	-
F10	87.38	15.00	-	-
F11	101.47	nd	-	-
F12	45.97	nd	-	-
F13	70.41	>1000	-	-
F14	7.43	nd	-	-
F15	26.71	nd	-	-
F16	16.99	nd	-	-
F17	5.29	nd	-	-
F18	3.54	nd	-	-
F19	35.33	nd	-	-
F20	-8.83	nd	-	-
F21	3.06	nd	-	-
F22	69.66	0.51	-	-
F23	12.52	nd	-	-
F24	19.77	nd	-	-
F25	3.96	nd	-	-
F26	-14.65	nd	-	-
F27	101.82	0.02	-	-
F28	85.35	42.00	-	-
F29	94.33	0.11	-	-
F30	92.69	11.00	-	-
F31	77.28	>1000	-	-

F32	-3.56	nd	-	-
G1	71.69	>1000	-	-
G2	101.49	0.04	-	-
G3	21.14	>1000	-	-
G4	54.17	>1000	-	-
G5	60.91	>1000	-	-
G6	99.68	22.00	-	-
G7	25.75	nd	-	-
G8	34.78	nd	-	-
G9	102.04	0.05	-	-
G10	100.03	nd	-	-
G11	103.37	nd	-	-
G12	19.00	nd	-	-
G13	2.47	nd	-	-
G14	37.69	nd	-	-
G15	100.54	2.10	-	-
G16	61.22	480.00	-	-
G17	76.15	280.00	-	-
G18	86.97	46.00	-	-
G19	100.64	1.40	-	-
G20	88.57	720.00	-	-
G21	101.66	0.00	-	-
G22	87.33	270.00	-	-
G23	18.37	nd	-	-
G24	40.69	>1000	-	-
H1	74.01	>1000	-	-
H2	90.95	10.00	-	-
H3	-19.12	nd	-	-
H4	-4.03	nd	-	-
H5	90.44	9.10	-	-
H6	-15.01	nd	-	-
H7	98.39	0.11	-	-

H8	105.52	85.00	-	-
H9	64.38	>1000	-	-
H10	10.08	nd	-	-
H11	64.04	>1000	-	-
H12	-5.39	nd	-	-
H13	1.72	nd	-	-
H14	6.39	nd	-	-
H15	1.05	nd	-	-
I1	9.96	nd	-	-
I2	93.01	4.00	-	-
I3	61.81	>1000	-	-
I4	85.29	8.80	-	-
I5	75.14	120.00	-	-
I6	99.20	5.40	-	-
I7	79.33	590.00	-	-
I8	25.09	nd	-	-
I9	86.04	180.00	-	-
I10	21.73	nd	-	-
I11	4.41	nd	-	-
I12	10.59	nd	-	-
I13	90.73	1.50	-	-
J1	94.25	nd	-	-
J2	101.22	0.12	-	-
J3	100.29	1.50	-	-
J4	101.33	nd	-	-
J5	103.42	0.03	-	-
J6	102.73	nd	-	-
J7	102.35	0.09	-	-
J8	103.74	nd	-	-
J9	104.92	0.07	-	-
J10	104.02	0.25	-	-
J11	106.25	0.05	-	-

J12	104.44	0.06	-	-
J13	103.55	0.02	-	-
J14	101.49	0.37	-	-
J15	101.99	0.36	-	-
J16	98.56	0.14	-	-
J17	96.47	0.05	-	-
J18	104.34	nd	-	-
J19	97.43	0.02	-	-
J20	93.48	0.03	-	-
J21	90.32	0.18	-	-
J22	92.78	0.25	-	-
J23	93.73	0.22	-	-
J24	79.04	nd	-	-
J25	93.94	0.53	-	-
J26	98.74	nd	-	-
J27	97.50	0.79	-	-
J28	96.47	1.40	-	-
J29	101.65	nd	-	-
J30	95.59	nd	-	-
J31	102.76	1.90	-	-
J32	102.31	nd	-	-
J33	97.27	0.12	-	-
J34	102.62	0.15	-	-
J35	103.04	nd	-	-
J36	101.02	0.04	-	-
J37	100.33	1.10	-	-
J38	99.69	nd	-	-
J39	88.79	nd	-	-
J40	96.44	0.29	-	-
J41	102.52	nd	-	-
J42	95.84	nd	-	-
J43	93.99	nd	-	-

J44	101.03	0.07	-	-
J45	102.49	0.14	-	-
J46	97.01	0.19	-	-
J47	95.65	0.05	-	-
J48	88.66	nd	-	-
J49	98.16	nd	-	-
J50	102.14	nd	-	-
J51	102.58	nd	-	-
J52	101.56	nd	-	-
J53	101.64	nd	-	-
J54	101.41	nd	-	-
J55	100.98	nd	-	-
J56	101.22	nd	-	-
J57	100.67	0.04	-	-
J58	101.50	nd	-	-
J59	100.29	0.08	-	-
J60	103.06	0.56	-	-
J61	99.01	0.02	-	-
J62	100.91	nd	-	-
J63	101.77	0.06	-	-
J64	101.06	nd	-	-
J65	109.09	3.80	-	-
J66	100.17	0.21	-	-
J67	101.04	0.06	-	-
J68	104.43	nd	-	-
J69	108.65	83.00	-	-
J70	102.00	nd	-	-
K6	92.17	0.03	-	-
K7	94.41	nd	-	-
K8	85.82	1.10	-	-
K9	78.60	nd	-	-
K10	76.07	0.39	-	-

K11	3.43	0.00	-	-
K12	54.15	>1000	-	-
K13	11.02	nd	-	-
K14	-0.69	nd	-	-
K15	86.00	100.00	-	-
K16	4.14	nd	-	-
K17	-11.16	nd	-	-
K18	-2.09	nd	-	-
K19	-5.01	nd	-	-
K20	1.90	nd	-	-
K21	7.92	nd	-	-
K22	-4.96	nd	-	-
K23	23.65	nd	-	-
L1	52.45	>1000	-	-
L2	91.31	160.00	-	-
L3	94.42	140.00	-	-
L4	47.91	nd	-	-
L5	86.02	>1000	-	-
M1	105.63	490.00	-	-
M2	5.34	nd	-	-
M3	116.52	69.00	-	-
M4	66.00	>1000	-	-
M5	70.22	>1000	-	-
M6	21.09	nd	-	-
M7	104.62	nd	-	-
M8	103.07	nd	-	-
M9	103.53	nd	-	-
M10	100.35	21.00	-	-
M11	105.90	0.62	-	-
N1	46.34	nd	-	-
N2	55.76	>1000	-	-
N3	66.29	>1000	-	-

N4	1.35	nd	-	-
N5	-1.56	nd	-	-
N6	103.82	24.00	-	-
N7	87.36	260.00	-	-
N8	92.67	86.00	-	-
O1	6.26	nd	-	-
O2	-2.93	nd	-	-
O3	17.64	nd	-	-
O4	24.67	nd	-	-
O5	3.69	nd	-	-
O6	-0.90	nd	-	-
O7	11.30	nd	-	-
O8	15.55	nd	-	-
O9	28.79	nd	-	-
O10	12.72	>1000	-	-
O11	-3.96	nd	-	-
Control A	100.94	0.073	1.38	98.56
Control B	102.48	0.012	1.17	101.34
Control C	101.79	0.015	1.39	101.00

Example 16

[1105] Cancer cachectic rats (Tumor) and control rats (Sham) were administered either TCMCB07 or saline control. Hypothalamic tissue was isolated and mRNA levels of the proinflammatory genes interleukin 1 beta (Il1b) (NCBI Gene ID: 16176; NCBI Transcript Accession Number: NM_008361.4), interleukin 1 receptor (Il1r1) (NCBI Gene ID: 16177; NCBI Transcript Accession Numbers: NM_008362.3, NM_001123382.2), interleukin 6 (Il6) (NCBI Gene ID: 16193; NCBI Transcript Accession Numbers: NM_031168.2; NM_001314054.1), tumor necrosis factor (Tnf) (NCBI Gene ID: 21926; NCBI Transcript Accession Numbers: NM_013693.3; NM_001278601.1), selectin P (Selp) (NCBI Gene ID: 20344; NCBI Transcript Accession Number: NM_011347.2), pro-opiomelanocortin (Pomc) (NCBO Gene ID: 18976; NCBI Transcript Accession Numbers: NM_001278581.1, NM_008895.4, NM_001278582.1, NM_001278584.1, NM_001278583.1), and agouti-related protein (Agrp) (NCBI Gene ID: 11604; NCBI

Transcript Accession Numbers: U89484.1, NM_007427.3, NM_001271806.1) were measured in each rat (FIG. 38). mRNA levels of Il1b, Il1r1, Il6, Selp, and Agrp were significantly reduced in cancer cachexia rats administered TCMCB07 relative to cancer cachexia rats administered saline.

Example 17

[1106] TCMCB07 nonclinical safety and toxicology was assessed in both rats and Beagle dogs (Table 19). A single TCMCB07 dose cardiovascular safety pharmacology evaluation in Beagle dogs with 1, 3, or 10 mg/kg via SC, resulted in no quantitative or qualitative ECG parameters changes. An increase in blood pressure and heart rate at 10 mg/kg was reversible 24 hours after dosing. TCMCB07 had virtually no effect on hERG current amplitude (4.9 ± 1.7% reduction at a nominal concentration of 100 μM)

Table 19. Nonclinical Safety and Toxicology Summary

Parameter	**S-D rats**	**Beagle Dogs**
TCMCB07 Doses (mg/kg/day)	0.5, 3, and 10	1, 3, or 10
Mortality	None	None
Urinalysis, ophthalmology, macroscopic findings, and histamine analysis	Non	Macroscopic observations of local skin discoloration and increased black melanin in the epithelium of anagen hair follicles in both sexes at the 3 and 10 mg/kg/day dosing
Clinical signs, body weight, food consumption, ophthalmology, safety pharmacology/clinical pathology, & pathology	Adverse changes were in serum chemistry and histologically with minimal to mild periportal hepatocellular vacuolation in both sexes at 10 mg/kg/day	none
Neurological Effects	None	None

Changes after recovery period	All Resolved	All Resolved

[1107] cAMP production from the MC1R in human, rat, and beagle dog tissue was assessed under different concentrations of TCMCB07. TCMCB07 bound to the human (FIG. 39A), rat (FIG. 39B), and dog (FIG. 39C) MC1R, but cAMP production was only stimulated from the dog MC1R upon TCMCB07 binding.

Example 18

[1108] Cancer cachectic rats and control rats were administered either saline or TCMCB07 according to Table 20 and FIG. 40. G1 rats were comprised of Sham control rats administered saline. G2 rats were comprised of cancer cachectic rats administered saline. G3 rats were comprised of cancer cachexic rats administered a high dose of TCMCB07 (3 mg/kg) for the entire testing period, including after a dose equivalence point was reached. G4 rats were comprised of cancer cachectic rats administered a high dose of TCMCB07 (3 mg/kg) until a dose equivalence point was reached, followed by administration of a low dose of TCMCB07 (1 mg/kg) after the equivalence point was reached. G5 rats were comprised of cancer cachectic rats administered a high dose of TCMCB07 (3 mg/kg) until a dose equivalence point was reached. No TCMCB07 was administered to G5 rats once the dose equivalence point was reached.

Table 20. Dosing Schema

Animal Group	**Test Article/Vehicle**	**Group Size**	**TCMCB07 Dose & Regimen**
Sham + Saline (G1)	Saline	14	
Cancer Cachectic + Saline (G2)	Saline	20	
Cancer Cachectic + TCMCB07 (G3)	TCMCB07-3 mg/kg	20	High dose for the entire testing period
Cancer Cachectic + TCMCB07 (G4)	TCMCB07-3/1 mg/kg	20	High dose, then low dose for maintenance after reaching equivalence point

Cancer Cachectic + TCMCB07 (G5)	TCMCB07-3mg/kg/ 0 mg/kg	20	High dose, then stop dosing after reaching equivalence point

[1109] Daily body weights of G1-G5 rats were recorded from day -1 through day 80 (FIG. 41). All dosing schemas incorporating TCMCB07 resulted in increased daily body weight relative to cancer cachexia rats administered saline, with the G3 rats having the highest final daily body weight measurement of all groups. Daily body weight changes are further detailed in Table 21.

Table 21. Daily Body Weight Changes

Body weight	D 6	D 14	D 15	D 16	D 17	D 18	D 19	D 20	D 21	D 22	D 23	D 24	D 25	D 26	D 27	D 28	D 29	D 30
G1 vs. G2	ns	*	*	**	*	*	**	**	**	**	**	**	**	**	**	**	***	***
G2 vs. G3	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	*	*	**
G2 vs. G4	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	*	*	*
G2 vs. G5	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	*	*	**
	D 31	D 32	D 33	D 34	D 35	D 36	D 37	D 38	D 39	D 40	D 41	D 42	D 43	D 44	D 45	D 46	D 47	D 48
G1 vs. G2	**	***	**	***	***	***	**	**	***	**	***	***	***	***	***	**	**	**
G2 vs. G3	**	***	***	***	***	***	***	***	***	***	***	***	***	***	***	***	***	***
G2 vs. G4	**	**	**	**	**	***	**	**	***	***	***	***	***	***	**	**	**	**
G2 vs. G5	**	***	***	**	***	***	**	**	***	***	****	***	***	***	**	*	*	*
	D 49	D 50	D 51	D 52	D 53	D 54	D 55	D 56	D 57	D 58	D 59	D 60	D 61	D 62	D 63	D 64	D 65	D 66
G1 vs. G2	***	**	**	**	**	**	**	**	**	**	**	**	**	**	*	*	*	*
G2 vs. G3	***	****	****	****	****	****	****	****	****	****	****	****	****	****	**	***	***	**
G2 vs. G4	**	**	*	*	*	**	*	*	*	*	*	*	*	*	ns	ns	ns	ns
G2 vs. G5	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	*	ns	ns	ns	ns	ns	ns
	D 67	D 68	D 69	D 70	D 71	D 72	D 73	D 74	D 75	D 76	D 77	D 78	D 79					
G1 vs. G2	**	*	*	**	**	**	**	ns	ns	ns	ns	*	ns					
G2 vs. G3	***	***	****	***	****	****	****	***	***	****	****	****	****					
G2 vs. G4	*	ns	*	ns	*	ns	*	ns	ns	ns	ns	ns	ns					
G2 vs. G5	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns					

Example 19. In Vivo Renal Failure Rat Model

[1110] Rat 5/6 nephrectomy models may be inflammatory and a satisfactory analog of late-stage human Chronic Kidney Disease (CKD). These models were used to determine whether TCMCB07 increased mass gain, increased food intake, and increased fat mass of rats having a disease which models late-stage human CKD (FIG. 42A-G). The model includes a two-stage 5/6 nephrectomy. In stage I (day 0) a unilateral partial nephrectomy was performed on the rat. In stage II (day 7), a contralateral total nephrectomy was performed on the rat. The results illustrate evidence of mass gain, food intake increase and fat mass in rats following subcutaneous administration of TCMCB07 (Neph/TCMCB07) compared to controls (Neph/saline). Sham operation with subcutaneous administration of saline was used as an experimental control for both the operation and TCMCB07. (Lean mass was * significant; not shown here.)

Example 20. TCMCB07 Dosing in CKD Rat Model

[1111] Three different dosing regimens were tested to determine the effect of continuous treatment of TCMCB07 on cachexia. As shown in FIG. 43A, the step I surgery ("Neph-I") for the CKD Rat Model ("Model") was performed on day 1 and the step II surgery ("Neph-II") was performed on day 6. Different rat groups were treated according to the regimen shown in Table 22. In group 3 (G3) rats were treated with 3mg/kg/day of TCMCB07 for the entire 12-week experiment. Group 4 (G4) rats were treated with 3mg/kg/day of TCMCB07 until the "equivalence point" where the mass of the treated rat was not significantly different from the sham control. After the equivalence point, G4 rats were treated with a lower dose (1mg/kg/day) of TCMCB07. G5 rats were treated with 3mg/kg/day of TCMCB07 and then stopped receiving the dose after the equivalence point. Body weight and food intake were measured daily. Sham rats (G1) were given a sham surgery and no treatment. G2 rats were Model rats that did not receive a treatment. Body composition was measured on days 12, 56, and 79. The experiment was terminated on day 80, and tissue weight, serum creatinine, and serum urea were measured.

Table 22. Study Design for CKD Dosing Study

Group Number	Animal Group	Test article/vehicle	N	TCMCB07 Dose & Regimen
G1	Sham+Saline	Saline	14	N/A
G2	Model+Saline	Saline	20	N/A
G3	Model+TCMCB07	TCMCB07-3mg/kg	20	3mg/kg for the entire 12 weeks
G4	Model+TCMCB07	TCMCB07-3/1mg/kg	20	3mg/kg, then 1mg/kg for maintenance after reaching equivalence point
G5	Model+TCMCB07	TCMCB07-3/0mg/kg	20	3mg/kg dose, then stop dosing after reaching equivalence point

[1112] As shown in FIGS. 43B-43E, rats treated with TCMCB07 had a greater increase of body weight than rats treated with saline alone. After the equivalence point, G3 rats continued to gain weight at a rate similar to the sham rats, while G4 and G5 rats had a lower weight gain than the G3 rats after the equivalence point.

[1113] As shown in FIG. 43F, the cumulative food intake for G3 rats was higher than sham, G4, and G5 rats, which had a higher cumulative food intake than untreated model rats. As shown in FIGS. 44A-F and 45A-D, the weight gain observed in rats treated with TCMCB07 was attributed to increased fat mass and fluid mass. As shown in FIGS. 45A-C, the weight of the rats' hearts, gastrocnemii, and spleen were generally not different between the model group and the G3-G5 groups, although the G4 group did have significantly lower gastrocnemii. As shown in FIG. 45D, the body length of the rats in each treatment group was not significantly different. As shown in FIG 46A and 46B, sham rats had lower serum creatinine and blood urea nitrogen (BUN) than G2-G5 rats. These results indicate that treatment with TCMCB07 is effective for improving appetite, increasing fat mass, and increasing body mass in renal failure rats. The data show that TCMCB07 rats had significantly increased body weight and food intake than rats that did not receive TCMCB07.

The data also suggest that when dosing of TCMCB07 is decreased or terminated, it reduces body weight gain and food intake in a dose-dependent manner. This indicates continued dosing of TCMCB07 after the equivalence promotes continued weight gain after kidney injury.

Example 21: Optimizing Body Mass Index (BMI) with TCMCB07 in Patients with Newly Diagnosed Metastatic Colorectal Cancer Undergoing Chemotherapy

[1114] While obesity is a risk factor for many diseases including cancer, survival is longer in patients with higher BMIs. Specifically, patients with BMIs > 30 kg/m^2 have markedly improved survival over those with lower BMIs in many tumor types.

[1115] TCMCB07 increases weight in animal models including animals with malignancies and healthy humans as shown in a Phase 1 clinical trial. A Phase II trial will be conducted to evaluate the effect of TCMCB07 on BMI in patients with newly diagnosed, metastatic colorectal cancer and sub-optimal BMIs (18 to ≤ 29 kg/m^2). It will also evaluate the safety, tolerability, and pharmacokinetics (PK) of TCMCB07. The potential benefit of this trial is to improve the survival of patients with colorectal cancer who have suboptimal BMIs.

[1116] The primary and secondary objectives and endpoints of the Phase II trial are outlined in Table 23.

Table 23. Objectives and Endpoints

Objectives	**Endpoints**
Primary	
To evaluate the effect of TCMCB07 on BMI, relative to placebo, over 13 weeks in newly diagnosed metastatic colorectal cancer patients.	Change in BMI over time.
To evaluate the safety of TCMCB07.	Incidence and severity of adverse events (AEs), AEs of special interest (AESIs), and serious AEs (SAEs).

	Incidence of changes from baseline of clinical laboratory evaluations (hematology, clinical chemistry), and vital signs. Assessment of injection site reactions.
Secondary	
To determine the durability of BMI change with continued administration of TCMCB07.	Maintenance of BMI in long term follow-up.
To examine the effect of TCMCB07 vs. placebo on appetite in newly diagnosed metastatic colorectal cancer patients.	Compare the effects of TCMCB07 vs placebo using the Functional Assessment of Anorexia Cachexia Therapy (FAACT) scale.
To evaluate the pharmacokinetics of TCMCB07 in this population.	C_{min} will be determined throughout the trial and compared to C_{min} in normal subjects.
To determine the immunogenicity profile of TCMCB07.	Assess the formation of antibodies to TCMCB07. Samples will be collected prior to the first dose of TCMCB07, the beginning of each study Cycles 2-6 prior to dosing with TCMCB07 / placebo, End of Treatment, and Follow-up Visit.
Exploratory	
Overall survival (OS).	Assess the OS from the start of 1st line therapy.
Progression-free survival (PFS).	Assess the PFS from the start of 1st line therapy to RECIST defined progression.
Time to cancer treatment failure.	Assess the time to cancer treatment failure as defined by change in primary cancer treatment.
To determine change in circulating tumor DNA (ctDNA).	Assess the change in ctDNA levels over time from prior to the first dose of TCMCB07.

Overall Design

[1117] The Phase II trial is a randomized, double-blind, placebo-controlled study of TCMCB07, administered daily by subcutaneous (SC) injection, in up to 70 patients with newly diagnosed metastatic colorectal cancer. The study is intended to evaluate the effect of TCMCB07 on the BMI of patients with newly diagnosed metastatic colorectal cancer and sub-optimal BMIs (18 to ≤ 29 kg/m^2) as well as the effect on appetite, prior to and during chemotherapy. It will also evaluate the safety and tolerability of TCMCB07 as well as determine the PK and immunogenicity profile of TCMCB07 in these patients. Exploratory objectives include the assessment of overall survival (OS), progression-free survival (PFS), time to cancer treatment failure, and change in Circulating Tumor DNA (ctDNA). The total duration of the study from first patient first visit to last patient last visit will be approximately 32 weeks. The duration for each patient will be approximately 20 weeks. The study will consist of the following stages: up to a 21-day screening period, a 13-week treatment period (1 week of TCMCB07 / placebo treatment before chemotherapy initiation then six 2-week cycles of daily TCMCB07 / placebo in combination with chemotherapy), and a 30-day follow-up period.

[1118] Treatment will start 1 week prior to the start of cancer treatment and continue during the first 12 weeks of cytotoxic therapy (13 weeks total) with a goal of optimizing BMI (≥ 30 kg/m^2) relative to placebo control. The primary endpoint will be change in BMI after 13 weeks of TCMCB07 vs placebo. Treatment with TCMCB07 may continue in an open label extension study for as long and the patient has clinical benefit.

Study Population

Inclusion Criteria: Participants are eligible to be included in the study only if all of the following criteria apply:

1. Must be at least 18 years of age.
2. An ECOG performance status of < 2.
3. Life expectancy of > 9 months.
4. Able to eat and process food normally.

5. Must have newly diagnosed colorectal cancer or recurrent metastatic disease at least 6 months after primary treatment for potentially curable disease with or without neoadjuvant or adjuvant therapy. Patients just starting neoadjuvant or adjuvant treatment are excluded. Starting chemotherapy routines allowed are: FOLFOX, FOLFIRI, or FOLFIRINOX with or without bevacizumab, or other monoclonals or other FDA approved agents to be dosed every 2 weeks.

6. Must have a BMI between 18 and < 29 kg/m^2.

7. Must be able to begin treatment with TCMCB07 / placebo 7 days prior to the planned initiation of first line therapy without delaying first line therapy.

8. Must be able and willing to safely self-inject daily or be injected by a care giver.

9. Must have an available tumor sample for ctDNA analysis. The sample may be in the form of fixed slides.

10. Must have adequate end organ function as defined by:

(a) Bone marrow function:

(i) Absolute neutrophil count (ANC) > 1.5×10^9/L

(ii) Platelets > 100×10^9/L

(iii) Hemoglobin > 9 g/dL

(b) Hepatic function

(i) AST and ALT < 3 × upper limit of normal (ULN); if liver metastases, then < 5 × ULN

(ii) Bilirubin < 1.5 × ULN or < 3 × ULN in the presence of documented Gilbert's Syndrome

(iii) Albumin between 3.4 and 5.4 gm/dL or within institutional normal levels

(c) Renal function

(i) Creatinine clearance > 50 mL/min (calculated by Cockcroft and Gault equation See Appendix 2 (Section 10.2)).

(d) Metabolic function

(i) Normal hemoglobin A1c levels based on local lab normal ranges

11. If a female of childbearing capacity, must have a negative pregnancy test within 2 weeks of starting treatment.

12. Fertile men and women must agree to use adequate contraception for the duration of the trial.

13. Willing and able to sign informed consent.

[1119] Exclusion Criteria: Patients are excluded from the study if any of the following criteria apply:

1. Patients receiving second line or later systemic treatment for stage IV disease.

2. Patients with swallowing abnormalities, malabsorption syndromes, short or inflammatory bowel syndromes, or other conditions that in the investigator's opinion could impair food consumption or metabolism.

3. History of weight loss surgery including gastric stapling, or bypass.

4. Unintentional weight loss > 10% of usual body weight in 4 months prior to screening or other weight loss considered significant by the investigator.

5. Currently using any agent designed to increase appetite or otherwise affect weight (increase or decrease).

(a) Taking any appetite stimulants including THC within 1 week prior to starting treatment with TCMCB07 / placebo.

(b) Has been on orexigenic or weight gain agents within 6 months of screening.

6. History of bulimia or anorexia.

7. Pregnancy or lactation or plans to become pregnant.

8. History of another malignancy except basal cell carcinoma of the skin, carcinoma *in situ* of the cervix or other noninvasive or indolent malignancy that has previously undergone potentially curative therapy.

9. Concurrent participation in any other clinical trial.

10. Patients with known brain or central nervous system (CNS) metastases.

11. Impaired cardiac function or significant cardiac issues, including but not limited to, any of the following:

(i) Greater than class II NYHA congestive heart failure

(ii) Congenital long QT syndrome

(iii) QTcF > 480 msec on screening ECG

(iv) Unstable angina pectoris

(v) Acute myocardial infarction ≤ 6 months prior to study entry

12. Known hypersensitivity to TCMCB07 or its excipients.

13. Known diagnosis of human immunodeficiency virus (HIV) infection (HIV testing is not mandatory).

14. Active infection with Hepatitis B, Hepatitis C, or another virion.

15. Unwilling or unable to comply with the protocol.

16. Any condition that, in the investigator's opinion, would impair the patients' ability to participate in this study.

Study Intervention(s) and Concomitant Therapy

[1120] Study Intervention(s) Administered: TCMCB07 (SEQ ID NO:3). Additional study interventions details are outlined in Table 24. The Schedule of Events (SoE) is outlined in Table 25.

Table 24. Study Interventions

Intervention Name	TCMCB07	Placebo
Type	Drug	Placebo
Dose Formulation	Sterile solution for injection	Placebo

Unit Dose		
Strength(s)	Single-use vials containing 1.2 mL of preservative-free aqueous solution at a concentration of 50 mg/mL	Placebo
Dosage Level(s)	50 mg/day	Placebo
Route of Administration	SC injection	SC injection
Use	Experimental	Placebo
Packaging and Labeling	Stored and transported in type I glass vials with bromobutyl elastomer stoppers and aluminum over seals with a foam-backed polytetrafluoroethylene liner.	Placebo
Storage	5°C ± 3°C	5°C ± 3°C

Table 25. Schedule of Events

Procedures	Screening	Treatment Period (Cycles Refer to and Coincide with a Q2 Week Chemotherapy Schedule Even if Chemotherapy is Delayed)				Follow-up Visit
	Up to 21 Days [1]	Cycle [1] 1 Day -7	Cycle [1] 1 Day 1 (D1 Chemo)	Cycles [1] 2-6 Day 1	ET [2]	30 days after last dose
Informed consent	X					
Inclusion/exclusion criteria review	X					
Randomization	X					
Demographics	X					
Medical/Surgical history [3]	X					
Cancer Diagnosis [4]	X					
Height – metric	X				X	
Weight - metric [5]	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X
Physical examination [6]	X	X	X	X	X	X

FAACT Scale		X	X	X	X	X
ECOG	X	X	X	X	X	X
12-Lead ECG	X		X			X
Pregnancy test (Serum or Urine) [7]	X					X
Blood collection for Safety Lab [8]	X	X	X	X	X	X
Blood collection for Circulating Tumor DNA (ctDNA) [9]		X		X[9]	X[9]	
Blood collection for PK [10]		X	X	X		
Blood collection for antibodies [11]		X		X	X	X
Train patient on Self Injection of TCMCB07 / placebo Treatment		X				
Administer Study Treatment [12]		X	X[11]	X[11]		
Dispense/Collect Study Treatment vials		X	X	X	X	
Injection site examination		X	X	X	X	
Cancer Treatment [13]			X	X	X	
AE/SAE Assessment [14]	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X

Abbreviations: AE=adverse event; BMI=body mass index; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; ET=end of treatment; FAACT=Functional Assessment of Anorexia Cachexia Therapy; PK=pharmacokinetic; SAE=serious adverse event; TSA=Transportation Security Administration

[1121] Screening window is up to 21 days and may be performed in less time based on study site schedule. Cycles refer to study cycles with TCMCB07 or placebo.

[1122] If a patient discontinues study early, then at the time of discontinuation an ET visit should be conducted if possible.

[1123] To include a history of prior hospitalizations and major illnesses (not common cold, seasonal flu, etc. but include COVID infections).

[1124] Cancer history will include history of current malignancy including date of diagnosis, stage at diagnosis, any neo- or adjuvant therapies, surgeries, current disease stage.

[1125] Weight will be collected at each clinic visit using a calibrated scale with patient "TSA screening ready": no shoes, belts, outer garments, jackets, sweatshirts, pockets empty.

[1126] A complete physical examination will be performed at screening and after end of TCMCB07 / placebo treatment at the End of Treatment (ET) visit. Focused examination as needed based on signs and symptoms at all other visits.

[1127] Serum or urine pregnancy test required only for women of childbearing potential.

[1128] Serum chemistry to include basic metabolic panel (Na, K, Cl, CO2, glucose, hemoglobin A1c, creatinine, creatine clearance, BUN), lipase, amylase, and liver functions (total protein, albumin, bilirubin, AST, ALT, LDH); hematology to include complete blood count with differential.

[1129] During screening the following samples are needed: one 6-mL EDTA tube, two 10-mL Streck tubes, or a minimum 0.5-cm formalin fixed paraffin embedded (FFPE) block with a minimum tumor content of 20%, *or* six to ten (10-microns thick) *or* twelve to twenty (5 microns thick) unstained slides and 1 hematoxylin & eosin (H&E) slide (10-micron thick) with a minimum tumor content of 20%. At Cycle 3 Day 1 and End of Treatment, two 10-mL Streck tubes are required.

[1130] PK blood samples will be collected prior to dosing with TCMCB07 / placebo on Cycle 1 Day -7. A PK sample will be collected prior to TCMCB07/placebo dosing on D1 of Cycles 1 to 6 to determine C_{min}.

[1131] An antibody sample will be collected prior to dosing with TCMCB07 / placebo on Cycle 1 Day -7. An antibody sample will be collected prior to dosing with TCMCB07/placebo dosing on D1 of Cycles 2 to 6, End of Treatment, and Follow up Period.

[1132] TCMCB07 / placebo will be dispensed following patient training to self-administer TCMCB07 / placebo treatment. Dose will be held on Cycles 1-6 Day 1 and administrated in clinic following collection of PK sample for C_{min} measurement.

[1133] Cancer treatment may consist of any recognized chemotherapy drug combination given on a 2-week schedule. Cancer treatment of the malignancy may continue after the 13-week evaluation of TCMCB07 / placebo is complete. If treatment of the metastatic colorectal cancer must be delayed, visits should continue every 2 weeks. Treatment with TCMCB07 / placebo will continue even if cancer treatment is held unless Treatment Discontinuation, Patient Discontinuation/Withdrawal criteria is met.

[1134] AE and SAE collection will start following first dose of TCMCB07 / placebo treatment. Baseline signs and symptoms will be collected as part of medical history.

Dose Modification

[1135] The dose of TCMCB07 / placebo may be adjusted to optimize weight management or may also be held at the investigator's discretion after discussion with the Sponsor and/or the medical monitor. The primary endpoint will be change in BMI at 13 weeks, but treatment with TCMCB07 may continue to in an open label extension study for as long as the patient has clinical benefit. Treatment with study drug will be administered daily for the duration of the study. Compliance will be assessed based on reconciliation between vials dispensed and collected at each visit.

[1136] Primary cancer treatment may be altered at the investigator's discretion. In addition, other supportive care with the exception of the use of appetite stimulants will be determined by the treating physician.

[1137] Changes at the injection sites will be evaluated by the Investigator. Any severe or serious AE will prompt a safety assessment to determine whether changes to the study protocol in treatment are needed (e.g., dosing adjustment, study pause). If any of the study treatment discontinuation criteria are met (see Treatment Discontinuation, Patient Discontinuation / Withdrawal section), the patient's study participation will be terminated.

Continued Access to Study Intervention after the End of the Study

[1138] Treatment with TCMCB07 may continue in an open label extension study for as long as the patient has clinical benefit.

Concomitant Therapy

[1139] Any medication needed to support the patient is allowed except for any other appetite stimulants or drugs prescribed for weight loss other than required diuretics. However, drugs or other agents thought to enhance appetite that the patient has taken on a regular basis for ≥ 6 months prior to the initial diagnosis of cancer should not be discontinued or the dose changed. This includes agents that contain tetrahydrocannabinol (THC) if taken on a regular basis.

[1140] Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the patient is receiving at the time of enrollment or receives during the study must be recorded along with: (1) reason for use, (2) dates of administration including start and end dates, (3) dosage information including dose and frequency.

Discontinuation of Study Intervention

[1141] Changes at the injection sites or other events believed secondary to treatment with TCMCB07 will be evaluated by the Investigator. Any SAE will prompt a safety assessment to determine whether changes to the study protocol are needed (e.g., dosing adjustment, study pause). If any of the study treatment discontinuation criteria are met (see Treatment Discontinuation, Patient Discontinuation / Withdrawal section), the patient's study participation will be terminated.

QTc Stopping Criteria

[1142] If a clinically significant finding is identified (including, but not limited to changes from baseline ECG in QT interval corrected using (Bazett's formula (QTcB) after enrollment, the investigator or qualified designee will determine if the patient may continue in the study and if any change in patient management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

Temporary Discontinuation

[1143] Dose may be changed or treatment with TCMCB07 / placebo discontinued after discussion with the Medical Monitor and/or sponsor. Dosage adjustments may be needed to appropriately control weight or AEs believed secondary to treatment with TCMCB07 / placebo occur.

Rechallenge

[1144] TCMCB07 / placebo may be restarted or dose increased after a dose hold or reduction after discussion with the medical monitor and/or the sponsor.

Patient Discontinuation/Withdrawal from the Study

[1145] A patient may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon. At the time of study discontinuation, if possible, an early discontinuation visit should be conducted. The patient will be permanently discontinued both from the treatment with the TCMCB07 / placebo and from the study at that time. If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a patient withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

Lost to Follow up

[1146] A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

Study Assessments and Procedures

[1147] All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

[1148] Procedures conducted as part of the patient's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the defined time frame. Routine samples for standard clinical care may also be used during the trial.

[1149] The maximum amount of blood collected from each patient over the duration of the study, including any extra assessments that may be required, will not exceed 200 mL.

[1150] Repeat or unscheduled samples may be collected for safety reasons or for technical issues with the sample.

Efficacy Assessments

[1151] The effects of study treatment will be evaluated based on: changes in BMI over 13 weeks, durability of BMI change over time, effect of TCMCB07 / placebo on appetite using the FAACT scale, OS, PFS, time to cancer treatment failure and change in Circulating Tumor DNA (ctDNA) over time.

Physical Examinations

[1152] Complete and focused physical examinations with be performed. A complete examination will include assessments of Cardiovascular, Respiratory, Skin, Gastrointestinal and (limited) Neurological systems, along with an ECOG assessment. A focused physical examination will be conducted based on signs and symptoms at all other visits. Assessments may include examination of the skin (including examination of the injection site), and ECOG.

[1153] Weight will be measured and recorded at every visit. Height will be measured at Screening and End of Treatment.

[1154] Clinical signs related to metastatic colorectal cancer and concurrent chemotherapy will be monitored.

Vital Signs

[1155] Vital signs will be assessed before blood collection for laboratory tests. Body temperature, pulse rate, respiratory rate, and blood pressure will be assessed. Blood pressure and pulse measurements will be assessed in a seated or supine position with a completely automated device. Manual techniques will be used only if an automated device is not available. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (e.g., television, cell phones).

Electrocardiograms

[1156] 12-lead ECGs will be obtained locally using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Each ECG tracing must be noted as "not clinically significant" (NCS) or "clinically significant" (CS), signed and dated by a medically-qualified investigator, and appropriately recorded. An ECG recorded after IP administration, which is considered CS, should be recorded as an AE.

Clinical Safety and Laboratory Assessments

[1157] The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

[1158] Abnormal laboratory findings are not considered clinically significant unless judged by the investigator to be more severe than expected for the patient's condition.

[1159] All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of TCMCB07 / placebo and possibly, probably or definitely related to treatment with TCMCB07 / placebo should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

[1160] If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the Sponsor notified.

[1161] If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded. Investigators must document their review of each laboratory safety report.

[1162] Clinical safety and laboratory assessments are outlined in Table 26.

Table 26. Protocol-Required Safety Laboratory Tests

Laboratory Tests	**Parameters**			
Hematology	Platelet Count	RBC Indices: MCV MCH %Reticulocytes		White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Red blood cell (RBC) Count			
	Hemoglobin			
	Hematocrit			
Clinical Chemistry[1]	Blood urea nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)	Total and direct bilirubin
	Creatinine and Creatine Clearance	Sodium	Alanine Aminotransferase (ALT)	Total Protein
	Glucose	Albumin	Chloride	Hemoglobin A1c
	Carbon dioxide	Lactate dehydrogenase	Lipase	Amylase
Pregnancy testing	Serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)			
Other Screening Tests	ctDNA will be evaluated by a central laboratory			

Pregnancy Testing

[1163] All females of child-bearing potential or partners of male patients are to undergo either a urine or serum pregnancy test at Screening and 30-days after the last dose of TCMCB07/placebo. Female patients must be discontinued from IP in the event of pregnancy.

[1164] If a patient becomes pregnant within 3 months of the last dose of study medication, it should be reported to the PI and followed through the completion of pregnancy form, or as appropriate. All pregnancies must be reported to the Sponsor within 24 hours of learning of its occurrence. Reports of all pregnancies in female patients or the partners of male patients will be collected after randomization and until the Day 30 follow-up visit.

Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

[1165] All AEs should be volunteered or observed. Solicitation of AEs is not allowed. AEs will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

[1166] The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up on all AEs that are serious, considered possibly, probably or definitely related to the TCMCB07 / placebo or study procedures, or that caused the patient to discontinue the TCMCB07 / placebo or the study.

[1167] AE and SAE definitions are outlined in Table 27 and Table 28. Reporting and follow-up guidelines are outlined in Table 29.

Table 27. AE definitions

AE Definition
• An AE is any untoward medical occurrence in a clinical study patient, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE may therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.
Definition of Unsolicited and Solicited AE
• An unsolicited adverse event is an adverse event that was not solicited that is communicated by a patient who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs.

• Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, or emergency room visit, or visit to/by a health care provider). The patient will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of patient concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the patient's records. • Unsolicited AEs that are not medically attended nor perceived as a concern by the patient will be collected during interview with the patient and by review of available medical records at the next visit.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments However, the signs, symptoms, and/or clinical sequelae resulting

from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Table 28. Definition of SAE

An SAE is defined as any serious adverse event that, at any dose:
Results in death
Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the patient has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether

"hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other situations: • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

Table 29. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information.

- It is not acceptable for the investigator to send photocopies of the patient's medical records to the Sponsor or their designee) in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor or their designee. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to the Sponsor or their designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and code it using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE).

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data.

• The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.
Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. • This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a patient dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology, if any. • New or updated information will be recorded in the originally submitted documents. • The investigator will submit any updated SAE data within 24 hours of receipt of the information.

Time Period and Frequency for Collecting AE and SAE Information

[1168] All AEs and SAEs will be collected following first dose of TCMCB07 / placebo treatment until completion of the follow-up visit at the time points specified in the SoE (Table 25). Medical occurrences that begin before the start of TCMCB07 / placebo administration but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions, not as AEs.

[1169] All SAEs will be recorded and reported to medical monitor and pharmacovigilance unit and to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours.

[1170] After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs and AEs of special interest (AESIs), will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up.

Adverse Events of Special Interest (AESI)

[1171] Skin pigmentation changes that are of concern to the patient and/or treating physician should be discussed with the medical monitor/sponsor prior to any change in TCMCB07/placebo dosing. These are anticipated to be: (1) Injection site reaction grade 3 or 4; (2) Hair color changes; (3) Skin hypopigmentation any grade; and (4) Skin hyperpigmentation any grade.

Pharmacokinetics

[1172] Blood samples of approximately 10 mL / sample will be collected to assess C_{min} of TCMCB07 as specified in Table 25.

Biomarkers – ctDNA Assessment

[1173] ctDNA will be assessed as a biomarker for tumor response. Planned time points for ctDNA assessments are provided in the SoE (Table 25). Samples for ctDNA will be stored until processed (up to 8 weeks).

Immunogenicity

[1174] Antibodies to TCMCB07 will be evaluated in serum samples collected from all patients according to the SoE (Table 25). Serum samples will be screened for antibodies binding to TCMCB07 and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to TCMCB07 and/or further characterize the immunogenicity of TCMCB07.

[1175] The detection and characterization of antibodies to TCMCB07 will be performed using a validated assay method by or under the supervision of the Sponsor. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study drug.

Statistical Considerations: Sample Size Determination

[1176] Approximately 70 subjects will be enrolled and randomly allocated to receive study treatment as either TCMCB07 or matching placebo. "Enrolled" means a patient agrees to participate in a clinical study following completion of the informed consent process, completed screening, and has been randomized. Patients who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled.

[1177] Two assumptions were made for sample size calculations:

[1178] (1) In assumption 1, the average BMI at baseline was assumed to be just below the upper limit of the normal BMI range or <25 kg/m^2.

(a) Average BMI at baseline is assumed to be 24.8 kg/m^2 in both groups.

(b) A 1 kg weekly weight increase is assumed to increase weekly for the TCMCB07 treatment group and no change for the placebo group (based on phase 1 data).

(c) At Week 13, the mean BMI will be 29.4 kg/m^2 in the TCMCB07 treatment group and 24.8 kg/m^2 in the placebo group, with standard deviations of 5.88 kg/m^2 and 4.96 kg/m^2 respectively (20% coefficient of variation).

[1179] A sample size of 70 subjects (35 in the TCMCB07 treatment group and 35 in the placebo group) will provide 94% power for a comparison of the mean differences in BMI (at Week 13) between the two groups. A two-sided, two-sample, unequal-variance t-test, with a Type I error rate (α) of 0.05, is used with the assumptions listed in the bullet points above.

[1180] (2) In assumption 2, the average BMI at baseline was assumed to be the average BMI for Americans; 29.7 kg/m^2 for men and 29.4 kg/m^2 for women and used 29.55 kg/m^2 as a mean. With this assumption:

(a) Average BMI at baseline is assumed to be 29.55 kg/m^2 in both groups.

(b) A 1 kg weekly weight increase is assumed for the TCMCB07 treatment group and no change for the placebo group (based on phase 1 data).

(c) At Week 13, the mean BMI will be 34.15 kg/m^2 in the TCMCB07 treatment group and 29.55 kg/m^2 in the placebo group, with standard deviations of 6.83 kg/m^2 and 5.91 kg/m^2 respectively (20% coefficient of variation).

[1181] A sample size of 70 subjects (35 in the TCMCB07 treatment group and 35 in the placebo group) will provide 84% power for a comparison of the mean differences in BMI (at Week 13) between the two groups. A two-sided, two-sample, unequal-variance t-test, with a Type I error rate (α) of 0.05, is used with the assumptions listed in the bullet points above.

Safety Set

[1182] The safety analysis set includes all randomized subjects who received any study treatment (B07 or placebo), including those who do not complete the study.

Full Analysis Set (FAS):

[1183] The FAS includes all subjects who are randomized. The analysis will be based on the treatment group that subjects is randomized to.

Statistical Analyses

[1184] General Considerations: All statistical analyses will be performed using SAS® version 9.4 or higher. Descriptive summaries of study data will be presented by TCMCB07 treatment group and placebo. The descriptive summaries for the categorical variables will include counts and percentages. The descriptive summaries for the continuous variables may include means (±SD), medians, minimum, maximum, and/or 25th and 75th percentiles. Median, 25th and 75th percentiles, and standard error will be presented for time-to-event data.

[1185] Primary Endpoints: The primary analysis will be performed using the Full Analysis Set (FAS). A two-sided t-test design will be used to test whether the mean BMI for the treatment group (μ1) is different from the placebo group mean (μ2) at Week 13,

H0: μ1 -μ2 = 0 versus H1: μ1 -μ2 ≠ 0 with a Type I error rate (α) of 0.05.

[1186] No formal statistical comparisons will be made between TCMCB07 and placebo for safety endpoints.

Data Quality Assurance

[1187] All patient data relating to the study will be recorded on an electronic CRF (eCRF) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

[1188] The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

[1189] Quality tolerance limits (QTLs) will be pre-defined in the Data Management Plan to identify systematic issues that may impact patient safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.

[1190] The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

[1191] The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

[1192] Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Additional Embodiments:

[1193] Various embodiments of the present technology are set forth below in paragraphs [1194]-[1509]:

[1194] 1. A method of treating, preventing, or reducing one or more side effects associated with an anti-cancer agent in a subject, comprising administering a non-naturally

occurring melanocortin analog to the subject prior to, during, and/or after administration of the anti-cancer agent, wherein the one or more side effects are selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

[1195] 2. A method of maintaining or increasing weight in a subject prior to, during, and/or after administration of an anti-cancer agent, comprising administering a non-naturally occurring melanocortin analog to the subject, wherein the weight of the subject is maintained or increased by preventing or reducing anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and/or loss of appetite in the subject.

[1196] 3. A method of maintaining or increasing weight in a subject prior to, during, and/or after administration of an anti-cancer agent, comprising administering a non-naturally occurring melanocortin analog to the subject, wherein the weight of the subject is maintained or increased by preventing or reducing one or more side effects associated with the anti-cancer agent selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

[1197] 4. The method of embodiment 2 or 3, wherein the subject experiences an increase in weight by at least about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%,10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 225%, 250%, 275%, 300%, 350%, 400%, 450%, or 500% compared to baseline or a control.

[1198] 5. A method of maintaining or increasing muscle mass, fat mass, or cardiac mass in a subject prior to, during, and/or after administration of an anti-cancer agent, comprising administering a non-naturally occurring melanocortin analog to the subject

[1199] 6. The method of embodiment 5, wherein the subject experiences an increase in muscle mass, fat mass, or cardiac mass by at least about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%,10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% compared to a baseline or a control.

[1200] 7. A method of maintaining or increasing bone density in a subject prior to, during, and/or after administration of an anti-cancer agent, comprising administering a non-naturally occurring melanocortin analog to the subject.

[1201] 8. The method of embodiment 7, wherein the subject experiences an increase in bone density by at least about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%,10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% compared to a baseline or a control.

[1202] 9. A method of increasing or maintaining a Functional Assessment of Anorexia/ Cachexia Therapy (FAACT) score in a subject prior to, during, and/or after administration of an anti-cancer agent, comprising administering a non-naturally occurring melanocortin analog to the subject.

[1203] 10. The method of embodiment 9, wherein the subject experiences an increase in the FAACT score compared to baseline or control by at least 1, 2, 3, 4, or 5 points.

[1204] 11. A method of stimulating appetite or reducing loss of appetite induced by an anti-cancer agent in a subject, comprising administering a non-naturally occurring melanocortin analog to the subject prior to, during, and/or after administration of the anti-cancer agent.

[1205] 12. The method of embodiment 11, wherein the subject experiences an increase in appetite as measured by an increased food intake by about 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1200, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000, 2500, 3000, or more calories compared to baseline a control.

[1206] 13. A method of preventing, reducing, or restoring weight loss induced by an anti-cancer agent in a subject, comprising administering a non-naturally occurring melanocortin analog to the subject prior to, during, and/or after administration of the anti-cancer agent.

[1207] 14. A method of treating, preventing, or reducing one or more side effects associated with an anti-cancer agent in a subject who failed to respond to an antiemetic

treatment, comprising administering a non-naturally occurring melanocortin analog to the subject prior to, during, and/or after administration of the anti-cancer agent, wherein the one or more side effects are selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

[1208] 15. A method of treating, preventing, or reducing one or more side effects associated with an anti-cancer agent in a subject who failed to respond to nutritional intervention, comprising administering a non-naturally occurring melanocortin analog to the subject prior to, during, and/or after administration of the anti-cancer agent, wherein the one or more side effects are selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

[1209] 16. A method of preventing or reducing an anti-cancer agent induced side effect in a subject having cancer, comprising administering the anti-cancer agent and a non-naturally occurring melanocortin analog to the subject.

[1210] 17. A method of treating, preventing, or reducing iatrogenic injury caused by an anti-cancer agent in a subject having cancer, comprising administering the anti-cancer agent and a non-naturally occurring melanocortin analog to the subject.

[1211] 18. A method of preventing reduction of, maintaining, or improving Eastern Cooperative Oncology Group (ECOG) and/or Karnofsky performance status (KPS) score of a subject having cancer relative to a baseline or a control, comprising administering an anti-cancer agent and a non-naturally occurring melanocortin analog to the subject.

[1212] 19. The method of embodiment 18, wherein the subject experiences a reduction in ECOG performance score by about 1, 2, or 3 compared to baseline or control.

[1213] 20. The method of embodiment 18, wherein the subject experiences an increase in KPS score by about 100, 90, 80, 70, 60, 50, 40, or 30 compared to baseline or control.

[1214] 21. A method of preventing reduction of, maintaining, or improving overall survival (OS) or progression free survival (PFS) in a subject having cancer relative to a baseline or a control, comprising administering an anti-cancer agent and a non-naturally occurring melanocortin analog to the subject.

[1215] 22. The method of embodiment 21, wherein the subject experiences an increase in OS or an increase in PFS compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%.

[1216] 23. A method of reducing time to cancer treatment failure in a subject having cancer relative to a baseline or a control, comprising administering an anti-cancer agent and a non-naturally occurring melanocortin analog to the subject.

[1217] 24. A method of increasing or maintaining body mass index (BMI) in a subject relative to a baseline or a control, comprising administering an anti-cancer agent and a non-naturally occurring melanocortin analog to the subject.

[1218] 25. The method of embodiment 24, wherein the subject experiences an increase in BMI compared to baseline or control by at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35 points.

[1219] 26. The method of embodiment 24 or 25, wherein the subject experiences in an increase in BMI durability compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%.

[1220] 27. A method of reducing a proinflammatory transcript or protein level in a subject having cancer relative to a baseline or a control, comprising administering an anti-cancer agent and a non-naturally occurring melanocortin analog to the subject.

[1221] 28. The method of embodiment 27, wherein the subject experiences a reduction in an inflammatory transcript level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%.

[1222] 29. The method of embodiment 27, wherein the subject experiences a reduction in an inflammatory protein level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%.

[1223] 30. The method of embodiment 27 or embodiment 28, wherein the proinflammatory transcript is a transcript selected from the group consisting of an IL1

transcript, an IL6 transcript, an IL1R1 transcript, a TNFα transcript, a Selectin P transcript, a cytokine transcript, and a chemokine transcript.

[1224] 31. The method of embodiment 27 or embodiment 29, wherein the proinflammatory protein is a protein selected from the group consisting of an IL1 protein, an IL6 protein, an IL1R1 protein, a TNFα protein, a Selectin P protein, and a cytokine protein.

[1225] 32. The method of embodiment 1, wherein the method maintains or increases lean body mass, fat body mass, and/or weight of the subject relative to a baseline or a control.

[1226] 33. The method of embodiment 11, wherein the method maintains or increases lean body mass, fat body mass, and/or body weight of the subject relative to a baseline or a control.

[1227] 34. The method of embodiment 14, wherein the failure to respond to an antiemetic treatment further comprises clinically and/or therapeutically insufficient weight gain, muscle mass gain, fat mass gain, increased appetite, and/or increased food intake in the subject.

[1228] 35. The method of embodiment 15, wherein the nutritional intervention further comprises nutritional supplementation.

[1229] 36. The method of embodiment 16, wherein the side effect is selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, loss of appetite, vomiting, diarrhea, nausea, and fatigue.

[1230] 37. The method of embodiment 17, wherein the iatrogenic injury is selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

[1231] 38. The method of embodiment 18, wherein the improvement, maintenance, or prevented reduction of ECOG and/or KPS score occurs by inhibiting or reducing anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and/or loss of appetite in the subject.

[1232] 39. The method of any one of embodiments 1-38, wherein the subject has a cancer.

[1233] 40. The method of any one of embodiments 1-39, wherein the anti-cancer agent comprises a chemotherapy.

[1234] 41. The method of embodiment 40, wherein the method reduces chemotherapy induced mass loss and/or wasting in the subject and increases lean body mass and body weight of the subject relative to a baseline or a control.

[1235] 42. The method of embodiment 40, wherein the method maintains or increases weight of the subject prior to, during, or after administration of the chemotherapy, and wherein the method reduces mass loss and/or wasting in the subject relative to a baseline or a control.

[1236] 43. The method of any one of embodiments 1-18, wherein the anorexia is associated with weight loss.

[1237] 44. The method of any one of embodiments 1-43, wherein the subject has not previously received an anti-cancer agent.

[1238] 45. The method of any one of embodiments 1-43, wherein the subject has previously received an anti-cancer agent.

[1239] 46. The method of any one of embodiments 1-43, wherein the subject is receiving an anti-cancer agent.

[1240] 47. The method of any one of embodiments 1-46, wherein the administration of the non-naturally occurring melanocortin analog enhances tolerability of the anti-cancer agent.

[1241] 48. The method of embodiment 47, wherein the enhanced tolerability results in a greater dosage, an increased frequency of administration, and/or an increased duration of administration of the anti-cancer agent, relative to a baseline or control, wherein the baseline or control is the subject prior to the administration of the non-naturally occurring melanocortin analog and/or a subject who is receiving or has received the anti-cancer agent without the non-naturally occurring melanocortin analog.

[1242] 49. The method of embodiment 47, wherein the anti-cancer agent comprises a chemotherapy comprising at least two chemotherapeutic agents, and wherein the enhanced tolerability results in a second chemotherapeutic agent being administered to the subject during or after administration of a first chemotherapeutic agent.

[1243] 50. The method of any one of embodiments 1-49, wherein the administration of the non-naturally occurring melanocortin analog prevents or reduces a downward titration in dosing regimen of the anti-cancer agent relative to a baseline or a control.

[1244] 51. The method of embodiment 50, wherein the downward titration comprises a decreased dosage, a decreased frequency of administration, and/or a decreased duration of administration, compared to a baseline or control, wherein the baseline or control is the subject prior to the administration of the non-naturally occurring melanocortin analog and/or a subject who is receiving or has received the anti-cancer agent without the non-naturally occurring melanocortin analog.

[1245] 52. The method of any one of embodiments 1-51, wherein the subject experiences loss of appetite, reduced appetite, decreased food consumption, and/or weight loss prior to the administration of the non-naturally occurring melanocortin analog.

[1246] 53. The method of embodiment 52, wherein the loss of appetite, reduced appetite, decreased food consumption, and/or weight loss is caused by cancer.

[1247] 54. The method of embodiment 52, wherein the loss of appetite, reduced appetite, decreased food consumption, and/or weight loss is caused by the anti-cancer agent.

[1248] 55. The method of any one of embodiments 1-54 wherein the subject is receiving or has received an antiemetic.

[1249] 56. The method of embodiment 55, wherein the antiemetic is marijuana, megestrol, somatropin, or dronabinol.

[1250] 57. The method of any one of embodiments 1-56, wherein the non-naturally occurring melanocortin analog and the anti-cancer agent are administered concurrently.

[1251] 58. The method of any one of embodiments 1-56, wherein the non-naturally occurring melanocortin analog is administered before and/or after the anti-cancer agent.

[1252] 59. The method of embodiment 1, wherein administration of the non-naturally occurring melanocortin analog treats, prevents or reduces the one or more side effects associated with an anti-cancer agent in a subject.

[1253] 60. The method of embodiment 2, wherein administration of the non-naturally occurring melanocortin analog maintains or increases weight in the subject relative to a baseline or a control by preventing or reducing anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and/or loss of appetite in the subject.

[1254] 61. The method of embodiment 3, wherein administration of the non-naturally occurring melanocortin analog maintains or increases weight in the subject relative to a baseline or a control by preventing or reducing one or more side effects selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

[1255] 62. The method of embodiment 11, wherein administration of the non-naturally occurring melanocortin analog stimulates appetite or reduces loss of appetite induced by an anti-cancer agent in the subject relative to a baseline or a control.

[1256] 63. The method of embodiment 13, wherein administration of the non-naturally occurring melanocortin analog prevents, reduces, or restores weight loss induced by an anti-cancer agent in the subject relative to a baseline or a control.

[1257] 64. The method of embodiment 14, wherein administration of the non-naturally occurring melanocortin analog treats, prevents, or reduces the one or more side effects in the subject who failed to respond clinically and/or therapeutically to an antiemetic treatment, relative to a baseline or a control.

[1258] 65. The method of embodiment 15, wherein administration of the non-naturally occurring melanocortin analog treats, prevents, or reduces the one or more side effects in the subject who failed to respond clinically and/or therapeutically to nutritional intervention, relative to a baseline or a control.

[1259] 66. The method of embodiment 16, wherein administration of the non-naturally occurring melanocortin analog prevents or reduces the anti-cancer agent induced side effect in the subject, relative to a baseline or a control.

[1260] 67. The method of embodiment 17, wherein administration of the non-naturally occurring melanocortin analog treats, prevents, or reduces the iatrogenic injury caused by an anti-cancer agent in the subject, relative to a baseline or a control.

[1261] 68. The method of embodiment 18, wherein administration of the non-naturally occurring melanocortin analog prevents reduction of, maintains, or improves ECOG and/or KPS score of the subject, relative to a baseline or a control.

[1262] 69. The method of any one of embodiments 1-18, wherein the subject's mass and/or weight is not more than 5% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent.

[1263] 70. The method of any one of embodiments 1-18, wherein the subject's mass and/or weight is not more than 10% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent.

[1264] 71. The method of any one of embodiments 1-70, wherein the subject has an ECOG score of 1 or higher prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent.

[1265] 72. The method of any one of embodiments 1-70, wherein the subject has an ECOG score of 2 or higher prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent.

[1266] 73. The method of embodiment 71 or 72, wherein the method lowers the ECOG scale of the subject, relative to a baseline or a control.

[1267] 74. The method of any one of embodiments 1-73, wherein the subject has a KPS score not more than 70 prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent.

[1268] 75. The method of any one of embodiments 1-73, wherein the subject has a KPS score not more than 50 prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent.

[1269] 76. The method of embodiment 74 or 75, wherein the method increases the KPS score of the subject relative to a baseline or control.

[1270] 77. The method of any one of embodiments 1-76, wherein the method increases the subject's cumulative mass relative to a baseline or control.

[1271] 78. The method of any one of embodiments 1-76, wherein the method reduces the subject's rate of loss of cumulative mass relative to a baseline or control.

[1272] 79. The method of any one of embodiments 1-76, wherein the method increases a net weight gain in the subject relative to a baseline or control.

[1273] 80. The method of embodiment 79, wherein the net weight gain is the change in weight between two or more time points.

[1274] 81. The method of embodiment 79 or 80, wherein the net weight gain is the change in weight between the start of treatment and the end of treatment with the non-naturally occurring melanocortin analog or the anti-cancer agent.

[1275] 82. The method of embodiment 80, wherein the two or more time points comprises an intermediate time point.

[1276] 83. The method of any one of embodiments 1-82, wherein the method increases the subject's cumulative food intake relative to a baseline or control.

[1277] 84. The method of embodiment 83, wherein the cumulative food intake is the total food intake between two or more time points.

[1278] 85. The method of embodiment 83 or 84, wherein the cumulative food intake is the total in food intake between the start of treatment and the end of treatment with the non-naturally occurring melanocortin analog or the anti-cancer agent.

[1279] 86. The method of embodiment 80, wherein the two or more time points comprises an intermediate time point.

[1280] 87. The method of any one of embodiments 1-86, wherein the method increases the subject's BMI relative to a baseline or control.

[1281] 88. The method of embodiment 87, wherein the increase in BMI is the change in BMI between two or more time points.

[1282] 89. The method of embodiment 87 or 88, wherein the increase in BMI is a change in BMI between the start of treatment and the end of treatment with the non-naturally occurring melanocortin analog or the anti-cancer agent.

[1283] 90. The method of embodiment 88, wherein the two or more time points comprises an intermediate time point.

[1284] 91. The method of any one of embodiments 87-90, wherein the non-naturally occurring melanocortin analog is administered to the subject based on the subject's BMI at the time of administration.

[1285] 92. The method of embodiment 91, wherein the subject is administered the non-naturally occurring melanocortin analog at two or more doses based on the subject's BMI at the time of each administration.

[1286] 93. The method of embodiment 92, wherein the two or more doses are inversely titrated based on the subject's BMI at the time of each administration.

[1287] 94. The method of any one of embodiments 1-93, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (I),

$X^1X^2X^3R^1R^2R^3R^4R^5R^6R^7R^8R^9R^{10}R^{11}R^{12}R^{13}R^{14}R^{15}R^{16}R^{17}R^{18}R^{19}R^{20}Y^1Y^2Y^3Y^4Y^5Y^6Y^7Y^8$ (I)

wherein:

R^1 is absent or is selected from the group consisting of cysteine, norleucine (Nle), acetylated norleucine (Ac-Nle), *trans*-4-guanidinyl-proline (*trans*Pro(guan)), *cis*-4-guanidinyl-proline (*cis*Pro(guan)), acetylated *trans*-4-guanidinyl-proline (Ac-*trans*Pro(guan)), acetylated *cis*-4-guanidinyl-proline (Ac-*cis*Pro(guan)), tyrosine, D-tyrosine, di-methyl tyrosine (Dmt), aspartic acid, glutaric acid, leucine, isoleucine, valine, norvaline (Nva), alanine, glycine, proline, methionine, lysine, phenylalanine, glutamic acid, asparagine, and acetylated glutamic acid;

R^2 is absent or is selected from the group consisting of proline, histidine, D-hydroxyproline (dHyp), *trans*Pro(guan), *cis*Pro(guan), aspartic acid, glutamic acid, glycine, lysine, alanine, D-alanine, cysteine, norleucine, arginine, succinic acid, glutaric acid, methionine, and phenylalanine;

R^3 is absent or is selected from the group consisting of histidine, L-proline, *trans*Pro(guan), *cis*Pro(guan), D-valine, glutamic acid, tryptylarginine (Trp-Arg), glycine, D-leucine, D-isoleucine, tryptophan, arginine, 4-amino-1,2,4,5-tetrahydro-2-benzazepin-3-one (Aba), 7-amino-7,8-dihydro-4H-(1,2,3)triazolo-(1,5-a)(1,4)diazepin-6(5H)-one (Ata), 4-amino-1,4,5,6-tetrahydroazepino(4,3-*b*)indol-3(*2H*)-one (Aia), octohydroindole-2-carboxylic acid (Oic), 1-amino-1-cyclohexanecarboxylic acid (Che), tetrahydro-isoquinoline-3-carboxylic acid (Tic), and indoline-2-carboxylic acid (Ioc),

R^4 is selected from the group consisting of histidine, D-phenylalanine, L-phenylalanine, D-Nal(2′), aspartic acid, dBip, glycine, proline, cysteine, para-chloro-D-phenylalanine (p(Cl)dPhe), para-iodo-D-phenylalanine (p(I)dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-trifluoromethyl-D-phenylalanine (p(CF_3)dPhe);

R^5 is absent or is selected from the group consisting of arginine, homoarginine, proline, *trans*Pro(guan), *cis*Pro(guan), Pip, Nip, Tic, Phg, Sar, Azt, phenylalanine, D-Nal(2′), D-histidine, D-alanine, D-aspartic acid, D-glutamic acid, cysteine, and p(I)dPhe;

R^6 is absent or is selected from the group consisting of L-tryptophan, D-phenylalanine, D-Nal(2′), L-Nal(2′), Tic, Bip, arginine, D-histidine, cysteine, D-Nal(1’), Aba, Ata, D-tyrosine, Pen, dPen, and D-alanine;

R^7 is absent or is selected from the group consisting of glycine, aspartic acid, glutamic acid, cysteine, lysine, ornithine, 2,3-diamino-propionic acid (Dap), methionine, proline, tryptophan, D-Nal(2′), and tetrahydro-isoquinoline-3-carboxylic acid (Tic);

R^8 is absent or is lysine;

R^9-R^{20} are absent;

X^1 is absent or is selected from the group consisting of D-cysteine, L-cysteine, D-threonine, D-proline, L-proline, D-alanine, L-alanine, β-alanine, D-arginine, L-arginine, D-valine, L-valine, D-leucine, L-leucine, D-isoleucine, L-isoleucine, norvaline, glycine, methionine, lysine, phenylalanine, tyrosine, glutamic acid, asparagine, aspartic acid, acetylated D-arginine, acetylated L-arginine, acetylated D-valine, and acetylated norleucine;

X^2 is absent or is D-proline;

X^3 is absent;

Y^1 is absent or is selected from the group consisting of D-valine, D-tert-leucine, L-tert-leucine, norleucine, and D-proline;

Y^2 is absent or is selected from the group consisting of D-proline, L-proline, Hyp, D-valine, L-valine, D-tert-leucine, L-tert-leucine, norleucine, and glycine;

Y^3 is absent or is selected from the group consisting of D-lysine, L-lysine, D-proline, L-proline, D-valine, and L-valine;

Y^4 is absent or is D-aspartic acid or aspartic acid;

Y^5-Y^8 are absent;

the non-naturally occurring melanocortin analog is optionally cyclized through a moiety selected from the group consisting of:

a disulfide bond between R^1 and R^7 when R^1 is cysteine and R^7 is cysteine;

a lactam bridge between R^1 and R^7 when R^1 is norleucine and R^7 is glutamic acid;

a side-chain lactam bridge between R^1 or R^2 and R^7 when R^1 or R^2 is glutamic acid or aspartic acid, and R^7 is lysine, Dap, or ornithine;

a side-chain lactam bridge between R^2 and R^7 when R^2 is lysine, and R^7 is glutamic acid or aspartic acid;

a side-chain lactam bridge between R^1 or R^2 and R^8 when R^1 or R^2 is glutamic acid or aspartic acid, R^8 is lysine, and R^7 is proline, glycine or tryptophan;

provided that:

when R^2 is dAsp, then R^7 is not dLys;

when R^2-R^4 is Asp-His-dNal(2'), Asp-Pro-dNal(2') or Asp-Pro-dPhe, then R^5-R^7 is not Arg-Trp-Lys;

when Y^1 is dPro, Y^2 is dVal, and Y^3-Y^8 are absent, then R^4 is not dNal(2') or R^4 is dNal(2') and the C-terminus is not modified;

when R^3 is Aba, Ata, or Aia, R^6 is Aia, or R^7 is Orn, then R^4 is not dNal(2'), or R^4 is dNal(2') and R^5 is not Arg;

when R^4 is p(Cl)dPhe, then R^3 is not Pro or His;

when R^4 is p(I)dPhe then the non-naturally occurring melanocortin analog is cyclized through a side-chain lactam bridge between R^1 and R^7 and at least one of R^2 and R^3 is Pro;

when Y^2-Y^4 are absent, then Y^1 is absent or is norleucine;

when R^2 is Pro or Y^2 is Hyp, then R^3 is not Pro;

when R^3, R^5, or R^6 is absent, then the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between R^1 and R^7 or X^1-X^2 are present and are Ac-dVal-dPro;

when R^2-R^7 is Asp-Pro-dNal(2')-Arg-Trp-Lys or Cys-Pro-dNal(2')-Arg-Trp-Cys, then R^1 is not Ac-Nle or Y^1-Y^2 is not dVal-dPro, dVal-dVal, dPro-dPro; and

when the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between R^2 and R^8, then R^3 is not His or Y^1 is not dVal.

[1288] 95. The method of any one of embodiments 1-18 and 73, wherein the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 10, 14, 33-39, 82-96, 108-111, 119-124, 126-135, 138, 192-199, 222-295, 408 and 413.

[1289] 96. The method of any one of embodiments 1-18 and 73-74, wherein the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3).

[1290] 97. The method of embodiment 40, wherein the chemotherapy comprises at least one chemotherapeutic agent.

[1291] 98. The method of embodiment 97, wherein the at least one chemotherapeutic agent comprises one or more chemotherapeutic agents selected from the group consisting of a platinum-coordination complex, an antimetabolite, a tubulin binding agent or a plant alkaloid, an alkylating antineoplastic agent, and a cytotoxic antibiotic.

[1292] 99. The method of embodiment 98, wherein the at least one chemotherapeutic agent comprises a platinum-coordination complex.

[1293] 100. The method of embodiment 98, wherein the at least one chemotherapeutic agent comprises an antimetabolite.

[1294] 101. The method of embodiment 98, wherein the at least one chemotherapeutic agent comprises a tubulin binding agent or a plant alkaloid.

[1295] 102. The method of embodiment 98, wherein the at least one chemotherapeutic agent comprises an alkylating antineoplastic agent.

[1296] 103. The method of embodiment 98, wherein the at least one chemotherapeutic agent comprises a cytotoxic antibiotic.

[1297] 104. The method of embodiment 99, wherein the platinum-coordination complex is carboplatin and/or cisplatin.

[1298] 105. The method of embodiment 100, wherein the antimetabolite is at least one selected from the group consisting of 5-fluorouracil (5-FU), 6-mercaptopurine, azacitidine, capecitabine, clofarabine, cytarabine, floxuridine, fludarabine, gemcitabine, methotrexate, pemetrexed, pentostatin, pralatrexate, trifluridine, and tipiracil.

[1299] 106. The method of embodiment 101, wherein the tubulin binding agent or the plant alkaloid is at least one selected from the group consisting of vincristine, vinblastine, vinorelbine, paclitaxel, docetaxel, etoposide, teniposide, irinotecan, and Topotecan.

[1300] 107. The method of embodiment 102, wherein the alkylating antineoplastic agent is at least one selected from the group consisting of altretamine, busulfan, carmustine, cyclophosphamide, dacarbazine, ifosfamide, lomustine, melphalan, temozolomide, and trabectedin.

[1301] 108. The method of embodiment 103, wherein the cytotoxic antibiotic is at least one selected from the group consisting of daunorubicin, doxorubicin, doxorubicin liposomal, epirubicin, idarubicin, and valrubicin.

[1302] 109. The method of embodiment 99, wherein the platinum-coordination complex is cisplatin.

[1303] 110. The method of embodiment 109, wherein the chemotherapy comprises cisplatin, and the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3).

[1304] 111. The method of embodiment 100, wherein the antimetabolite is 5-fluorouracil (5-FU).

[1305] 112. The method of embodiment 111, wherein the chemotherapy comprises 5-FU, and the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3).

[1306] 113. The method of embodiment 101, wherein the tubulin binding agent or the plant alkaloid is vincristine.

[1307] 114. The method of embodiment 102, wherein the alkylating antineoplastic agent is cyclophosphamide.

[1308] 115. The method of embodiment 103, wherein the cytotoxic antibiotic is doxorubicin.

[1309] 116. The method of embodiment 115, wherein the chemotherapy comprises doxorubicin, and the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3).

[1310] 117. The method of embodiments 39 or 40, wherein the cancer is at least one selected from the group consisting of bone cancer, testicular cancer, gastric cancer, sarcoma, lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, leukemia, head and neck cancer, squamous cell head and neck cancer, thymic cancer, epithelial cancer, salivary cancer, liver cancer, stomach cancer, thyroid cancer, lung cancer, ovarian cancer, breast cancer, prostate cancer, esophageal cancer, pancreatic cancer, glioma, leukemia, multiple

myeloma, renal cell carcinoma, bladder cancer, cervical cancer, choriocarcinoma, colorectal cancer, oral cancer, skin cancer, and melanoma.

[1311] 118. The method of embodiment 39 or 40, wherein the cancer is at least one selected from the group consisting of bone cancer, lung cancer, testicular cancer, breast cancer, prostate cancer, colorectal cancer, non-Hodgkin's lymphoma, ovarian cancer, cervical cancer, bladder cancer, and head and neck cancer.

[1312] 119. The method of embodiment 39 or 40, wherein the cancer is breast cancer, and wherein the anti-cancer agent is at least one selected from the group consisting of an anthracycline, cyclophosphamide, epirubicin, fluorouracil, methotrexate, a taxane, and docetaxel.

[1313] 120. The method of embodiment 119, wherein the anthracycline is doxorubicin.

[1314] 121. The method of embodiment 119, wherein the taxane is paclitaxel.

[1315] 122. The method of embodiment 39 or 40, wherein the cancer is lung cancer, and wherein the anti-cancer agent is at least one selected from the group consisting of cisplatin, carboplatin, paclitaxel, albumin-bound paclitaxel, docetaxel, gemcitabine, vinorelbine, etoposide, and pemetrexed.

[1316] 123. The method of embodiment 39 or 40, wherein the cancer is prostate cancer, and wherein the anti-cancer agent is at least one selected from the group consisting of docetaxel, cabazitaxel, mitoxantrone, and estramustine.

[1317] 124. The method of embodiment 39 or 40, wherein the cancer is colorectal cancer, and wherein the anti-cancer agent is at least one selected from the group consisting of 5-FU, capecitabine, irinotecan, oxaliplatin, trifluridine, and tipiracil.

[1318] 125. The method of embodiment 40 or 41, wherein the cancer is colorectal cancer, wherein the subject is receiving radiation therapy, and wherein the chemotherapy is at least one selected from the group consisting of cisplatin, cisplatin plus 5-FU, and mitomycin plus 5-FU.

[1319] 126. The method of embodiment 40 or 41, wherein the cancer is colorectal cancer, wherein the subject is not receiving radiation therapy, and wherein the chemotherapy is at least one selected from the group consisting of gemcitabine plus cisplatin, methotrexate, vinblastine, doxorubicin, plus cisplatin, cisplatin, methotrexate, plus vinblastine, and gemcitabine plus paclitaxel.

[1320] 127. The method of any one of embodiments 39-41, wherein the cancer is melanoma, and wherein the anti-cancer agent is dacarbazine and/or temozolomide.

[1321] 128. The method of embodiment 39 or 40, wherein the cancer is non-Hodgkin's lymphoma, and wherein the anti-cancer agent is at least one selected from the group consisting of cyclophosphamide, chlorambucil, bendamustine, ifosfamide, prednisone, dexamethasone, cisplatin, carboplatin, oxaliplatin, fludarabine, pentostatin, cladribine (2-CdA), cytarabine (ara-C), gemcitabine, methotrexate, pralatrexate, doxorubicin, liposomal doxorubicin, hydroxydaunorubicin, vincristine, mitoxantrone, etoposide, and bleomycin.

[1322] 129. The method of any one of embodiments 1-128, wherein the method does not reduce efficacy of the anti-cancer agent.

[1323] 130. The method of embodiment 39 or 40, wherein the subject with a cancer has previously undergone a treatment with the anti-cancer agent.

[1324] 131. The method of embodiment 130, wherein the subject has previously experienced one or more adverse side effects when treated with the anti-cancer agent, wherein the adverse side effects are selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, and appetite reduction or loss of appetite.

[1325] 132. The method of any one of embodiments 1-131, wherein the subject is a human.

[1326] 133. The method of any one of embodiments 1-131, wherein the subject is an animal.

[1327] 134. The method of any one of embodiments 1-38, wherein the muscle mass loss is cardiac muscle mass loss, skeletal muscle mass loss, or both.

[1328] 135. The method of embodiment 134, wherein the cardiac muscle mass loss is determined by measuring change in heart weight.

[1329] 136. The method of embodiment 134, wherein the skeletal muscle mass loss is determined by measuring change in gastrocnemius tissue weight.

[1330] 137. The method of any one of embodiments 1-38, wherein anorexia is determined by daily food intake, daily food consumption, and/or weekly food intake.

[1331] 138. The method of embodiment 137, wherein the daily food intake is determined by total calories (kcal) consumed in 1 day or mass of food (grams or kilograms) consumed in 1 day.

[1332] 139. The method of embodiment 137, wherein the daily food consumption is determined by the daily food intake normalized to daily body weight of the subject.

[1333] 140. The method of embodiment 137, wherein the weekly food intake is determined total calories (kcal) consumed in 1 day or mass of food (grams or kilograms) consumed in 1 week.

[1334] 141. The method of any one of embodiments 1-38, wherein the weight loss is determined by daily body weight, and/or daily body weight gain.

[1335] 142. The method of any one of embodiments 1-38, wherein the fat mass of the subject treated with the method is at least 10% to 100% greater than a baseline or control, wherein the baseline or control is the subject prior to the administration of the non-naturally occurring melanocortin analog and/or a subject who is receiving or has received the anti-cancer agent without the non-naturally occurring melanocortin analog.

[1336] 143. The method of any one of embodiments 1-38, wherein the heart weight of the subject treated with the method is at least 0.1% to 10% greater than a baseline or control, wherein the baseline or control is the subject prior to the administration of the non-naturally occurring melanocortin analog and/or a subject who is receiving or has received the anti-cancer agent without the non-naturally occurring melanocortin analog.

[1337] 144. The method of any one of embodiments 1-38, wherein the gastrocnemius tissue weight of the subject treated with the method is at least 0.1% to 10%

greater than a baseline or control, wherein the baseline or control is the subject prior to the administration of the non-naturally occurring melanocortin analog and/or a subject who is receiving or has received the anti-cancer agent without the non-naturally occurring melanocortin analog.

[1338] 145. The method of any one of embodiments 1-38, wherein the daily food intake of the subject treated with the method is at least 5% to 50% greater than a baseline or control, wherein the baseline or control is the subject prior to the administration of the non-naturally occurring melanocortin analog and/or a subject who is receiving or has received the anti-cancer agent without the non-naturally occurring melanocortin analog.

[1339] 146. The method of any one of embodiments 1-38, wherein the daily body weight of the subject treated with the method is at least 1% to 15% greater than a baseline or control, wherein the baseline or control is the subject prior to the administration of the non-naturally occurring melanocortin analog and/or a subject who is receiving or has received the anti-cancer agent without the non-naturally occurring melanocortin analog.

[1340] 147. The method of any one of embodiments 1-38, wherein appetite of the subject is increased by at least 10% to 200% after the administration of the non-naturally occurring melanocortin analog.

[1341] 148. The method of any one of embodiments 1-38, wherein appetite of the subject is increased by at least 25% to 100% after the administration of the non-naturally occurring melanocortin analog.

[1342] 149. The method of embodiment 147 or 148, wherein appetite is increased for at least 1 day, 1 week, 1 month, 3 months, 6 months, 1 year, or 5 years during the administration.

[1343] 150. The method of embodiment 147 or 148, wherein appetite is increased for at least 1 day, 5 days, 7 days, 14 days, 21 days, 28 days, 35 days, 40 days, 45 days, 50 days, 60 days, 75 days, 90 days, 100 days, 110 days, or 120 days during the administration.

[1344] 151. The method of any one of embodiments 147-150, wherein the increased appetite is maintained for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days,

1 week, 2 weeks, 3 weeks, 1 month, 3 months, 6 months, 1 year, or 5 years, after the administration is stopped.

[1345] 152. The method of any one of embodiments 147-151, wherein the appetite is assessed by a scale for measuring desire to eat, feeling of hunger, and/or level of satiety.

[1346] 153. The method of embodiment 152, wherein the appetite is assessed between meals.

[1347] 154. The method of any one of embodiments 147-152, wherein the subject comprises two or more subjects, and wherein the appetite is an average appetite of the two or more subjects.

[1348] 155. The method of any one of embodiments 1-38, wherein anorexia is determined by food consumption.

[1349] 156. The method of any one of embodiments 1-18, wherein the non-naturally occurring melanocortin analog is present in a pharmaceutical composition.

[1350] 157. The method of embodiment 156, wherein the pharmaceutical composition further comprises a pharmaceutical salt.

[1351] 158. The method of embodiment 156, wherein the pharmaceutical composition further comprises a pharmaceutical carrier.

[1352] 159. The method of embodiment 156, wherein the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of 0.1 mg/mL to 500 mg/mL, relative to a total volume of the pharmaceutical composition.

[1353] 160. The method of embodiment 159, wherein the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3), and wherein the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of 5 mg/mL to 100 mg/mL, relative to a total volume of the pharmaceutical composition.

[1354] 161. The method of embodiment 160, wherein the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of

about 10 mg/mL, about 20 mg/mL, about 30 mg/mL, about 40 mg/mL, about 50 mg/mL, or about 60 mg/mL, relative to a total volume of the pharmaceutical composition.

[1355] 162. The method of embodiment 161, wherein the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of about 50 mg/mL, relative to a total volume of the pharmaceutical composition.

[1356] 163. The method of any one of embodiments 1-18, wherein the non-naturally occurring melanocortin analog is administered via intraperitoneal, intravenous, parenteral, subcutaneous, intramuscular, intracerebroventricular, intranasal, or oral administration.

[1357] 164. The method of any one of embodiments 156-162, wherein the pharmaceutical composition comprising the non-naturally occurring melanocortin analog is administered to the subject parenterally.

[1358] 165. The method of any one of embodiments 156-162, wherein the pharmaceutical composition comprising the non-naturally occurring melanocortin analog is administered to the subject subcutaneously.

[1359] 166. The method of any one of embodiments 1-18, wherein the non-naturally occurring melanocortin analog crosses the blood-brain-barrier of the subject.

[1360] 167. The method of embodiment 158, wherein the pharmaceutical carrier comprises water.

[1361] 168. The method of any one of embodiments 1-18, wherein the non-naturally occurring melanocortin analog is administered to a subject prior to or after a meal.

[1362] 169. The method of any one of embodiments 1-18, wherein the non-naturally occurring melanocortin analog is administered to a subject with a meal.

[1363] 170. The method of any one of embodiments 1-18, wherein a therapeutically effective amount of the non-naturally occurring melanocortin analog is administered, and wherein the therapeutically effective amount of the non-naturally occurring melanocortin analog is from 0.001 mg/kg to 25 mg/kg per body weight of the subject.

[1364] 171. The method of any one of embodiments 170, wherein the therapeutically effective amount of the non-naturally occurring melanocortin analog is from 0.5 mg/kg to 10 mg/kg per body weight of the subject.

[1365] 172. The method of any one of embodiments 1-18, wherein the non-naturally occurring melanocortin analog is administered at least once daily in an amount ranging from 0.001 mg/kg to 25 mg/kg per body weight of the subject.

[1366] 173. The method of any one of embodiments 1-18, wherein the non-naturally occurring melanocortin analog is administered at least once daily in an amount ranging from about 0.5 mg/kg to about 10 mg/kg per body weight of the subject.

[1367] 174. The method of embodiment 173, wherein the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3), and the non-naturally occurring melanocortin analog is administered at least once daily in an amount ranging from 0.001 mg/kg to 25 mg/kg per body weight of the subject.

[1368] 175. The method of embodiment 173, wherein the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3), and the non-naturally occurring melanocortin analog is administered at least once daily in an amount ranging from 0.5 mg/kg to 10 mg/kg per body weight of the subject.

[1369] 176. The method of any one of embodiments 1-18, wherein the non-naturally occurring melanocortin analog is administered to the subject for at least 1 day, 1 week, 1 month, 3 months, 6 months, 1 year, or 5 years.

[1370] 177. The method of any one of embodiments 1-18, wherein the non-naturally occurring melanocortin analog is administered to the subject for 1 day, 5 days, 7 days, 14 days, 21 days, 28 days, 35 days, 40 days, 45 days, 50 days, 60 days, 75 days, 90 days, 100 days, 110 days, or 120 days.

[1371] 178. The method of any one of embodiments 1-18, wherein the anti-cancer agent and the non-naturally occurring melanocortin analog are administered simultaneously as a single composition.

[1372] 179. The method of embodiment 178, wherein the non-naturally occurring melanocortin analog is present in the single composition in a concentration of 0.1 mg/mL to 500 mg/mL, relative to a total volume of the single composition.

[1373] 180. The method of embodiment 179, wherein the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3), and wherein the non-naturally occurring melanocortin analog is present in the single composition in a concentration of 5 mg/mL to 100 mg/mL, relative to a total volume of the single composition.

[1374] 181. The method of embodiment 180, wherein the non-naturally occurring melanocortin analog is present in the single composition in a concentration of about 10 mg/mL, about 20 mg/mL, about 30 mg/mL, about 40 mg/mL, about 50 mg/mL, or about 60 mg/mL, relative to a total volume of the single composition.

[1375] 182. The method of embodiment 180, wherein the non-naturally occurring melanocortin analog is present in the single composition in a concentration of about 50 mg/mL, relative to a total volume of the single composition.

[1376] 183. The method of embodiment 180, wherein the non-naturally occurring melanocortin analog is present in the single composition at a dose of about 5 mg to about 500 mg in a dose volume of about 1 mL to 20 mL, and wherein the administration is performed once, twice, 3 times, 4 times, 5 times, or 10 times per day.

[1377] 184. The method of embodiment 180, wherein the non-naturally occurring melanocortin analog is present in the single composition at a dose of about 50 mg to about 100 mg in a dose volume of about 2 mL to 10 mL, and wherein the administration is performed once, twice, 3 times, 4 times, 5 times, or 10 times per day.

[1378] 185. The method of embodiment 180, wherein the non-naturally occurring melanocortin analog is present in the single composition at a dose of about 75 mg in a dose volume of about 5 mL, and wherein the administration is performed once, twice, 3 times, 4 times, 5 times, or 10 times per day.

[1379] 186. The method of any one of embodiments 183-185, wherein the administration is performed once per day.

[1380] 187. The method of any one of embodiments 1-18, wherein:

[1381] the anti-cancer agent is present in a first pharmaceutical composition; and

[1382] the non-naturally occurring melanocortin analog is present in a second pharmaceutical composition.

[1383] 188. The method of embodiment 187, wherein the first and the second pharmaceutical compositions are different and are administered sequentially.

[1384] 189. The method of embodiment 187, wherein the first and the second pharmaceutical compositions are different and are administered simultaneously but separately.

[1385] 190. The method of any one of embodiments 187-189, wherein the second pharmaceutical composition is administered subcutaneously.

[1386] 191. The method of any one of embodiments 187-190, wherein the anti-cancer agent comprises a chemotherapy, and the chemotherapy is present in the first pharmaceutical composition in a concentration of 0.001 mg/mL to 1,000 mg/mL, relative to a total volume of the first pharmaceutical composition.

[1387] 192. The method of embodiment 191, wherein the chemotherapy is cisplatin, and cisplatin is present in the first pharmaceutical composition in a concentration of 0.01 mg/mL to 50 mg/mL, relative to a total volume of the first pharmaceutical composition.

[1388] 193. The method of embodiment 191, wherein the chemotherapy is 5-FU, and 5-FU is present in the first pharmaceutical composition in a concentration of 0.1 mg/mL to 500 mg/mL, relative to a total volume of the first pharmaceutical composition.

[1389] 194. The method of embodiment 191, wherein the chemotherapy is doxorubicin, and doxorubicin is present in the first pharmaceutical composition in a concentration of 0.01 mg/mL to 50, relative to a total volume of the first pharmaceutical composition.

[1390] 195. The method of embodiment 187, wherein the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition in a concentration

of 0.1 mg/mL to 500 mg/mL, relative to a total volume of the second pharmaceutical composition.

[1391] 196. The method of embodiment 195, wherein the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3), and wherein the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition in a concentration of 5 mg/mL to 100 mg/mL, relative to a total volume of the second pharmaceutical composition.

[1392] 197. The method of embodiment 196, wherein the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition in a concentration of about 10 mg/mL, about 20 mg/mL, about 30 mg/mL, about 40 mg/mL, about 50 mg/mL, or about 60 mg/mL, relative to a total volume of the second pharmaceutical composition.

[1393] 198. The method of embodiment 196, wherein the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition in a concentration of about 50 mg/mL, relative to a total volume of the second pharmaceutical composition.

[1394] 199. The method of embodiment 187, wherein the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition at a dose of about 5 mg to about 500 mg in a dose volume of about 1 mL to 20 mL, and wherein the administration is performed once, twice, 3 times, 4 times, 5 times, or 10 times per day.

[1395] 200. The method of embodiment 187, wherein the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition at a dose of about 50 mg to about 100 mg in a dose volume of about 2 mL to 10 mL, and wherein the administration is performed once, twice, 3 times, 4 times, 5 times, or 10 times per day.

[1396] 201. The method of embodiment 187, wherein the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition at a dose of about 75 mg in a dose volume of about 5 mL, and wherein the administration is performed once, twice, 3 times, 4 times, 5 times, or 10 times per day.

[1397] 202. The method of any one of embodiments 199-201, wherein the administration is performed once per day.

[1398] 203. The method of embodiment 187, wherein the anti-cancer agent comprises cisplatin, and wherein cisplatin is administered orally and/or intraperitoneally.

[1399] 204. The method of embodiment 187, wherein the anti-cancer agent comprises 5-FU, and wherein 5-FU is administered orally and/or intraperitoneally.

[1400] 205. The method of embodiment 187, wherein the anti-cancer agent comprises doxorubicin, and wherein doxorubicin is administered intraperitoneally.

[1401] 206. The method of embodiment 187, wherein the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO:3).

[1402] 207. The method of any one of embodiments 187-206, wherein a therapeutically effective amount of the anti-cancer agent is administered at least once per week.

[1403] 208. The method of embodiment 207, wherein the anti-cancer agent comprises cisplatin, and the therapeutically effective amount of cisplatin is from 0.01 mg/kg to 25 mg/kg per body weight of the subject.

[1404] 209. The method of embodiment 208, wherein the therapeutically effective amount of cisplatin is about 2.5 mg/kg per body weight of the subject.

[1405] 210. The method of embodiment 207, wherein the anti-cancer agent comprises 5-FU, and the therapeutically effective amount of 5-FU is from 0.1 mg/kg to 700 mg/kg per body weight of the subject.

[1406] 211. The method of embodiment 210, wherein the therapeutically effective amount of 5-FU is about 70 mg/kg per body weight of the subject.

[1407] 212. The method of embodiment 207, wherein the anti-cancer agent comprises doxorubicin, and the therapeutically effective amount of doxorubicin is from 0.005 mg/kg to 50mg/kg per body weight of the subject.

[1408] 213. The method of embodiment 212, wherein the therapeutically effective amount of doxorubicin is about 2 mg/kg per body weight of the subject.

[1409] 214. The method of any one of embodiments 207-213, wherein the non-naturally occurring melanocortin analog is administered at least once daily in an amount ranging from 0.001 mg/kg to 25 mg/kg per body weight of the subject.

[1410] 215. The method of any one of embodiments 207-213, wherein the non-naturally occurring melanocortin analog is administered at least once daily in an amount ranging from about 0.5 mg/kg to about 10 mg/kg per body weight of the subject.

[1411] 216. The method of embodiment 187, wherein the anti-cancer agent comprises cisplatin, and cisplatin is administered at a dose of 0.01 mg/kg to 25 mg/kg per body weight of the subject at intervals of about 7 days, about 14 days, about 21 days, or about 28 days.

[1412] 217. The method of embodiment 187, wherein the anti-cancer agent comprises 5-FU, and 5-FU is administered at a dose of 0.1 mg/kg to 700 mg/kg per body weight of the subject at intervals of about 7 days, about 14 days, about 21 days, or about 28 days.

[1413] 218. The method of embodiment 187, wherein the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3), and the non-naturally occurring melanocortin analog is administered at a daily dose of 0.001 mg/kg to 25 mg/kg per body weight of the subject.

[1414] 219. Use of a non-naturally occurring melanocortin analog to treat, prevent, or reduce one or more side effects associated with an anti-cancer agent in a subject, the one or more side effects are selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite, wherein the non-naturally occurring melanocortin analog is administered to the subject prior to, during, and/or after administration of the anti-cancer agent

[1415] 220. Use of a non-naturally occurring melanocortin analog to maintain or increase weight in a subject prior to, during, and/or after administration of an anti-cancer agent, wherein the weight of the subject is maintained or increased by preventing or reducing anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and/or loss of appetite in the subject.

[1416] 221. Use of a non-naturally occurring melanocortin analog to maintain or increase weight in a subject prior to, during, and/or after administration of an anti-cancer agent, comprising administering a non-naturally occurring melanocortin analog to the subject, wherein the weight of the subject is maintained or increased by preventing or reducing one or more side effects associated with the anti-cancer agent selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

[1417] 222. The use of embodiment 220 or 221, wherein the subject experiences an increase in weight by at least about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%,10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 225%, 250%, 275%, 300%, 350%, 400%, 450%, or 500% compared to baseline or a control.

[1418] 223. Use of a non-naturally occurring melanocortin analog to maintain or increase muscle mass, fat mass, or cardiac mass in a subject prior to, during, and/or after administration of an anti-cancer agent.

[1419] 224. The use of embodiment 223, wherein the subject experiences an increase in muscle mass, fat mass, or cardiac mass by at least about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%,10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% compared to a baseline or a control.

[1420] 225. Use of a non-naturally occurring melanocortin analog to maintain or increase bone density in a subject prior to, during, and/or after administration of an anti-cancer agent.

[1421] 226. The use of embodiment 225, wherein the subject experiences an increase in bone density by at least about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%,10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% compared to a baseline or a control.

[1422] 227. Use of a non-naturally occurring melanocortin analog to maintain or increase a Functional Assessment of Anorexia/ Cachexia Therapy (FAACT) score in a subject prior to, during, and/or after administration of an anti-cancer agent.

[1423] 228. The use of embodiment 227, wherein the subject experiences an increase in the FAACT score compared to baseline or control by at least 1, 2, 3, 4, or 5 points.

[1424] 229. Use of a non-naturally occurring melanocortin analog to stimulate appetite or reduce loss of appetite induced by an anti-cancer agent in a subject.

[1425] 230. The use of embodiment 229, wherein the subject experiences an increase in appetite as measured by an increased food intake by about 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1200, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000, 2500, 3000, or more calories compared to baseline a control.

[1426] 231. Use of a non-naturally occurring melanocortin analog for preventing, reducing, or restoring weight loss induced by an anti-cancer agent in a subject.

[1427] 232. Use of a non-naturally occurring melanocortin analog for treating, preventing, or reducing one or more side effects associated with an anti-cancer agent in a subject who failed to respond to an antiemetic treatment, the one or more side effects are selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

[1428] 233. Use of a non-naturally occurring melanocortin analog for treating, preventing, or reducing one or more side effects associated with an anti-cancer agent in a subject who failed to respond to nutritional intervention, the one or more side effects are selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

[1429] 234. Use of a non-naturally occurring melanocortin analog for preventing or reducing an anti-cancer agent induced side effect in a subject having cancer.

[1430] 235. Use of a non-naturally occurring melanocortin analog for treating, preventing, or reducing iatrogenic injury caused by an anti-cancer agent in a subject having cancer.

[1431] 236. Use of a non-naturally occurring melanocortin analog prior to, during, and/or after administration of an anti-cancer agent for preventing reduction of, maintaining, or improving ECOG and/or KPS score of a subject having cancer relative to a baseline or a control.

[1432] 237. The use of embodiment 236, wherein the subject experiences a reduction in ECOG performance score by about 1, 2, or 3 compared to baseline or control.

[1433] 238. The use of embodiment 236, wherein the subject experiences an increase in KPS score by about 100, 90, 80, 70, 60, 50, 40, or 30 compared to baseline or control.

[1434] 239. Use of a non-naturally occurring melanocortin analog prior to, during, and/or after administration of an anti-cancer agent for preventing reduction of, maintaining, or improving overall survival (OS) or progression free survival (PFS) in a subject having cancer relative to a baseline or a control.

[1435] 240. The use of embodiment 239, wherein the subject experiences an increase in OS or an increase in PFS compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%.

[1436] 241. Use of a non-naturally occurring analog for reducing time to cancer treatment failure in a subject having cancer relative to a baseline or a control, prior to, during, and/or after administration of an anti-cancer agent.

[1437] 242. Use of a non-naturally occurring melanocortin analog for increasing or maintaining body mass index (BMI) in a subject relative to a baseline or a control, prior to, during, and/or after administration of an anti-cancer agent.

[1438] 243. The use of embodiment 242, wherein the subject experiences an increase in BMI compared to baseline or control by at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11,

12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35 points.

[1439] 244. The use of embodiment 242 or 243, wherein the subject experiences in an increase in BMI durability compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%.

[1440] 245. Use of a non-naturally occurring melanocortin analog for reducing a proinflammatory transcript or protein level in a subject having cancer relative to a baseline or a control, prior to, during, and/or after administration of an anti-cancer agent.

[1441] 246. The use of embodiment 245, wherein the subject experiences a reduction in an inflammatory transcript level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%.

[1442] 247. The use of embodiment 245, wherein the subject experiences a reduction in an inflammatory protein level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%.

[1443] 248. The use of embodiment 245 or embodiment 329, wherein the proinflammatory transcript is a transcript selected from the group consisting of an IL1 transcript, an IL6 transcript, an IL1R1 transcript, a TNFα transcript, a Selectin P transcript, a cytokine transcript, and a chemokine transcript.

[1444] 249. The use of embodiment 245 or embodiment 329, wherein the proinflammatory protein is a protein selected from the group consisting of an IL1 protein, an IL6 protein, an IL1R1 protein, a TNFα protein, a Selectin P protein, a cytokine protein, and a chemokine protein.

[1445] 250. The use of embodiment 219, wherein the use maintains or increases lean body mass, fat body mass, and/or weight of the subject relative to a baseline or a control.

[1446] 251. The use of embodiment 229, wherein the use maintains or increases lean body mass, fat body mass, and/or body weight of the subject relative to a baseline or a control.

[1447] 252. The use of embodiment 232, wherein the failure to respond to an antiemetic treatment further comprises clinically and/or therapeutically insufficient weight gain, muscle mass gain, fat mass gain, increased appetite, and/or increased food intake in the subject.

[1448] 253. The use of embodiment 233, wherein the nutritional intervention further comprises nutritional supplementation.

[1449] 254. The use of embodiment 234, wherein the side effect is selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, loss of appetite, vomiting, diarrhea, nausea, and fatigue.

[1450] 255. The use of embodiment 235, wherein the iatrogenic injury is selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

[1451] 256. The use of embodiment 236, wherein the improvement, maintenance, or prevented reduction of ECOG and/or KPS score occurs by inhibiting or reducing anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and/or loss of appetite in the subject.

[1452] 257. The use of any one of embodiments 219-256, wherein the subject has a cancer.

[1453] 258. The use of any one of embodiments 219-257, wherein the anti-cancer agent comprises a chemotherapy.

[1454] 259. The use of embodiment 258, wherein the use reduces chemotherapy induced mass loss and/or wasting in the subject and increases lean body mass and body weight of the subject relative to a baseline or a control.

[1455] 260. The use of embodiment 258, wherein the use maintains or increases weight of the subject prior to, during, or after administration of the chemotherapy, and wherein the use reduces mass loss and/or wasting in the subject relative to a baseline or a control.

[1456] 261. The use of any one of embodiments 219-236, wherein the anorexia is associated with weight loss.

[1457] 262. The use of any one of embodiments 219-261, wherein the subject has not previously received an anti-cancer agent.

[1458] 263. The use of any one of embodiments 219-261, wherein the subject has previously received an anti-cancer agent.

[1459] 264. The use of any one of embodiments 219-261, wherein the subject is receiving an anti-cancer agent.

[1460] 265. The use of any one of embodiments 219-264, wherein the administration of the non-naturally occurring melanocortin analog enhances tolerability of the anti-cancer agent.

[1461] 266. The use of embodiment 265, wherein the enhanced tolerability results in a greater dosage, an increased frequency of administration, and/or an increased duration of administration of the anti-cancer agent, relative to a baseline or control, wherein the baseline or control is the subject prior to the administration of the non-naturally occurring melanocortin analog and/or a subject who is receiving or has received the anti-cancer agent without the non-naturally occurring melanocortin analog.

[1462] 267. The use of embodiment 265, wherein the anti-cancer agent comprises a chemotherapy comprising at least two chemotherapeutic agents, and wherein the enhanced tolerability results in a second chemotherapeutic agent being administered to the subject during or after administration of a first chemotherapeutic agent.

[1463] 268. The use of any one of embodiments 219-267, wherein the administration of the non-naturally occurring melanocortin analog prevents or reduces a downward titration in dosing regimen of the anti-cancer agent relative to a baseline or a control.

[1464] 269. The use of embodiment 268, wherein the downward titration comprises a decreased dosage, a decreased frequency of administration, and/or a decreased duration of administration, compared to a baseline or control, wherein the baseline or control is the

subject prior to the administration of the non-naturally occurring melanocortin analog and/or a subject who is receiving or has received the anti-cancer agent without the non-naturally occurring melanocortin analog.

[1465] 270. The use of any one of embodiments 219-269, wherein the subject experiences loss of appetite, reduced appetite, decreased food consumption, and/or weight loss prior to the administration of the non-naturally occurring melanocortin analog.

[1466] 271. The use of embodiment 270, wherein the loss of appetite, reduced appetite, decreased food consumption, and/or weight loss is caused by a cancer.

[1467] 272. The use of embodiment 270, wherein the loss of appetite, reduced appetite, decreased food consumption, and/or weight loss is caused by the anti-cancer agent.

[1468] 273. The use of any one of embodiments 219-272, wherein the subject is receiving or has received an antiemetic.

[1469] 274. The use of embodiment 273, wherein the antiemetic is marijuana, megestrol, somatropin, or dronabinol.

[1470] 275. The use of any one of embodiments 219-274, wherein the non-naturally occurring melanocortin analog and the anti-cancer agent are administered concurrently.

[1471] 276. The use of any one of embodiments 219-274, wherein the non-naturally occurring melanocortin analog is administered before and/or after the anti-cancer agent.

[1472] 277. The use of embodiment 219, wherein administration of the non-naturally occurring melanocortin analog treats, prevents or reduces the one or more side effects associated with an anti-cancer agent in a subject.

[1473] 278. The use of embodiment 220, wherein administration of the non-naturally occurring melanocortin analog maintains or increases weight in the subject relative to a baseline or a control by preventing or reducing anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and/or loss of appetite in the subject.

[1474] 279. The use of embodiment 221, wherein administration of the non-naturally occurring melanocortin analog maintains or increases weight in the subject relative

to a baseline or a control by preventing or reducing one or more side effects selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

[1475] 280. The use of embodiment 229, wherein administration of the non-naturally occurring melanocortin analog stimulates appetite or reduces loss of appetite induced by an anti-cancer agent in the subject relative to a baseline or a control.

[1476] 281. The use of embodiment 231, wherein administration of the non-naturally occurring melanocortin analog prevents, reduces, or restores weight loss induced by an anti-cancer agent in the subject relative to a baseline or a control.

[1477] 282. The use of embodiment 232, wherein administration of the non-naturally occurring melanocortin analog treats, prevents, or reduces the one or more side effects in the subject who failed to respond clinically and/or therapeutically to an antiemetic treatment, relative to a baseline or a control.

[1478] 283. The use of embodiment 233, wherein administration of the non-naturally occurring melanocortin analog treats, prevents, or reduces the one or more side effects in the subject who failed to respond clinically and/or therapeutically to nutritional intervention, relative to a baseline or a control.

[1479] 284. The use of embodiment 234, wherein administration of the non-naturally occurring melanocortin analog prevents or reduces the anti-cancer agent induced side effect in the subject, relative to a baseline or a control.

[1480] 285. The use of embodiment 235, wherein administration of the non-naturally occurring melanocortin analog treats, prevents, or reduces the iatrogenic injury caused by an anti-cancer agent in the subject, relative to a baseline or a control.

[1481] 286. The use of embodiment 236, wherein administration of the non-naturally occurring melanocortin analog prevents reduction of, maintains, or improves ECOG and/or KPS score of the subject, relative to a baseline or a control.

[1482] 287. The use of any one of embodiments 219-236, wherein the subject's mass and/or weight is not more than 5% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent.

[1483] 288. The use of any one of embodiments 219-236, wherein the subject's mass and/or weight is not more than 10% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent.

[1484] 289. The use of any one of embodiments 219-288, wherein the subject has an ECOG score of 1 or higher prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent.

[1485] 290. The use of any one of embodiments 219-288, wherein the subject has an ECOG score of 2 or higher prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent.

[1486] 291. The use of embodiment 289 or 290, wherein the use lowers the ECOG score of the subject, relative to a baseline or a control.

[1487] 292. The use of any one of embodiments 219-291, wherein the subject's KPS score is not more than 70 prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent.

[1488] 293. The use of any one of embodiments 219-291, wherein the subject's KPS score is not more than 50 prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent.

[1489] 294. The use of embodiment 292 or 293, wherein the use increases the subject's KPS score relative to a baseline or control.

[1490] 295. The use of any one of embodiments 219-294, wherein the use increases the subject's cumulative mass relative to a baseline or control.

[1491] 296. The use of any one of embodiments 219-294, wherein the use reduces the subject's rate of loss of cumulative mass relative to a baseline or control.

[1492] 297. The use of any one of embodiments 219-294, wherein the use increases the subject's net weight gain relative to a baseline or control.

[1493] 298. The use of embodiment 297, wherein the net weight gain is a change in weight between two or more time points.

[1494] 299. The use of embodiment 297, wherein the net weight gain is a change in weight between the start of treatment and the end of treatment with the non-naturally occurring melanocortin analog or the anti-cancer agent.

[1495] 300. The use of embodiment 298, wherein the two or more time points comprises an intermediate time point.

[1496] 301. The use of any one of embodiments 219-300, wherein the use increases the subject's cumulative food intake relative to a baseline or control.

[1497] 302. The use of embodiment 301, wherein the cumulative food intake is a total food intake between two or more time points.

[1498] 303. The use of embodiment 301, wherein the cumulative food intake is a total in food intake between the start of treatment and the end of treatment with the non-naturally occurring melanocortin analog or the anti-cancer agent.

[1499] 304. The use of 366, wherein the two or more time points comprises an intermediate time point.

[1500] 305. The use of any one of embodiments 219-304, wherein the use increases the subject's BMI relative to a baseline or control.

[1501] 306. The use of embodiment 305, wherein the increase in BMI is a change in BMI between two or more time points.

[1502] 307. The use of embodiment 305, wherein the increase in BMI is a change in BMI between the start of treatment and the end of treatment with the non-naturally occurring melanocortin analog or the anti-cancer agent.

[1503] 308. The use of embodiment 306, wherein the two or more time points comprises an intermediate time point.

[1504] 309. The use of any one of embodiments 305 to 390, wherein the non-naturally occurring melanocortin analog is administered to the subject based on the subject's BMI at the time of administration.

[1505] 310. The use of embodiment 309, wherein the subject is administered the non-naturally occurring melanocortin analog at two or more doses based on the subject's BMI at the time of each administration.

[1506] 311. The use of embodiment 310, wherein the two or more doses are inversely titrated based on the subject's BMI at the time of each administration.

[1507] 312. The use of any one of embodiments 219-311, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (I),

$X^1X^2X^3R^1R^2R^3R^4R^5R^6R^7R^8R^9R^{10}R^{11}R^{12}R^{13}R^{14}R^{15}R^{16}R^{17}R^{18}R^{19}R^{20}Y^1Y^2Y^3Y^4Y^5Y^6Y^7Y^8$ (I)

wherein:

R^1 is absent or is selected from the group consisting of cysteine, norleucine (Nle), acetylated norleucine (Ac-Nle), *trans*-4-guanidinyl-proline (*trans*Pro(guan)), *cis*-4-guanidinyl-proline (*cis*Pro(guan)), acetylated *trans*-4-guanidinyl-proline (Ac-*trans*Pro(guan)), acetylated *cis*-4-guanidinyl-proline (Ac-*cis*Pro(guan)), tyrosine, D-tyrosine, di-methyl tyrosine (Dmt), aspartic acid, glutaric acid, leucine, isoleucine, valine, norvaline (Nva), alanine, glycine, proline, methionine, lysine, phenylalanine, glutamic acid, asparagine, and acetylated glutamic acid;

R^2 is absent or is selected from the group consisting of proline, histidine, D-hydroxyproline (dHyp), *trans*Pro(guan), *cis*Pro(guan), aspartic acid, glutamic acid, glycine, lysine, alanine, D-alanine, cysteine, norleucine, arginine, succinic acid, glutaric acid, methionine, and phenylalanine;

R^3 is absent or is selected from the group consisting of histidine, L-proline, *trans*Pro(guan), *cis*Pro(guan), D-valine, glutamic acid, tryptylarginine (Trp-Arg), glycine, D-leucine, D-isoleucine, tryptophan, arginine, 4-amino-1,2,4,5-tetrahydro-2-benzazepin-3-one (Aba), 7-amino-7,8-dihydro-4H-(1,2,3)triazolo-(1,5-a)(1,4)diazepin-6(5H)-one (Ata), 4-

amino-1,4,5,6-tetrahydroazepino(4,3-*b*)indol-3(2*H*)-one (Aia), octohydroindole-2-carboxylic acid (Oic), 1-amino-1-cyclohexanecarboxylic acid (Che), tetrahydro-isoquinoline-3-carboxylic acid (Tic), and indoline-2-carboxylic acid (Ioc),

R^4 is selected from the group consisting of histidine, D-phenylalanine, L-phenylalanine, D-Nal(2'), aspartic acid, dBip, glycine, proline, cysteine, para-chloro-D-phenylalanine (p(Cl)dPhe), para-iodo-D-phenylalanine (p(I)dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-trifluoromethyl-D-phenylalanine ($p(CF_3)$dPhe);

R^5 is absent or is selected from the group consisting of arginine, homoarginine, proline, *trans*Pro(guan), *cis*Pro(guan), Pip, Nip, Tic, Phg, Sar, Azt, phenylalanine, D-Nal(2'), D-histidine, D-alanine, D-aspartic acid, D-glutamic acid, cysteine, and p(I)dPhe;

R^6 is absent or is selected from the group consisting of L-tryptophan, D-phenylalanine, D-Nal(2'), L-Nal(2'), Tic, Bip, arginine, D-histidine, cysteine, D-Nal(1'), Aba, Ata, D-tyrosine, Pen, dPen, and D-alanine;

R^7 is absent or is selected from the group consisting of glycine, aspartic acid, glutamic acid, cysteine, lysine, ornithine, 2,3-diamino-propionic acid (Dap), methionine, proline, tryptophan, D-Nal(2'), and tetrahydro-isoquinoline-3-carboxylic acid (Tic);

R^8 is absent or is lysine;

R^9-R^{20} are absent;

X^1 is absent or is selected from the group consisting of D-cysteine, L-cysteine, D-threonine, D-proline, L-proline, D-alanine, L-alanine, β-alanine, D-arginine, L-arginine, D-valine, L-valine, D-leucine, L-leucine, D-isoleucine, L-isoleucine, norvaline, glycine, methionine, lysine, phenylalanine, tyrosine, glutamic acid, asparagine, aspartic acid, acetylated D-arginine, acetylated L-arginine, acetylated D-valine, and acetylated norleucine;

X^2 is absent or is D-proline;

X^3 is absent;

Y^1 is absent or is selected from the group consisting of D-valine, D-tert-leucine, L-tert-leucine, norleucine, and D-proline;

Y^2 is absent or is selected from the group consisting of D-proline, L-proline, Hyp, D-valine, L-valine, D-tert-leucine, L-tert-leucine, norleucine, and glycine;

Y^3 is absent or is selected from the group consisting of D-lysine, L-lysine, D-proline, L-proline, D-valine, and L-valine;

Y^4 is absent or is D-aspartic acid or aspartic acid;

Y^5-Y^8 are absent;

the non-naturally occurring melanocortin analog is optionally cyclized through a moiety selected from the group consisting of:

a disulfide bond between R^1 and R^7 when R^1 is cysteine and R^7 is cysteine;

a lactam bridge between R^1 and R^7 when R^1 is norleucine and R^7 is glutamic acid;

a side-chain lactam bridge between R^1 or R^2 and R^7 when R^1 or R^2 is glutamic acid or aspartic acid, and R^7 is lysine, Dap, or ornithine;

a side-chain lactam bridge between R^2 and R^7 when R^2 is lysine, and R^7 is glutamic acid or aspartic acid;

a side-chain lactam bridge between R^1 or R^2 and R^8 when R^1 or R^2 is glutamic acid or aspartic acid, R^8 is lysine, and R^7 is proline, glycine or tryptophan;

provided that:

when R^2 is dAsp, then R^7 is not dLys;

when R^2-R^4 is Asp-His-dNal(2'), Asp-Pro-dNal(2') or Asp-Pro-dPhe, then R^5-R^7 is not Arg-Trp-Lys;

when Y^1 is dPro, Y^2 is dVal, and Y^3-Y^8 are absent, then R^4 is not dNal(2') or R^4 is dNal(2') and the C-terminus is not modified;

when R^3 is Aba, Ata, or Aia, R^6 is Aia, or R^7 is Orn, then R^4 is not dNal(2'), or R^4 is dNal(2') and R^5 is not Arg;

when R^4 is p(Cl)dPhe, then R^3 is not Pro or His;

when R^4 is p(I)dPhe then the non-naturally occurring melanocortin analog is cyclized through a side-chain lactam bridge between R^1 and R^7 and at least one of R^2 and R^3 is Pro;

when Y^2-Y^4 are absent, then Y^1 is absent or is norleucine;

when R^2 is Pro or Y^2 is Hyp, then R^3 is not Pro;

when R^3, R^5, or R^6 is absent, then the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between R^1 and R^7 or X^1-X^2 are present and are Ac-dVal-dPro;

when R^2-R^7 is Asp-Pro-dNal(2')-Arg-Trp-Lys (SEQ ID NO: 526) or Cys-Pro-dNal(2')-Arg-Trp-Cys (SEQ ID NO: 527), then R^1 is not Ac-Nle or Y^1-Y^2 is not dVal-dPro, dVal-dVal, dPro-dPro; and

when the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between R^2 and R^8, then R^3 is not His or Y^1 is not dVal.

[1508] 313. The use of any one of embodiments 219-236 and 373, wherein the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 10, 14, 33-39, 82-96, 108-111, 119-124, 126-135, 138, 192-199, 222-295, 408 and 413.

[1509] 314. The use of any one of embodiments 219-236 and 373-374, wherein the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3).

CLAIMS

I/We claim:

1. A method of treating, preventing, or reducing one or more side effects associated with an anti-cancer agent in a subject, comprising administering a non-naturally occurring melanocortin analog to the subject prior to, during, and/or after administration of the anti-cancer agent, wherein the one or more side effects are selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

2. A method of maintaining or increasing weight in a subject prior to, during, and/or after administration of an anti-cancer agent, comprising administering a non-naturally occurring melanocortin analog to the subject, wherein the weight of the subject is maintained or increased by preventing or reducing anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and/or loss of appetite in the subject.

3. A method of maintaining or increasing weight in a subject prior to, during, and/or after administration of an anti-cancer agent, comprising administering a non-naturally occurring melanocortin analog to the subject, wherein the weight of the subject is maintained or increased by preventing or reducing one or more side effects associated with the anti-cancer agent selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

4. The method of claim 2 or 3, wherein the subject experiences an increase in weight by at least about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%,10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 225%, 250%, 275%, 300%, 350%, 400%, 450%, or 500% compared to baseline or a control.

5. A method of maintaining or increasing muscle mass, fat mass, or cardiac mass in a subject prior to, during, and/or after administration of an anti-cancer agent, comprising administering a non-naturally occurring melanocortin analog to the subject

6. The method of claim 5, wherein the subject experiences an increase in muscle mass, fat mass, or cardiac mass by at least about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%,10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% compared to a baseline or a control.

7. A method of maintaining or increasing bone density in a subject prior to, during, and/or after administration of an anti-cancer agent, comprising administering a non-naturally occurring melanocortin analog to the subject.

8. The method of claim 7, wherein the subject experiences an increase in bone density by at least about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%,10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% compared to a baseline or a control.

9. A method of increasing or maintaining a Functional Assessment of Anorexia/ Cachexia Therapy (FAACT) score in a subject prior to, during, and/or after administration of an anti-cancer agent, comprising administering a non-naturally occurring melanocortin analog to the subject.

10. The method of claim 9, wherein the subject experiences an increase in the FAACT score compared to baseline or control by at least 1, 2, 3, 4, or 5 points.

11. A method of stimulating appetite or reducing loss of appetite induced by an anti-cancer agent in a subject, comprising administering a non-naturally occurring melanocortin analog to the subject prior to, during, and/or after administration of the anti-cancer agent.

12. The method of claim 11, wherein the subject experiences an increase in appetite as measured by an increased food intake by about 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1200, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000, 2500, 3000, or more calories compared to baseline a control.

13. A method of preventing, reducing, or restoring weight loss induced by an anti-cancer agent in a subject, comprising administering a non-naturally occurring melanocortin analog to the subject prior to, during, and/or after administration of the anti-cancer agent.

14. A method of treating, preventing, or reducing one or more side effects associated with an anti-cancer agent in a subject who failed to respond to an antiemetic treatment, comprising administering a non-naturally occurring melanocortin analog to the subject prior to, during, and/or after administration of the anti-cancer agent, wherein the one or more side effects are selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

15. A method of treating, preventing, or reducing one or more side effects associated with an anti-cancer agent in a subject who failed to respond to nutritional intervention, comprising administering a non-naturally occurring melanocortin analog to the subject prior to, during, and/or after administration of the anti-cancer agent, wherein the one or more side effects are selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

16. A method of preventing or reducing an anti-cancer agent induced side effect in a subject having cancer, comprising administering the anti-cancer agent and a non-naturally occurring melanocortin analog to the subject.

17. A method of treating, preventing, or reducing iatrogenic injury caused by an anti-cancer agent in a subject having cancer, comprising administering the anti-cancer agent and a non-naturally occurring melanocortin analog to the subject.

18. A method of preventing reduction of, maintaining, or improving Eastern Cooperative Oncology Group (ECOG) and/or Karnofsky performance status (KPS) score of a subject having cancer relative to a baseline or a control, comprising administering an anti-cancer agent and a non-naturally occurring melanocortin analog to the subject.

19. The method of claim 18, wherein the subject experiences a reduction in ECOG performance score by about 1, 2, or 3 compared to baseline or control.

20. The method of claim 18, wherein the subject experiences an increase in KPS score by about 100, 90, 80, 70, 60, 50, 40, or 30 compared to baseline or control.

21. A method of preventing reduction of, maintaining, or improving overall survival (OS) or progression free survival (PFS) in a subject having cancer relative to a baseline or a control, comprising administering an anti-cancer agent and a non-naturally occurring melanocortin analog to the subject.

22. The method of claim 21, wherein the subject experiences an increase in OS or an increase in PFS compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%.

23. A method of reducing time to cancer treatment failure in a subject having cancer relative to a baseline or a control, comprising administering an anti-cancer agent and a non-naturally occurring melanocortin analog to the subject.

24. A method of increasing or maintaining body mass index (BMI) in a subject relative to a baseline or a control, comprising administering an anti-cancer agent and a non-naturally occurring melanocortin analog to the subject.

25. The method of claim 24, wherein the subject experiences an increase in BMI compared to baseline or control by at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35 points.

26. The method of claim 24 or 25, wherein the subject experiences in an increase in BMI durability compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%.

27. A method of reducing a proinflammatory transcript or protein level in a subject having cancer relative to a baseline or a control, comprising administering an anti-cancer agent and a non-naturally occurring melanocortin analog to the subject.

28. The method of claim 27, wherein the subject experiences a reduction in an inflammatory transcript level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%.

29. The method of claim 27, wherein the subject experiences a reduction in an inflammatory protein level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%.

30. The method of claim 27 or claim 28, wherein the proinflammatory transcript is a transcript selected from the group consisting of an IL1 transcript, an IL6 transcript, an IL1R1 transcript, a TNFα transcript, a Selectin P transcript, a cytokine transcript, and a chemokine transcript.

31. The method of claim 27 or claim 29, wherein the proinflammatory protein is a protein selected from the group consisting of an IL1 protein, an IL6 protein, an IL1R1 protein, a TNFα protein, a Selectin P protein, and a cytokine protein.

32. The method of claim 1, wherein the method maintains or increases lean body mass, fat body mass, and/or weight of the subject relative to a baseline or a control.

33. The method of claim 11, wherein the method maintains or increases lean body mass, fat body mass, and/or body weight of the subject relative to a baseline or a control.

34. The method of claim 14, wherein the failure to respond to an antiemetic treatment further comprises clinically and/or therapeutically insufficient weight gain, muscle mass gain, fat mass gain, increased appetite, and/or increased food intake in the subject.

35. The method of claim 15, wherein the nutritional intervention further comprises nutritional supplementation.

36. The method of claim 16, wherein the side effect is selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, loss of appetite, vomiting, diarrhea, nausea, and fatigue.

37. The method of claim 17, wherein the iatrogenic injury is selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

38. The method of claim 18, wherein the improvement, maintenance, or prevented reduction of ECOG and/or KPS score occurs by inhibiting or reducing anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and/or loss of appetite in the subject.

39. The method of any one of claims 1-38, wherein the subject has a cancer.

40. The method of any one of claims 1-39, wherein the anti-cancer agent comprises a chemotherapy.

41. The method of claim 40, wherein the method reduces chemotherapy induced mass loss and/or wasting in the subject and increases lean body mass and body weight of the subject relative to a baseline or a control.

42. The method of claim 40, wherein the method maintains or increases weight of the subject prior to, during, or after administration of the chemotherapy, and wherein the method reduces mass loss and/or wasting in the subject relative to a baseline or a control.

43. The method of any one of claims 1-18, wherein the anorexia is associated with weight loss.

44. The method of any one of claims 1-43, wherein the subject has not previously received an anti-cancer agent.

45. The method of any one of claims 1-43, wherein the subject has previously received an anti-cancer agent.

46. The method of any one of claims 1-43, wherein the subject is receiving an anti-cancer agent.

47. The method of any one of claims 1-46, wherein the administration of the non-naturally occurring melanocortin analog enhances tolerability of the anti-cancer agent.

48. The method of claim 47, wherein the enhanced tolerability results in a greater dosage, an increased frequency of administration, and/or an increased duration of administration of the anti-cancer agent, relative to a baseline or control, wherein the baseline or control is the subject prior to the administration of the non-naturally occurring melanocortin analog and/or a subject who is receiving or has received the anti-cancer agent without the non-naturally occurring melanocortin analog.

49. The method of claim 47, wherein the anti-cancer agent comprises a chemotherapy comprising at least two chemotherapeutic agents, and wherein the enhanced tolerability results in a second chemotherapeutic agent being administered to the subject during or after administration of a first chemotherapeutic agent.

50. The method of any one of claims 1-49, wherein the administration of the non-naturally occurring melanocortin analog prevents or reduces a downward titration in dosing regimen of the anti-cancer agent relative to a baseline or a control.

51. The method of claim 50, wherein the downward titration comprises a decreased dosage, a decreased frequency of administration, and/or a decreased duration of administration, compared to a baseline or control, wherein the baseline or control is the subject prior to the administration of the non-naturally occurring melanocortin analog and/or a subject who is receiving or has received the anti-cancer agent without the non-naturally occurring melanocortin analog.

52. The method of any one of claims 1-51, wherein the subject experiences loss of appetite, reduced appetite, decreased food consumption, and/or weight loss prior to the administration of the non-naturally occurring melanocortin analog.

53. The method of claim 52, wherein the loss of appetite, reduced appetite, decreased food consumption, and/or weight loss is caused by cancer.

54. The method of claim 52, wherein the loss of appetite, reduced appetite, decreased food consumption, and/or weight loss is caused by the anti-cancer agent.

55. The method of any one of claims 1-54 wherein the subject is receiving or has received an antiemetic.

56. The method of claim 55, wherein the antiemetic is marijuana, megestrol, somatropin, or dronabinol.

57. The method of any one of claims 1-56, wherein the non-naturally occurring melanocortin analog and the anti-cancer agent are administered concurrently.

58. The method of any one of claims 1-56, wherein the non-naturally occurring melanocortin analog is administered before and/or after the anti-cancer agent.

59. The method of claim 1, wherein administration of the non-naturally occurring melanocortin analog treats, prevents or reduces the one or more side effects associated with an anti-cancer agent in a subject.

60. The method of claim 2, wherein administration of the non-naturally occurring melanocortin analog maintains or increases weight in the subject relative to a baseline or a control by preventing or reducing anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and/or loss of appetite in the subject.

61. The method of claim 3, wherein administration of the non-naturally occurring melanocortin analog maintains or increases weight in the subject relative to a baseline or a control by preventing or reducing one or more side effects selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

62. The method of claim 11, wherein administration of the non-naturally occurring melanocortin analog stimulates appetite or reduces loss of appetite induced by an anti-cancer agent in the subject relative to a baseline or a control.

63. The method of claim 13, wherein administration of the non-naturally occurring melanocortin analog prevents, reduces, or restores weight loss induced by an anti-cancer agent in the subject relative to a baseline or a control.

64. The method of claim 14, wherein administration of the non-naturally occurring melanocortin analog treats, prevents, or reduces the one or more side effects in the subject who failed to respond clinically and/or therapeutically to an antiemetic treatment, relative to a baseline or a control.

65. The method of claim 15, wherein administration of the non-naturally occurring melanocortin analog treats, prevents, or reduces the one or more side effects in the subject who failed to respond clinically and/or therapeutically to nutritional intervention, relative to a baseline or a control.

66. The method of claim 16, wherein administration of the non-naturally occurring melanocortin analog prevents or reduces the anti-cancer agent induced side effect in the subject, relative to a baseline or a control.

67. The method of claim 17, wherein administration of the non-naturally occurring melanocortin analog treats, prevents, or reduces the iatrogenic injury caused by an anti-cancer agent in the subject, relative to a baseline or a control.

68. The method of claim 18, wherein administration of the non-naturally occurring melanocortin analog prevents reduction of, maintains, or improves ECOG and/or KPS score of the subject, relative to a baseline or a control.

69. The method of any one of claims 1-18, wherein the subject's mass and/or weight is not more than 5% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent.

70. The method of any one of claims 1-18, wherein the subject's mass and/or weight is not more than 10% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent.

71. The method of any one of claims 1-70, wherein the subject has an ECOG score of 1 or higher prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent.

72. The method of any one of claims 1-70, wherein the subject has an ECOG score of 2 or higher prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent.

73. The method of claim 71 or 72, wherein the method lowers the ECOG scale of the subject, relative to a baseline or a control.

74. The method of any one of claims 1-73, wherein the subject has a KPS score not more than 70 prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent.

75. The method of any one of claims 1-73, wherein the subject has a KPS score not more than 50 prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent.

76. The method of claim 74 or 75, wherein the method increases the KPS score of the subject relative to a baseline or control.

77. The method of any one of claims 1-76, wherein the method increases the subject's cumulative mass relative to a baseline or control.

78. The method of any one of claims 1-76, wherein the method reduces the subject's rate of loss of cumulative mass relative to a baseline or control.

79. The method of any one of claims 1-76, wherein the method increases a net weight gain in the subject relative to a baseline or control.

80. The method of claim 79, wherein the net weight gain is the change in weight between two or more time points.

81. The method of claim 79 or 80, wherein the net weight gain is the change in weight between the start of treatment and the end of treatment with the non-naturally occurring melanocortin analog or the anti-cancer agent.

82. The method of claim 80, wherein the two or more time points comprises an intermediate time point.

83. The method of any one of claims 1-82, wherein the method increases the subject's cumulative food intake relative to a baseline or control.

84. The method of claim 83, wherein the cumulative food intake is the total food intake between two or more time points.

85. The method of claim 83 or 84, wherein the cumulative food intake is the total in food intake between the start of treatment and the end of treatment with the non-naturally occurring melanocortin analog or the anti-cancer agent.

86. The method of claim 80, wherein the two or more time points comprises an intermediate time point.

87. The method of any one of claims 1-86, wherein the method increases the subject's BMI relative to a baseline or control.

88. The method of claim 87, wherein the increase in BMI is the change in BMI between two or more time points.

89. The method of claim 87 or 88, wherein the increase in BMI is a change in BMI between the start of treatment and the end of treatment with the non-naturally occurring melanocortin analog or the anti-cancer agent.

90. The method of claim 88, wherein the two or more time points comprises an intermediate time point.

91. The method of any one of claims 87-90, wherein the non-naturally occurring melanocortin analog is administered to the subject based on the subject's BMI at the time of administration.

92. The method of claim 91, wherein the subject is administered the non-naturally occurring melanocortin analog at two or more doses based on the subject's BMI at the time of each administration.

93. The method of claim 92, wherein the two or more doses are inversely titrated based on the subject's BMI at the time of each administration.

94. The method of any one of claims 1-93, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (I),

$X^1X^2X^3R^1R^2R^3R^4R^5R^6R^7R^8R^9R^{10}R^{11}R^{12}R^{13}R^{14}R^{15}R^{16}R^{17}R^{18}R^{19}R^{20}Y^1Y^2Y^3Y^4Y^5Y^6Y^7Y^8$ (I)

wherein:

R^1 is absent or is selected from the group consisting of cysteine, norleucine (Nle), acetylated norleucine (Ac-Nle), *trans*-4-guanidinyl-proline (*trans*Pro(guan)), *cis*-4-guanidinyl-proline (*cis*Pro(guan)), acetylated *trans*-4-guanidinyl-proline (Ac-*trans*Pro(guan)), acetylated *cis*-4-guanidinyl-proline (Ac-*cis*Pro(guan)), tyrosine, D-tyrosine, di-methyl tyrosine (Dmt), aspartic acid, glutaric acid, leucine, isoleucine, valine, norvaline (Nva), alanine, glycine, proline, methionine, lysine, phenylalanine, glutamic acid, asparagine, and acetylated glutamic acid;

R^2 is absent or is selected from the group consisting of proline, histidine, D-hydroxyproline (dHyp), *trans*Pro(guan), *cis*Pro(guan), aspartic acid, glutamic acid, glycine, lysine, alanine, D-alanine, cysteine, norleucine, arginine, succinic acid, glutaric acid, methionine, and phenylalanine;

R^3 is absent or is selected from the group consisting of histidine, L-proline, *trans*Pro(guan), *cis*Pro(guan), D-valine, glutamic acid, tryptylarginine (Trp-Arg), glycine, D-leucine, D-isoleucine, tryptophan, arginine, 4-amino-1,2,4,5-tetrahydro-2-benzazepin-3-one (Aba), 7-amino-7,8-dihydro-4H-(1,2,3)triazolo-(1,5-a)(1,4)diazepin-6(5H)-one (Ata), 4-amino-1,4,5,6-tetrahydroazepino(4,3-*b*)indol-3(*2H*)-one (Aia), octohydroindole-2-carboxylic acid (Oic), 1-amino-1-cyclohexanecarboxylic acid (Che), tetrahydro-isoquinoline-3-carboxylic acid (Tic), and indoline-2-carboxylic acid (Ioc),

R^4 is selected from the group consisting of histidine, D-phenylalanine, L-phenylalanine, D-Nal(2′), aspartic acid, dBip, glycine, proline, cysteine, para-chloro-D-phenylalanine (p(Cl)dPhe), para-iodo-D-phenylalanine (p(I)dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-trifluoromethyl-D-phenylalanine (p(CF_3)dPhe);

R^5 is absent or is selected from the group consisting of arginine, homoarginine, proline, *trans*Pro(guan), *cis*Pro(guan), Pip, Nip, Tic, Phg, Sar, Azt, phenylalanine, D-Nal(2′), D-histidine, D-alanine, D-aspartic acid, D-glutamic acid, cysteine, and p(I)dPhe;

R^6 is absent or is selected from the group consisting of L-tryptophan, D-phenylalanine, D-Nal(2′), L-Nal(2′), Tic, Bip, arginine, D-histidine, cysteine, D-Nal(1′), Aba, Ata, D-tyrosine, Pen, dPen, and D-alanine;

R^7 is absent or is selected from the group consisting of glycine, aspartic acid, glutamic acid, cysteine, lysine, ornithine, 2,3-diamino-propionic acid (Dap), methionine, proline, tryptophan, D-Nal(2′), and tetrahydro-isoquinoline-3-carboxylic acid (Tic);

R^8 is absent or is lysine;

R^9-R^{20} are absent;

X^1 is absent or is selected from the group consisting of D-cysteine, L-cysteine, D-threonine, D-proline, L-proline, D-alanine, L-alanine, β-alanine, D-arginine, L-arginine, D-valine, L-valine, D-leucine, L-leucine, D-isoleucine, L-isoleucine, norvaline, glycine, methionine, lysine, phenylalanine, tyrosine, glutamic acid,

asparagine, aspartic acid, acetylated D-arginine, acetylated L-arginine, acetylated D-valine, and acetylated norleucine;

X^2 is absent or is D-proline;

X^3 is absent;

Y^1 is absent or is selected from the group consisting of D-valine, D-tert-leucine, L-tert-leucine, norleucine, and D-proline;

Y^2 is absent or is selected from the group consisting of D-proline, L-proline, Hyp, D-valine, L-valine, D-tert-leucine, L-tert-leucine, norleucine, and glycine;

Y^3 is absent or is selected from the group consisting of D-lysine, L-lysine, D-proline, L-proline, D-valine, and L-valine;

Y^4 is absent or is D-aspartic acid or aspartic acid;

Y^5-Y^8 are absent;

the non-naturally occurring melanocortin analog is optionally cyclized through a moiety selected from the group consisting of:

a disulfide bond between R^1 and R^7 when R^1 is cysteine and R^7 is cysteine;

a lactam bridge between R^1 and R^7 when R^1 is norleucine and R^7 is glutamic acid;

a side-chain lactam bridge between R^1 or R^2 and R^7 when R^1 or R^2 is glutamic acid or aspartic acid, and R^7 is lysine, Dap, or ornithine;

a side-chain lactam bridge between R^2 and R^7 when R^2 is lysine, and R^7 is glutamic acid or aspartic acid;

a side-chain lactam bridge between R^1 or R^2 and R^8 when R^1 or R^2 is glutamic acid or aspartic acid, R^8 is lysine, and R^7 is proline, glycine or tryptophan;

provided that:

when R^2 is dAsp, then R^7 is not dLys;

when R^2-R^4 is Asp-His-dNal(2'), Asp-Pro-dNal(2') or Asp-Pro-dPhe, then R^5-R^7 is not Arg-Trp-Lys;

when Y^1 is dPro, Y^2 is dVal, and Y^3-Y^8 are absent, then R^4 is not dNal(2') or R^4 is dNal(2') and the C-terminus is not modified;

when R^3 is Aba, Ata, or Aia, R^6 is Aia, or R^7 is Orn, then R^4 is not dNal(2'), or R^4 is dNal(2') and R^5 is not Arg;

when R^4 is p(Cl)dPhe, then R^3 is not Pro or His;

when R^4 is p(I)dPhe then the non-naturally occurring melanocortin analog is cyclized through a side-chain lactam bridge between R^1 and R^7 and at least one of R^2 and R^3 is Pro;

when Y^2-Y^4 are absent, then Y^1 is absent or is norleucine;

when R^2 is Pro or Y^2 is Hyp, then R^3 is not Pro;

when R^3, R^5, or R^6 is absent, then the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between R^1 and R^7 or X^1-X^2 are present and are Ac-dVal-dPro;

when R^2-R^7 is Asp-Pro-dNal(2')-Arg-Trp-Lys (SEQ ID NO: 526) or Cys-Pro-dNal(2')-Arg-Trp-Cys (SEQ ID NO: 527), then R^1 is not Ac-Nle or Y^1-Y^2 is not dVal-dPro, dVal-dVal, dPro-dPro; and

when the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between R^2 and R^8, then R^3 is not His or Y^1 is not dVal.

95. The method of any one of claims 1-18 and 73, wherein the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 10, 14, 33-39, 82-96, 108-111, 119-124, 126-135, 138, 192-199, 222-295, 408 and 413.

96. The method of any one of claims 1-18 and 73-74, wherein the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3).

97. The method of claim 40, wherein the chemotherapy comprises at least one chemotherapeutic agent.

98. The method of claim 97, wherein the at least one chemotherapeutic agent comprises one or more chemotherapeutic agents selected from the group consisting of a

platinum-coordination complex, an antimetabolite, a tubulin binding agent or a plant alkaloid, an alkylating antineoplastic agent, and a cytotoxic antibiotic.

99. The method of claim 98, wherein the at least one chemotherapeutic agent comprises a platinum-coordination complex.

100. The method of claim 98, wherein the at least one chemotherapeutic agent comprises an antimetabolite.

101. The method of claim 98, wherein the at least one chemotherapeutic agent comprises a tubulin binding agent or a plant alkaloid.

102. The method of claim 98, wherein the at least one chemotherapeutic agent comprises an alkylating antineoplastic agent.

103. The method of claim 98, wherein the at least one chemotherapeutic agent comprises a cytotoxic antibiotic.

104. The method of claim 99, wherein the platinum-coordination complex is carboplatin and/or cisplatin.

105. The method of claim 100, wherein the antimetabolite is at least one selected from the group consisting of 5-fluorouracil (5-FU), 6-mercaptopurine, azacitidine, capecitabine, clofarabine, cytarabine, floxuridine, fludarabine, gemcitabine, methotrexate, pemetrexed, pentostatin, pralatrexate, trifluridine, and tipiracil.

106. The method of claim 101, wherein the tubulin binding agent or the plant alkaloid is at least one selected from the group consisting of vincristine, vinblastine, vinorelbine, paclitaxel, docetaxel, etoposide, teniposide, irinotecan, and Topotecan.

107. The method of claim 102, wherein the alkylating antineoplastic agent is at least one selected from the group consisting of altretamine, busulfan, carmustine, cyclophosphamide, dacarbazine, ifosfamide, lomustine, melphalan, temozolomide, and trabectedin.

108. The method of claim 103, wherein the cytotoxic antibiotic is at least one selected from the group consisting of daunorubicin, doxorubicin, doxorubicin liposomal, epirubicin, idarubicin, and valrubicin.

109. The method of claim 99, wherein the platinum-coordination complex is cisplatin.

110. The method of claim 109, wherein the chemotherapy comprises cisplatin, and the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3).

111. The method of claim 100, wherein the antimetabolite is 5-fluorouracil (5-FU).

112. The method of claim 111, wherein the chemotherapy comprises 5-FU, and the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3).

113. The method of claim 101, wherein the tubulin binding agent or the plant alkaloid is vincristine.

114. The method of claim 102, wherein the alkylating antineoplastic agent is cyclophosphamide.

115. The method of claim 103, wherein the cytotoxic antibiotic is doxorubicin.

116. The method of claim 115, wherein the chemotherapy comprises doxorubicin, and the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3).

117. The method of claims 39 or 40, wherein the cancer is at least one selected from the group consisting of bone cancer, testicular cancer, gastric cancer, sarcoma, lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, leukemia, head and neck cancer, squamous cell head and neck cancer, thymic cancer, epithelial cancer, salivary cancer, liver cancer, stomach cancer, thyroid cancer, lung cancer, ovarian cancer, breast cancer, prostate cancer, esophageal cancer, pancreatic cancer, glioma, leukemia, multiple myeloma, renal cell carcinoma, bladder cancer, cervical cancer, choriocarcinoma, colorectal cancer, oral cancer, skin cancer, and melanoma.

118. The method of claim 39 or 40, wherein the cancer is at least one selected from the group consisting of bone cancer, lung cancer, testicular cancer, breast cancer, prostate cancer, colorectal cancer, non-Hodgkin's lymphoma, ovarian cancer, cervical cancer, bladder cancer, and head and neck cancer.

119. The method of claim 39 or 40, wherein the cancer is breast cancer, and wherein the anti-cancer agent is at least one selected from the group consisting of an anthracycline, cyclophosphamide, epirubicin, fluorouracil, methotrexate, a taxane, and docetaxel.

120. The method of claim 119, wherein the anthracycline is doxorubicin.

121. The method of claim 119, wherein the taxane is paclitaxel.

122. The method of claim 39 or 40, wherein the cancer is lung cancer, and wherein the anti-cancer agent is at least one selected from the group consisting of cisplatin, carboplatin, paclitaxel, albumin-bound paclitaxel, docetaxel, gemcitabine, vinorelbine, etoposide, and pemetrexed.

123. The method of claim 39 or 40, wherein the cancer is prostate cancer, and wherein the anti-cancer agent is at least one selected from the group consisting of docetaxel, cabazitaxel, mitoxantrone, and estramustine.

124. The method of claim 39 or 40, wherein the cancer is colorectal cancer, and wherein the anti-cancer agent is at least one selected from the group consisting of 5-FU, capecitabine, irinotecan, oxaliplatin, trifluridine, and tipiracil.

125. The method of claim 40 or 41, wherein the cancer is colorectal cancer, wherein the subject is receiving radiation therapy, and wherein the chemotherapy is at least one selected from the group consisting of cisplatin, cisplatin plus 5-FU, and mitomycin plus 5-FU.

126. The method of claim 40 or 41, wherein the cancer is colorectal cancer, wherein the subject is not receiving radiation therapy, and wherein the chemotherapy is at least one selected from the group consisting of gemcitabine plus cisplatin, methotrexate, vinblastine, doxorubicin, plus cisplatin, cisplatin, methotrexate, plus vinblastine, and gemcitabine plus paclitaxel.

127. The method of any one of claims 39-41, wherein the cancer is melanoma, and wherein the anti-cancer agent is dacarbazine and/or temozolomide.

128. The method of claim 39 or 40, wherein the cancer is non-Hodgkin's lymphoma, and wherein the anti-cancer agent is at least one selected from the group consisting of cyclophosphamide, chlorambucil, bendamustine, ifosfamide, prednisone, dexamethasone, cisplatin, carboplatin, oxaliplatin, fludarabine, pentostatin, cladribine (2-CdA), cytarabine (ara-C), gemcitabine, methotrexate, pralatrexate, doxorubicin, liposomal doxorubicin, hydroxydaunorubicin, vincristine, mitoxantrone, etoposide, and bleomycin.

129. The method of any one of claims 1-128, wherein the method does not reduce efficacy of the anti-cancer agent.

130. The method of claim 39 or 40, wherein the subject with a cancer has previously undergone a treatment with the anti-cancer agent.

131. The method of claim 130, wherein the subject has previously experienced one or more adverse side effects when treated with the anti-cancer agent, wherein the adverse side effects are selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, and appetite reduction or loss of appetite.

132. The method of any one of claims 1-131, wherein the subject is a human.

133. The method of any one of claims 1-131, wherein the subject is an animal.

134. The method of any one of claims 1-38, wherein the muscle mass loss is cardiac muscle mass loss, skeletal muscle mass loss, or both.

135. The method of claim 134, wherein the cardiac muscle mass loss is determined by measuring change in heart weight.

136. The method of claim 134, wherein the skeletal muscle mass loss is determined by measuring change in gastrocnemius tissue weight.

137. The method of any one of claims 1-38, wherein anorexia is determined by daily food intake, daily food consumption, and/or weekly food intake.

138. The method of claim 137, wherein the daily food intake is determined by total calories (kcal) consumed in 1 day or mass of food (grams or kilograms) consumed in 1 day.

139. The method of claim 137, wherein the daily food consumption is determined by the daily food intake normalized to daily body weight of the subject.

140. The method of claim 137, wherein the weekly food intake is determined total calories (kcal) consumed in 1 day or mass of food (grams or kilograms) consumed in 1 week.

141. The method of any one of claims 1-38, wherein the weight loss is determined by daily body weight, and/or daily body weight gain.

142. The method of any one of claims 1-38, wherein the fat mass of the subject treated with the method is at least 10% to 100% greater than a baseline or control, wherein the baseline or control is the subject prior to the administration of the non-naturally occurring melanocortin analog and/or a subject who is receiving or has received the anti-cancer agent without the non-naturally occurring melanocortin analog.

143. The method of any one of claims 1-38, wherein the heart weight of the subject treated with the method is at least 0.1% to 10% greater than a baseline or control, wherein the baseline or control is the subject prior to the administration of the non-naturally occurring melanocortin analog and/or a subject who is receiving or has received the anti-cancer agent without the non-naturally occurring melanocortin analog.

144. The method of any one of claims 1-38, wherein the gastrocnemius tissue weight of the subject treated with the method is at least 0.1% to 10% greater than a baseline or control, wherein the baseline or control is the subject prior to the administration of the non-naturally occurring melanocortin analog and/or a subject who is receiving or has received the anti-cancer agent without the non-naturally occurring melanocortin analog.

145. The method of any one of claims 1-38, wherein the daily food intake of the subject treated with the method is at least 5% to 50% greater than a baseline or control, wherein the baseline or control is the subject prior to the administration of the non-naturally occurring melanocortin analog and/or a subject who is receiving or has received the anti-cancer agent without the non-naturally occurring melanocortin analog.

146. The method of any one of claims 1-38, wherein the daily body weight of the subject treated with the method is at least 1% to 15% greater than a baseline or control, wherein the baseline or control is the subject prior to the administration of the non-naturally occurring melanocortin analog and/or a subject who is receiving or has received the anti-cancer agent without the non-naturally occurring melanocortin analog.

147. The method of any one of claims 1-38, wherein appetite of the subject is increased by at least 10% to 200% after the administration of the non-naturally occurring melanocortin analog.

148. The method of any one of claims 1-38, wherein appetite of the subject is increased by at least 25% to 100% after the administration of the non-naturally occurring melanocortin analog.

149. The method of claim 147 or 148, wherein appetite is increased for at least 1 day, 1 week, 1 month, 3 months, 6 months, 1 year, or 5 years during the administration.

150. The method of claim 147 or 148, wherein appetite is increased for at least 1 day, 5 days, 7 days, 14 days, 21 days, 28 days, 35 days, 40 days, 45 days, 50 days, 60 days, 75 days, 90 days, 100 days, 110 days, or 120 days during the administration.

151. The method of any one of claims 147-150, wherein the increased appetite is maintained for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks, 3 weeks, 1 month, 3 months, 6 months, 1 year, or 5 years, after the administration is stopped.

152. The method of any one of claims 147-151, wherein the appetite is assessed by a scale for measuring desire to eat, feeling of hunger, and/or level of satiety.

153. The method of claim 152, wherein the appetite is assessed between meals.

154. The method of any one of claims 147-152, wherein the subject comprises two or more subjects, and wherein the appetite is an average appetite of the two or more subjects.

155. The method of any one of claims 1-38, wherein anorexia is determined by food consumption.

156. The method of any one of claims 1-18, wherein the non-naturally occurring melanocortin analog is present in a pharmaceutical composition.

157. The method of claim 156, wherein the pharmaceutical composition further comprises a pharmaceutical salt.

158. The method of claim 156, wherein the pharmaceutical composition further comprises a pharmaceutical carrier.

159. The method of claim 156, wherein the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of 0.1 mg/mL to 500 mg/mL, relative to a total volume of the pharmaceutical composition.

160. The method of claim 159, wherein the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3), and wherein the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of 5 mg/mL to 100 mg/mL, relative to a total volume of the pharmaceutical composition.

161. The method of claim 160, wherein the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of about 10 mg/mL, about 20 mg/mL, about 30 mg/mL, about 40 mg/mL, about 50 mg/mL, or about 60 mg/mL, relative to a total volume of the pharmaceutical composition.

162. The method of claim 161, wherein the non-naturally occurring melanocortin analog is present in the pharmaceutical composition in a concentration of about 50 mg/mL, relative to a total volume of the pharmaceutical composition.

163. The method of any one of claims 1-18, wherein the non-naturally occurring melanocortin analog is administered via intraperitoneal, intravenous, parenteral, subcutaneous, intramuscular, intracerebroventricular, intranasal, or oral administration.

164. The method of any one of claims 156-162, wherein the pharmaceutical composition comprising the non-naturally occurring melanocortin analog is administered to the subject parenterally.

165. The method of any one of claims 156-162, wherein the pharmaceutical composition comprising the non-naturally occurring melanocortin analog is administered to the subject subcutaneously.

166. The method of any one of claims 1-18, wherein the non-naturally occurring melanocortin analog crosses the blood-brain-barrier of the subject.

167. The method of claim 158, wherein the pharmaceutical carrier comprises water.

168. The method of any one of claims 1-18, wherein the non-naturally occurring melanocortin analog is administered to a subject prior to or after a meal.

169. The method of any one of claims 1-18, wherein the non-naturally occurring melanocortin analog is administered to a subject with a meal.

170. The method of any one of claims 1-18, wherein a therapeutically effective amount of the non-naturally occurring melanocortin analog is administered, and wherein the

therapeutically effective amount of the non-naturally occurring melanocortin analog is from 0.001 mg/kg to 25 mg/kg per body weight of the subject.

171. The method of any one of claims 170, wherein the therapeutically effective amount of the non-naturally occurring melanocortin analog is from 0.5 mg/kg to 10 mg/kg per body weight of the subject.

172. The method of any one of claims 1-18, wherein the non-naturally occurring melanocortin analog is administered at least once daily in an amount ranging from 0.001 mg/kg to 25 mg/kg per body weight of the subject.

173. The method of any one of claims 1-18, wherein the non-naturally occurring melanocortin analog is administered at least once daily in an amount ranging from about 0.5 mg/kg to about 10 mg/kg per body weight of the subject.

174. The method of claim 173, wherein the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3), and the non-naturally occurring melanocortin analog is administered at least once daily in an amount ranging from 0.001 mg/kg to 25 mg/kg per body weight of the subject.

175. The method of claim 173, wherein the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3), and the non-naturally occurring melanocortin analog is administered at least once daily in an amount ranging from 0.5 mg/kg to 10 mg/kg per body weight of the subject.

176. The method of any one of claims 1-18, wherein the non-naturally occurring melanocortin analog is administered to the subject for at least 1 day, 1 week, 1 month, 3 months, 6 months, 1 year, or 5 years.

177. The method of any one of claims 1-18, wherein the non-naturally occurring melanocortin analog is administered to the subject for 1 day, 5 days, 7 days, 14 days, 21 days, 28 days, 35 days, 40 days, 45 days, 50 days, 60 days, 75 days, 90 days, 100 days, 110 days, or 120 days.

178. The method of any one of claims 1-18, wherein the anti-cancer agent and the non-naturally occurring melanocortin analog are administered simultaneously as a single composition.

179. The method of claim 178, wherein the non-naturally occurring melanocortin analog is present in the single composition in a concentration of 0.1 mg/mL to 500 mg/mL, relative to a total volume of the single composition.

180. The method of claim 179, wherein the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3), and wherein the non-naturally occurring melanocortin analog is present in the single composition in a concentration of 5 mg/mL to 100 mg/mL, relative to a total volume of the single composition.

181. The method of claim 180, wherein the non-naturally occurring melanocortin analog is present in the single composition in a concentration of about 10 mg/mL, about 20 mg/mL, about 30 mg/mL, about 40 mg/mL, about 50 mg/mL, or about 60 mg/mL, relative to a total volume of the single composition.

182. The method of claim 180, wherein the non-naturally occurring melanocortin analog is present in the single composition in a concentration of about 50 mg/mL, relative to a total volume of the single composition.

183. The method of claim 180, wherein the non-naturally occurring melanocortin analog is present in the single composition at a dose of about 5 mg to about 500 mg in a

dose volume of about 1 mL to 20 mL, and wherein the administration is performed once, twice, 3 times, 4 times, 5 times, or 10 times per day.

184. The method of claim 180, wherein the non-naturally occurring melanocortin analog is present in the single composition at a dose of about 50 mg to about 100 mg in a dose volume of about 2 mL to 10 mL, and wherein the administration is performed once, twice, 3 times, 4 times, 5 times, or 10 times per day.

185. The method of claim 180, wherein the non-naturally occurring melanocortin analog is present in the single composition at a dose of about 75 mg in a dose volume of about 5 mL, and wherein the administration is performed once, twice, 3 times, 4 times, 5 times, or 10 times per day.

186. The method of any one of claims 183-185, wherein the administration is performed once per day.

187. The method of any one of claims 1-18, wherein:

the anti-cancer agent is present in a first pharmaceutical composition; and

the non-naturally occurring melanocortin analog is present in a second pharmaceutical composition.

188. The method of claim 187, wherein the first and the second pharmaceutical compositions are different and are administered sequentially.

189. The method of claim 187, wherein the first and the second pharmaceutical compositions are different and are administered simultaneously but separately.

190. The method of any one of claims 187-189, wherein the second pharmaceutical composition is administered subcutaneously.

191. The method of any one of claims 187-190, wherein the anti-cancer agent comprises a chemotherapy, and the chemotherapy is present in the first pharmaceutical composition in a concentration of 0.001 mg/mL to 1,000 mg/mL, relative to a total volume of the first pharmaceutical composition.

192. The method of claim 191, wherein the chemotherapy is cisplatin, and cisplatin is present in the first pharmaceutical composition in a concentration of 0.01 mg/mL to 50 mg/mL, relative to a total volume of the first pharmaceutical composition.

193. The method of claim 191, wherein the chemotherapy is 5-FU, and 5-FU is present in the first pharmaceutical composition in a concentration of 0.1 mg/mL to 500 mg/mL, relative to a total volume of the first pharmaceutical composition.

194. The method of claim 191, wherein the chemotherapy is doxorubicin, and doxorubicin is present in the first pharmaceutical composition in a concentration of 0.01 mg/mL to 50, relative to a total volume of the first pharmaceutical composition.

195. The method of claim 187, wherein the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition in a concentration of 0.1 mg/mL to 500 mg/mL, relative to a total volume of the second pharmaceutical composition.

196. The method of claim 195, wherein the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3), and wherein the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition in a concentration of 5 mg/mL to 100 mg/mL, relative to a total volume of the second pharmaceutical composition.

197. The method of claim 196, wherein the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition in a concentration of about 10 mg/mL, about 20 mg/mL, about 30 mg/mL, about 40 mg/mL, about 50 mg/mL, or about 60 mg/mL, relative to a total volume of the second pharmaceutical composition.

198. The method of claim 196, wherein the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition in a concentration of about 50 mg/mL, relative to a total volume of the second pharmaceutical composition.

199. The method of claim 187, wherein the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition at a dose of about 5 mg to about 500 mg in a dose volume of about 1 mL to 20 mL, and wherein the administration is performed once, twice, 3 times, 4 times, 5 times, or 10 times per day.

200. The method of claim 187, wherein the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition at a dose of about 50 mg to about 100 mg in a dose volume of about 2 mL to 10 mL, and wherein the administration is performed once, twice, 3 times, 4 times, 5 times, or 10 times per day.

201. The method of claim 187, wherein the non-naturally occurring melanocortin analog is present in the second pharmaceutical composition at a dose of about 75 mg in a dose volume of about 5 mL, and wherein the administration is performed once, twice, 3 times, 4 times, 5 times, or 10 times per day.

202. The method of any one of claims 199-201, wherein the administration is performed once per day.

203. The method of claim 187, wherein the anti-cancer agent comprises cisplatin, and wherein cisplatin is administered orally and/or intraperitoneally.

204. The method of claim 187, wherein the anti-cancer agent comprises 5-FU, and wherein 5-FU is administered orally and/or intraperitoneally.

205. The method of claim 187, wherein the anti-cancer agent comprises doxorubicin, and wherein doxorubicin is administered intraperitoneally.

206. The method of claim 187, wherein the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO:3).

207. The method of any one of claims 187-206, wherein a therapeutically effective amount of the anti-cancer agent is administered at least once per week.

208. The method of claim 207, wherein the anti-cancer agent comprises cisplatin, and the therapeutically effective amount of cisplatin is from 0.01 mg/kg to 25 mg/kg per body weight of the subject.

209. The method of claim 208, wherein the therapeutically effective amount of cisplatin is about 2.5 mg/kg per body weight of the subject.

210. The method of claim 207, wherein the anti-cancer agent comprises 5-FU, and the therapeutically effective amount of 5-FU is from 0.1 mg/kg to 700 mg/kg per body weight of the subject.

211. The method of claim 210, wherein the therapeutically effective amount of 5-FU is about 70 mg/kg per body weight of the subject.

212. The method of claim 207, wherein the anti-cancer agent comprises doxorubicin, and the therapeutically effective amount of doxorubicin is from 0.005 mg/kg to 50mg/kg per body weight of the subject.

213. The method of claim 212, wherein the therapeutically effective amount of doxorubicin is about 2 mg/kg per body weight of the subject.

214. The method of any one of claims 207-213, wherein the non-naturally occurring melanocortin analog is administered at least once daily in an amount ranging from 0.001 mg/kg to 25 mg/kg per body weight of the subject.

215. The method of any one of claims 207-213, wherein the non-naturally occurring melanocortin analog is administered at least once daily in an amount ranging from about 0.5 mg/kg to about 10 mg/kg per body weight of the subject.

216. The method of claim 187, wherein the anti-cancer agent comprises cisplatin, and cisplatin is administered at a dose of 0.01 mg/kg to 25 mg/kg per body weight of the subject at intervals of about 7 days, about 14 days, about 21 days, or about 28 days.

217. The method of claim 187, wherein the anti-cancer agent comprises 5-FU, and 5-FU is administered at a dose of 0.1 mg/kg to 700 mg/kg per body weight of the subject at intervals of about 7 days, about 14 days, about 21 days, or about 28 days.

218. The method of claim 187, wherein the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3), and the non-naturally occurring melanocortin analog is administered at a daily dose of 0.001 mg/kg to 25 mg/kg per body weight of the subject.

219. Use of a non-naturally occurring melanocortin analog to treat, prevent, or reduce one or more side effects associated with an anti-cancer agent in a subject, the one or more side effects are selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite, wherein the non-naturally occurring melanocortin analog is administered to the subject prior to, during, and/or after administration of the anti-cancer agent

220. Use of a non-naturally occurring melanocortin analog to maintain or increase weight in a subject prior to, during, and/or after administration of an anti-cancer agent, wherein the weight of the subject is maintained or increased by preventing or reducing

anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and/or loss of appetite in the subject.

221. Use of a non-naturally occurring melanocortin analog to maintain or increase weight in a subject prior to, during, and/or after administration of an anti-cancer agent, comprising administering a non-naturally occurring melanocortin analog to the subject, wherein the weight of the subject is maintained or increased by preventing or reducing one or more side effects associated with the anti-cancer agent selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

222. The use of claim 220 or 221, wherein the subject experiences an increase in weight by at least about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%,10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 225%, 250%, 275%, 300%, 350%, 400%, 450%, or 500% compared to baseline or a control.

223. Use of a non-naturally occurring melanocortin analog to maintain or increase muscle mass, fat mass, or cardiac mass in a subject prior to, during, and/or after administration of an anti-cancer agent.

224. The use of claim 223, wherein the subject experiences an increase in muscle mass, fat mass, or cardiac mass by at least about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%,10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% compared to a baseline or a control.

225. Use of a non-naturally occurring melanocortin analog to maintain or increase bone density in a subject prior to, during, and/or after administration of an anti-cancer agent.

226. The use of claim 225, wherein the subject experiences an increase in bone density by at least about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%,10%, 12%, 14%, 16%, 18%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% compared to a baseline or a control.

227. Use of a non-naturally occurring melanocortin analog to maintain or increase a Functional Assessment of Anorexia/ Cachexia Therapy (FAACT) score in a subject prior to, during, and/or after administration of an anti-cancer agent.

228. The use of claim 227, wherein the subject experiences an increase in the FAACT score compared to baseline or control by at least 1, 2, 3, 4, or 5 points.

229. Use of a non-naturally occurring melanocortin analog to stimulate appetite or reduce loss of appetite induced by an anti-cancer agent in a subject.

230. The use of claim 229, wherein the subject experiences an increase in appetite as measured by an increased food intake by about 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1200, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000, 2500, 3000, or more calories compared to baseline a control.

231. Use of a non-naturally occurring melanocortin analog for preventing, reducing, or restoring weight loss induced by an anti-cancer agent in a subject.

232. Use of a non-naturally occurring melanocortin analog for treating, preventing, or reducing one or more side effects associated with an anti-cancer agent in a subject who failed to respond to an antiemetic treatment, the one or more side effects are selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

233. Use of a non-naturally occurring melanocortin analog for treating, preventing, or reducing one or more side effects associated with an anti-cancer agent in a subject who failed to respond to nutritional intervention, the one or more side effects are selected from

the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

234. Use of a non-naturally occurring melanocortin analog for preventing or reducing an anti-cancer agent induced side effect in a subject having cancer.

235. Use of a non-naturally occurring melanocortin analog for treating, preventing, or reducing iatrogenic injury caused by an anti-cancer agent in a subject having cancer.

236. Use of a non-naturally occurring melanocortin analog prior to, during, and/or after administration of an anti-cancer agent for preventing reduction of, maintaining, or improving ECOG and/or KPS score of a subject having cancer relative to a baseline or a control.

237. The use of claim 236, wherein the subject experiences a reduction in ECOG performance score by about 1, 2, or 3 compared to baseline or control.

238. The use of claim 236, wherein the subject experiences an increase in KPS score by about 100, 90, 80, 70, 60, 50, 40, or 30 compared to baseline or control.

239. Use of a non-naturally occurring melanocortin analog prior to, during, and/or after administration of an anti-cancer agent for preventing reduction of, maintaining, or improving overall survival (OS) or progression free survival (PFS) in a subject having cancer relative to a baseline or a control.

240. The use of claim 239, wherein the subject experiences an increase in OS or an increase in PFS compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%.

241. Use of a non-naturally occurring analog for reducing time to cancer treatment failure in a subject having cancer relative to a baseline or a control, prior to, during, and/or after administration of an anti-cancer agent.

242. Use of a non-naturally occurring melanocortin analog for increasing or maintaining body mass index (BMI) in a subject relative to a baseline or a control, prior to, during, and/or after administration of an anti-cancer agent.

243. The use of claim 242, wherein the subject experiences an increase in BMI compared to baseline or control by at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35 points.

244. The use of claim 242 or 243, wherein the subject experiences in an increase in BMI durability compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%.

245. Use of a non-naturally occurring melanocortin analog for reducing a proinflammatory transcript or protein level in a subject having cancer relative to a baseline or a control, prior to, during, and/or after administration of an anti-cancer agent.

246. The use of claim 245, wherein the subject experiences a reduction in an inflammatory transcript level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%.

247. The use of claim 245, wherein the subject experiences a reduction in an inflammatory protein level compared to baseline or control by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 100%.

248. The use of claim 245 or claim 329, wherein the proinflammatory transcript is a transcript selected from the group consisting of an IL1 transcript, an IL6 transcript, an IL1R1

transcript, a TNFα transcript, a Selectin P transcript, a cytokine transcript, and a chemokine transcript.

249. The use of claim 245 or claim 329, wherein the proinflammatory protein is a protein selected from the group consisting of an IL1 protein, an IL6 protein, an IL1R1 protein, a TNFα protein, a Selectin P protein, a cytokine protein, and a chemokine protein.

250. The use of claim 219, wherein the use maintains or increases lean body mass, fat body mass, and/or weight of the subject relative to a baseline or a control.

251. The use of claim 229, wherein the use maintains or increases lean body mass, fat body mass, and/or body weight of the subject relative to a baseline or a control.

252. The use of claim 232, wherein the failure to respond to an antiemetic treatment further comprises clinically and/or therapeutically insufficient weight gain, muscle mass gain, fat mass gain, increased appetite, and/or increased food intake in the subject.

253. The use of claim 233, wherein the nutritional intervention further comprises nutritional supplementation.

254. The use of claim 234, wherein the side effect is selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, loss of appetite, vomiting, diarrhea, nausea, and fatigue.

255. The use of claim 235, wherein the iatrogenic injury is selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

256. The use of claim 236, wherein the improvement, maintenance, or prevented reduction of ECOG and/or KPS score occurs by inhibiting or reducing anorexia, weight loss,

muscle mass loss, fat mass loss, wasting, reduced appetite, and/or loss of appetite in the subject.

257. The use of any one of claims 219-256, wherein the subject has a cancer.

258. The use of any one of claims 219-257, wherein the anti-cancer agent comprises a chemotherapy.

259. The use of claim 258, wherein the use reduces chemotherapy induced mass loss and/or wasting in the subject and increases lean body mass and body weight of the subject relative to a baseline or a control.

260. The use of claim 258, wherein the use maintains or increases weight of the subject prior to, during, or after administration of the chemotherapy, and wherein the use reduces mass loss and/or wasting in the subject relative to a baseline or a control.

261. The use of any one of claims 219-236, wherein the anorexia is associated with weight loss.

262. The use of any one of claims 219-261, wherein the subject has not previously received an anti-cancer agent.

263. The use of any one of claims 219-261, wherein the subject has previously received an anti-cancer agent.

264. The use of any one of claims 219-261, wherein the subject is receiving an anti-cancer agent.

265. The use of any one of claims 219-264, wherein the administration of the non-naturally occurring melanocortin analog enhances tolerability of the anti-cancer agent.

266. The use of claim 265, wherein the enhanced tolerability results in a greater dosage, an increased frequency of administration, and/or an increased duration of administration of the anti-cancer agent, relative to a baseline or control, wherein the baseline or control is the subject prior to the administration of the non-naturally occurring melanocortin analog and/or a subject who is receiving or has received the anti-cancer agent without the non-naturally occurring melanocortin analog.

267. The use of claim 265, wherein the anti-cancer agent comprises a chemotherapy comprising at least two chemotherapeutic agents, and wherein the enhanced tolerability results in a second chemotherapeutic agent being administered to the subject during or after administration of a first chemotherapeutic agent.

268. The use of any one of claims 219-267, wherein the administration of the non-naturally occurring melanocortin analog prevents or reduces a downward titration in dosing regimen of the anti-cancer agent relative to a baseline or a control.

269. The use of claim 268, wherein the downward titration comprises a decreased dosage, a decreased frequency of administration, and/or a decreased duration of administration, compared to a baseline or control, wherein the baseline or control is the subject prior to the administration of the non-naturally occurring melanocortin analog and/or a subject who is receiving or has received the anti-cancer agent without the non-naturally occurring melanocortin analog.

270. The use of any one of claims 219-269, wherein the subject experiences loss of appetite, reduced appetite, decreased food consumption, and/or weight loss prior to the administration of the non-naturally occurring melanocortin analog.

271. The use of claim 270, wherein the loss of appetite, reduced appetite, decreased food consumption, and/or weight loss is caused by a cancer.

272. The use of claim 270, wherein the loss of appetite, reduced appetite, decreased food consumption, and/or weight loss is caused by the anti-cancer agent.

273. The use of any one of claims 219-272, wherein the subject is receiving or has received an antiemetic.

274. The use of claim 273, wherein the antiemetic is marijuana, megestrol, somatropin, or dronabinol.

275. The use of any one of claims 219-274, wherein the non-naturally occurring melanocortin analog and the anti-cancer agent are administered concurrently.

276. The use of any one of claims 219-274, wherein the non-naturally occurring melanocortin analog is administered before and/or after the anti-cancer agent.

277. The use of claim 219, wherein administration of the non-naturally occurring melanocortin analog treats, prevents or reduces the one or more side effects associated with an anti-cancer agent in a subject.

278. The use of claim 220, wherein administration of the non-naturally occurring melanocortin analog maintains or increases weight in the subject relative to a baseline or a control by preventing or reducing anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and/or loss of appetite in the subject.

279. The use of claim 221, wherein administration of the non-naturally occurring melanocortin analog maintains or increases weight in the subject relative to a baseline or a control by preventing or reducing one or more side effects selected from the group consisting of anorexia, weight loss, muscle mass loss, fat mass loss, wasting, reduced appetite, and loss of appetite.

280. The use of claim 229, wherein administration of the non-naturally occurring melanocortin analog stimulates appetite or reduces loss of appetite induced by an anti-cancer agent in the subject relative to a baseline or a control.

281. The use of claim 231, wherein administration of the non-naturally occurring melanocortin analog prevents, reduces, or restores weight loss induced by an anti-cancer agent in the subject relative to a baseline or a control.

282. The use of claim 232, wherein administration of the non-naturally occurring melanocortin analog treats, prevents, or reduces the one or more side effects in the subject who failed to respond clinically and/or therapeutically to an antiemetic treatment, relative to a baseline or a control.

283. The use of claim 233, wherein administration of the non-naturally occurring melanocortin analog treats, prevents, or reduces the one or more side effects in the subject who failed to respond clinically and/or therapeutically to nutritional intervention, relative to a baseline or a control.

284. The use of claim 234, wherein administration of the non-naturally occurring melanocortin analog prevents or reduces the anti-cancer agent induced side effect in the subject, relative to a baseline or a control.

285. The use of claim 235, wherein administration of the non-naturally occurring melanocortin analog treats, prevents, or reduces the iatrogenic injury caused by an anti-cancer agent in the subject, relative to a baseline or a control.

286. The use of claim 236, wherein administration of the non-naturally occurring melanocortin analog prevents reduction of, maintains, or improves ECOG and/or KPS score of the subject, relative to a baseline or a control.

287. The use of any one of claims 219-236, wherein the subject's mass and/or weight is not more than 5% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent.

288. The use of any one of claims 219-236, wherein the subject's mass and/or weight is not more than 10% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent.

289. The use of any one of claims 219-288, wherein the subject has an ECOG score of 1 or higher prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent.

290. The use of any one of claims 219-288, wherein the subject has an ECOG score of 2 or higher prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent.

291. The use of claim 289 or 290, wherein the use lowers the ECOG score of the subject, relative to a baseline or a control.

292. The use of any one of claims 219-291, wherein the subject's KPS score is not more than 70 prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent.

293. The use of any one of claims 219-291, wherein the subject's KPS score is not more than 50 prior to administration of the non-naturally occurring melanocortin analog and/or the anti-cancer agent.

294. The use of claim 292 or 293, wherein the use increases the subject's KPS score relative to a baseline or control.

295. The use of any one of claims 219-294, wherein the use increases the subject's cumulative mass relative to a baseline or control.

296. The use of any one of claims 219-294, wherein the use reduces the subject's rate of loss of cumulative mass relative to a baseline or control.

297. The use of any one of claims 219-294, wherein the use increases the subject's net weight gain relative to a baseline or control.

298. The use of claim 297, wherein the net weight gain is a change in weight between two or more time points.

299. The use of claim 297, wherein the net weight gain is a change in weight between the start of treatment and the end of treatment with the non-naturally occurring melanocortin analog or the anti-cancer agent.

300. The use of claim 298, wherein the two or more time points comprises an intermediate time point.

301. The use of any one of claims 219-300, wherein the use increases the subject's cumulative food intake relative to a baseline or control.

302. The use of claim 301, wherein the cumulative food intake is a total food intake between two or more time points.

303. The use of claim 301, wherein the cumulative food intake is a total in food intake between the start of treatment and the end of treatment with the non-naturally occurring melanocortin analog or the anti-cancer agent.

304. The use of 366, wherein the two or more time points comprises an intermediate time point.

305. The use of any one of claims 219-304, wherein the use increases the subject's BMI relative to a baseline or control.

306. The use of claim 305, wherein the increase in BMI is a change in BMI between two or more time points.

307. The use of claim 305, wherein the increase in BMI is a change in BMI between the start of treatment and the end of treatment with the non-naturally occurring melanocortin analog or the anti-cancer agent.

308. The use of claim 306, wherein the two or more time points comprises an intermediate time point.

309. The use of any one of claims 305 to 390, wherein the non-naturally occurring melanocortin analog is administered to the subject based on the subject's BMI at the time of administration.

310. The use of claim 309, wherein the subject is administered the non-naturally occurring melanocortin analog at two or more doses based on the subject's BMI at the time of each administration.

311. The use of claim 310, wherein the two or more doses are inversely titrated based on the subject's BMI at the time of each administration.

312. The use of any one of claims 219-311, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (I),

$X^1X^2X^3R^1R^2R^3R^4R^5R^6R^7R^8R^9R^{10}R^{11}R^{12}R^{13}R^{14}R^{15}R^{16}R^{17}R^{18}R^{19}R^{20}Y^1Y^2Y^3Y^4Y^5Y^6Y^7Y^8$ (I)

wherein:

R^1 is absent or is selected from the group consisting of cysteine, norleucine (Nle), acetylated norleucine (Ac-Nle), *trans*-4-guanidinyl-proline (*trans*Pro(guan)), *cis*-4-guanidinyl-proline (*cis*Pro(guan)), acetylated *trans*-4-guanidinyl-proline (Ac-*trans*Pro(guan)), acetylated *cis*-4-guanidinyl-proline (Ac-*cis*Pro(guan)), tyrosine, D-tyrosine, di-methyl tyrosine (Dmt), aspartic acid, glutaric acid, leucine, isoleucine, valine, norvaline (Nva), alanine, glycine, proline, methionine, lysine, phenylalanine, glutamic acid, asparagine, and acetylated glutamic acid;

R^2 is absent or is selected from the group consisting of proline, histidine, D-hydroxyproline (dHyp), *trans*Pro(guan), *cis*Pro(guan), aspartic acid, glutamic acid, glycine, lysine, alanine, D-alanine, cysteine, norleucine, arginine, succinic acid, glutaric acid, methionine, and phenylalanine;

R^3 is absent or is selected from the group consisting of histidine, L-proline, *trans*Pro(guan), *cis*Pro(guan), D-valine, glutamic acid, tryptylarginine (Trp-Arg), glycine, D-leucine, D-isoleucine, tryptophan, arginine, 4-amino-1,2,4,5-tetrahydro-2-benzazepin-3-one (Aba), 7-amino-7,8-dihydro-4H-(1,2,3)triazolo-(1,5-a)(1,4)diazepin-6(5H)-one (Ata), 4-amino-1,4,5,6-tetrahydroazepino(4,3-*b*)indol-3(*2H*)-one (Aia), octohydroindole-2-carboxylic acid (Oic), 1-amino-1-cyclohexanecarboxylic acid (Che), tetrahydro-isoquinoline-3-carboxylic acid (Tic), and indoline-2-carboxylic acid (Ioc),

R^4 is selected from the group consisting of histidine, D-phenylalanine, L-phenylalanine, D-Nal(2′), aspartic acid, dBip, glycine, proline, cysteine, para-chloro-D-phenylalanine (p(Cl)dPhe), para-iodo-D-phenylalanine (p(I)dPhe), para-fluoro-D-phenylalanine (p(F)dPhe), and para-trifluoromethyl-D-phenylalanine ($p(CF_3)$dPhe);

R^5 is absent or is selected from the group consisting of arginine, homoarginine, proline, *trans*Pro(guan), *cis*Pro(guan), Pip, Nip, Tic, Phg, Sar, Azt, phenylalanine, D-Nal(2'), D-histidine, D-alanine, D-aspartic acid, D-glutamic acid, cysteine, and p(I)dPhe;

R^6 is absent or is selected from the group consisting of L-tryptophan, D-phenylalanine, D-Nal(2'), L-Nal(2'), Tic, Bip, arginine, D-histidine, cysteine, D-Nal(1'), Aba, Ata, D-tyrosine, Pen, dPen, and D-alanine;

R^7 is absent or is selected from the group consisting of glycine, aspartic acid, glutamic acid, cysteine, lysine, ornithine, 2,3-diamino-propionic acid (Dap), methionine, proline, tryptophan, D-Nal(2'), and tetrahydro-isoquinoline-3-carboxylic acid (Tic);

R^8 is absent or is lysine;

R^9-R^{20} are absent;

X^1 is absent or is selected from the group consisting of D-cysteine, L-cysteine, D-threonine, D-proline, L-proline, D-alanine, L-alanine, β-alanine, D-arginine, L-arginine, D-valine, L-valine, D-leucine, L-leucine, D-isoleucine, L-isoleucine, norvaline, glycine, methionine, lysine, phenylalanine, tyrosine, glutamic acid, asparagine, aspartic acid, acetylated D-arginine, acetylated L-arginine, acetylated D-valine, and acetylated norleucine;

X^2 is absent or is D-proline;

X^3 is absent;

Y^1 is absent or is selected from the group consisting of D-valine, D-tert-leucine, L-tert-leucine, norleucine, and D-proline;

Y^2 is absent or is selected from the group consisting of D-proline, L-proline, Hyp, D-valine, L-valine, D-tert-leucine, L-tert-leucine, norleucine, and glycine;

Y^3 is absent or is selected from the group consisting of D-lysine, L-lysine, D-proline, L-proline, D-valine, and L-valine;

Y^4 is absent or is D-aspartic acid or aspartic acid;

Y^5-Y^8 are absent;

the non-naturally occurring melanocortin analog is optionally cyclized through a moiety selected from the group consisting of:

a disulfide bond between R^1 and R^7 when R^1 is cysteine and R^7 is cysteine;

a lactam bridge between R^1 and R^7 when R^1 is norleucine and R^7 is glutamic acid;

a side-chain lactam bridge between R^1 or R^2 and R^7 when R^1 or R^2 is glutamic acid or aspartic acid, and R^7 is lysine, Dap, or ornithine;

a side-chain lactam bridge between R^2 and R^7 when R^2 is lysine, and R^7 is glutamic acid or aspartic acid;

a side-chain lactam bridge between R^1 or R^2 and R^8 when R^1 or R^2 is glutamic acid or aspartic acid, R^8 is lysine, and R^7 is proline, glycine or tryptophan;

provided that:

when R^2 is dAsp, then R^7 is not dLys;

when R^2-R^4 is Asp-His-dNal(2'), Asp-Pro-dNal(2') or Asp-Pro-dPhe, then R^5-R^7 is not Arg-Trp-Lys;

when Y^1 is dPro, Y^2 is dVal, and Y^3-Y^8 are absent, then R^4 is not dNal(2') or R^4 is dNal(2') and the C-terminus is not modified;

when R^3 is Aba, Ata, or Aia, R^6 is Aia, or R^7 is Orn, then R^4 is not dNal(2'), or R^4 is dNal(2') and R^5 is not Arg;

when R^4 is p(Cl)dPhe, then R^3 is not Pro or His;

when R^4 is p(I)dPhe then the non-naturally occurring melanocortin analog is cyclized through a side-chain lactam bridge between R^1 and R^7 and at least one of R^2 and R^3 is Pro;

when Y^2-Y^4 are absent, then Y^1 is absent or is norleucine;

when R^2 is Pro or Y^2 is Hyp, then R^3 is not Pro;

when R^3, R^5, or R^6 is absent, then the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between R^1 and R^7 or X^1-X^2 are present and are Ac-dVal-dPro;

when R^2-R^7 is Asp-Pro-dNal(2')-Arg-Trp-Lys (SEQ ID NO: 526) or Cys-Pro-dNal(2')-Arg-Trp-Cys (SEQ ID NO: 527), then R^1 is not Ac-Nle or Y^1-Y^2 is not dVal-dPro, dVal-dVal, dPro-dPro; and

when the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between R^2 and R^8, then R^3 is not His or Y^1 is not dVal.

313. The use of any one of claims 219-236 and 373, wherein the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 10, 14, 33-39, 82-96, 108-111, 119-124, 126-135, 138, 192-199, 222-295, 408 and 413.

314. The use of any one of claims 219-236 and 373-374, wherein the non-naturally occurring melanocortin analog comprises a sequence of Ac-Nle-c(Asp-Pro-dNal(2')-Arg-Trp-Lys)-dVal-dPro-NH_2 (SEQ ID NO: 3).