ORALLY DELIVERABLE NON-NATURALLY OCCURRING MELANOCORTIN ANALOGS AND USES THEREOF FOR MODULATING WEIGHT LOSS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 63/554,944, filed February 16, 2024; U.S. Provisional Patent Application No. 63/557,409, filed February 23, 2024; U.S. Provisional Patent Application No. 63/572,896, filed April 1, 2024; U.S. Provisional Patent Application No. 63/573,433, filed April 2, 2024; U.S. Provisional Patent Application No. 63/632,496, filed April 10, 2024; U.S. Provisional Patent Application No. 63/637,285, filed April 22, 2024; U.S. Provisional Patent Application No. 63/640,864, filed April 30, 2024; U.S. Provisional Patent Application No. 63/647,545, filed May 14, 2024; U.S. Provisional Patent Application No. 63/650,368, filed May 21, 2024; U.S. Provisional Patent Application No. 63/654,876, filed May 31, 2024; U.S. Provisional Patent Application No. 63/656,579, field June 5, 2024; U.S. Provisional Patent Application No. 63/663,689, filed June 24, 2024; U.S. Provisional Patent Application No. 63/675,219, filed July 24, 2024; U.S. Provisional Patent Application No. 63/681,055, filed August 8, 2024; and of U.S. Provisional Patent Application No. 63/692,605, filed September 9, 2024, all of which are incorporated herein by reference in their entirety.

INCORPORATION BY REFERENCE OF SEQUENCE LISTING

[0002] This application contains an ST.26 compliant Sequence Listing, which is submitted concurrently in xml format and is hereby incorporated by reference in its entirety. The .xml copy, created on February 13, 2025, is titled “146316_8023_WO00_SL.xml” and is 490,839 bytes in size.

BACKGROUND

[0003] The prevalence of obesity, diabetes, and metabolic syndrome has reached pandemic proportions, and is expected to continue to rise in the next two decades. These conditions place enormous stress on healthcare systems globally. Accordingly, various

weight loss agents have been developed in an attempt to treat such conditions. Although some weight loss agents have been approved for ongoing use, many are not sufficiently effective in achieving desired amounts or types of weight loss. Further, commonly used weight loss agents are administered subcutaneously, requiring self-administered injections on a daily or weekly basis which may cause administration site irritation and discomfort.

[0004] Accordingly, despite recent advances treatment for obesity, diabetes, and metabolic syndrome, there is a demand for novel and effective weight loss agents that may be delivered via less invasive administration routes.

SUMMARY

[0005] The present technology comprises methods of reducing body weight and/or fat mass in a subject in need thereof, comprising administering to the subject a non-naturally occurring melanocortin analog.

[0006] In some embodiments, the present technology comprises a non-naturally occurring melanocortin analog comprising a sequence according to Formula (IF),

$$R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}Y^1\text{-}Y^2 \text{ (IF)},$$

wherein:

R^1 is Nle;

R^2 is Asp or Glu;

R^3 is His;

R^4 is selected from dPhe, p(F)dPhe, and p(Cl)dPhe;

R^5 is Arg or His;

R^6 is Trp;

R^7 is Orn;

Y^1 is dVal;

Y^2 is dPro; and

the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between Asp or Glu at R^2 and Orn at R^7.

[0007] In some embodiments, the present technology comprises a method of reducing body weight and/or fat mass in a subject in need thereof, comprising orally administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I):

$$X^1\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}R^8\text{-}R^9\text{-}Y^1\text{-}Y^2\text{-}Y^3\text{-}Y^4 \text{ (I)},$$

wherein:

X^1 is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

R^1 is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R^2 is selected from the group consisting of Asp, D-cysteine (dCys), Ala, D-alanine (dAla), proline (Pro), glutamic acid (Glu), and phenylalanine (Phe);

R^3 is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln);

R^4 is selected from the group consisting of D-phenylalanine (dPhe), Pro, para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

R^5 is selected from the group consisting of Arg, His, *cis*-4-guanidyl-proline (*cis*Pro(guan)), and *trans*-4-guanidyl-proline (*trans*Pro(guan));

R^6 is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2')));

R^7 is selected from the group consisting of Arg, Pro, ornithine (Orn), cysteine (Cys) and lysine (Lys);

R^8 is absent, Lys, or Trp;

R^9 is absent or Lys;

Y^1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y^2 is selected from the group consisting of dVal, dPro, and dTle;

Y^3 is absent, dVal, or dPro;

Y^4 is absent or dPro; and

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

a disulfide bond between R^2 and R^7 when R^2 is dCys, R^4 is p(Cl)dPhe, and R^7 is Cys;

a lactam bridge between R^1 or R^2 and any one of R^7-R^9 when R^1 or R^2 is Asp, R^4 is dPhe, or p(F)dPhe, and any one of R^7-R^9 is Lys; and

a lactam bridge between R^2 and R^7 when R^2 is Asp or Glu and R^7 is Orn,

provided that:

when R^3 is Pro, then X^1 and Y^3 are present and R^4 is dPhe,

when R^4 is p(Cl)dPhe, then the non-naturally occurring melanocortin analog is not cyclized through a lactam bond between Asp at R^2 and Lys at R^7,

when R^2 and/or R^3 is Phe, then R^4 is Pro and R^6 is dPhe,

when R^4 is dPhe and R^2 is Pro, then X^1 is present and R^5 is Arg, and

when R^4 is dPhe, R^2 is Ala, and R^3 is His, then R^5 is Arg.

[0008] In some embodiments, the present technology comprises a method of reducing body weight and/or fat mass in an obese subject, comprising orally administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I)

[0009] In some embodiments, the present technology comprises a method of treating, preventing, or reducing hyperplasia in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0010] In some embodiments, the present technology comprises a method of treating, preventing, or reducing hypothalamic obesity in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0011] In some embodiments, the present technology comprises a method of treating, preventing, or reducing a proopiomelanocortin (POMC) deficiency in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0012] In some embodiments, the present technology comprises a method of treating, preventing, or reducing a leptin deficiency in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0013] In some embodiments, the present technology comprises a method of treating, preventing, or reducing a syndromic obesity in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0014] In some embodiments, the present technology comprises a method of treating, preventing, or reducing non-alcoholic steatohepatitis (NASH) in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0015] In some embodiments, the present technology comprises a method of treating, preventing, or reducing hyperinsulinism in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0016] In some embodiments, the present technology comprises a method of treating, preventing, or reducing a cardiovascular disease in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0017] In some embodiments, the present technology comprises a method of treating, preventing, or reducing osteoarthritis in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0018] In some embodiments, the present technology comprises a method of treating, preventing, or reducing a cancer in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0019] In some embodiments, the present technology comprises a method of treating, preventing, or reducing erectile dysfunction in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0020] In some embodiments, the present technology comprises a method of treating, preventing, or reducing body weight gain after a weight loss in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0021] In some embodiments, the present technology comprises a method of maintaining body weight after a weight loss in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0022] In some embodiments, the present technology comprises a method of treating, preventing, or reducing fat mass gain after a weight loss in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0023] In some embodiments, the present technology comprises a method of treating, preventing, or reducing glucose intolerance and/or diabetes mellitus in a subject in need thereof, comprising orally administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0024] In some embodiments, the present technology comprises a method of reducing obesity-related inflammation in a subject in need thereof, comprising orally administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0025] In some embodiments, the present technology comprises a method of preserving or improving kidney function in a subject in need thereof, comprising orally administering a non-naturally occurring melanocortin 4 receptor agonist to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0026] In some embodiments, the present technology comprises a method of reducing body weight and/or fat mass in a subject in need thereof, comprising orally administering about 15 mg/kg to about 100 mg/kg of a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (IF).

[0027] In some embodiments, the present technology comprises a method of treating, preventing, or reducing glucose intolerance and/or diabetes mellitus in a subject in need thereof, comprising orally administering about 15 mg/kg to about 100 mg/kg of a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (IF).

[0028] In some embodiments, the present technology comprises a method of reducing obesity-related inflammation in a subject in need thereof, comprising orally administering about 15 mg/kg to about 100 mg/kg of a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (IF).

[0029] A method of preserving or improving kidney function in a subject in need thereof, comprising orally administering about 15 mg/kg to about 100 mg/kg of a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (IF).

BRIEF DESCRIPTION OF THE DRAWINGS

[0030] FIG. 1 illustrates 24-hour plasma concentrations of non-naturally occurring melanocortin analogs of the present technology following oral administration of Compound Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 14; C2) to Cynomolgus Monkeys at 30.0 mg/kg.

[0031] FIGS. 2A-2F illustrates 24-hour plasma concentrations of non-naturally occurring melanocortin analogs of the present technology following PO administration of Compound E (Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 43; O10)) to Cynomolgus Monkeys at 3 mg/kg, 10.0 mg/kg, 30.0 mg/kg, or 60 mg/kg.

[0032] FIGS. 3A-3C illustrates 24-hour plasma and cerebrospinal fluid (CSF) concentrations of non-naturally occurring melanocortin analogs of the present technology following SC administration of Compound E of FIGS. 2A-2F to Rats at 1.0 mg/kg, 3.0 mg/kg, and 10.0 mg/kg.

[0033] FIGS. 4A-4G illustrate plasma and CSF concentrations of non-naturally occurring melanocortin analogs of the present technology. FIGS. 4A-4G illustrate 24-hour plasma and CSF concentrations of non-naturally occurring melanocortin analogs following IP administration of Compound E of FIGS. 2A-2I to Rats at 1.0 mg/kg, 3.0 mg/kg, and 10.0 mg/kg. FIGS. 4H-4K illustrate 24-hour plasma and cerebrospinal fluid (CSF) concentrations of non-naturally occurring melanocortin analogs of the present technology following IP administration of Compound E ("O10") at 10 mg/kg relative to setmelanotide. The shaded areas of 4D-4G represent the drug exposure at concentrations greater than the EC_{50}. Area under the depicted lines represent the non-naturally occurring melanocortin analog exposure at concentrations greater than the EC_{50}.

[0034] FIGS. 5A-5C illustrates 24-hour plasma and CSF concentrations of non-naturally occurring melanocortin analogs of the present technology following PO administration of Compound E of FIGS. 2A-2I to Rats at 10.0 mg/kg and 30.0 mg/kg.

[0035] FIGS. 6A and 6B show preliminary weight loss and daily food intake results in animals administered 3 mg/kg of O10 (Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2; SEQ ID NO: 43).

[0036] FIGS. 7A-7D show food intake (g) at baseline in monkeys having diet-induced obesity (n=6) from 0.5 to 72 hours after saline administration at day 1 (D1). FIG. 7A shows net weight of food intake among individual monkeys. FIG. 7B shows net weight of food intake for each group average. FIG. 7C shows cumulative food intake among individual monkeys. FIG. 7D shows cumulative food intake for each group average.

[0037] FIGS. 8A-8H show food intake (g) in the same monkeys as FIGS. 7A-7D administered 1 mg/kg or 3 mg/kg of O10 (Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2; SEQ ID NO: 43) on day 8 (D8). FIG. 8A shows net weight of food intake among individual monkeys at day 8 (D8). FIG. 8B shows net weight of food intake for each group average of monkeys administered the same compound at D8. FIG. 8C shows cumulative food intake among individual monkeys of FIG. 8A at D8. FIG. 8D shows cumulative food intake for each group average of monkeys of FIG.8C administered the same compound at D8. FIG. 8E shows net weight of food intake among individual monkeys at day 12 (D12). FIG. 8F shows net weight of food intake for each group average of monkeys administered the same compound at D12. FIG. 8G shows cumulative food intake among individual monkeys at D12. FIG. 8H shows cumulative food intake for each group average of monkeys administered the same compound at D12.

[0038] FIGS. 9A and 9B show food intake patterns in diet-induced obese monkeys administered saline, compared to the same monkeys administered 1mg/kg or 3 mg/kg of O10 (Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2; SEQ ID NO: 43) in FIGS. 8A-8H.

[0039] FIGS. 10A-10C show changes in daily caloric intake (FIG. 10A), cumulative caloric intake (FIG. 10B), percent change in caloric consumption from baseline through day 6 (FIG. 10C) for diet-induced obese monkeys orally administered 10 mg/kg of or O10 (Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2; SEQ ID NO: 43) (QD: once daily).

[0040] FIGS. 11A-11P show changes in cumulative caloric intake, percent change in caloric consumption from baseline, food intake of a normal diet, food intake of a high fat diet, food intake in calories, and food preference for diet-induced obese monkeys orally administered O10 (Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2; SEQ ID NO:

43), saline, or semaglutide (sema) (PO: oral administration; SC: subcutaneous administration; QD: once daily; BID: twice daily; BIW: twice weekly).

[0041] FIG. 11Q shows normalized cumulative food consumption in rats subcutaneously administered 1 mg.kg or 3 mg/kg of MC4R selective agonists (A07D (Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2; SEQ ID NO: 48), O7 (Ac-Nle-c[Glu-Pro-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2; SEQ ID NO: 106), or O11 (Ac-Nle-c[Glu-Pro-dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2; SEQ ID NO: 62)) (n=5 per group) or MC3R/MC4R co-agonists (O10) (Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2; SEQ ID NO: 43) (n=5) compared to saline controls (n=4).

[0042] FIG. 11R shows an average percent change in caloric consumption from baseline in moneys orally administered O10 (Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2; SEQ ID NO: 43) at a starting dose of 10 mg/kg and increased to 20 mg/kg and 30 mg/kg.

[0043] FIGS. 12A-12K show changes in body weight for diet included obese monkeys administered O10 (Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2; SEQ ID NO: 43) orally and/or subcutaneously. Shown are changes in daily body weight and percent change in body weight from baseline (FIGS. 12A and 12B) for the diet-induced obese monkeys of FIGS. 11A-11P through day 8. FIGS. 12C shows percent change in body weight as a percentage of initial weight for the monkeys of FIGS. 12A and 12B through day 15 compared to those administered semaglutide (sema) alone. FIG. 12D shows body weight change as a percentage of initial weight in diet induced obese monkeys orally administered O10 at increasing dosages or administered semaglutide. FIG. 12E shows body weight change in the monkeys of FIG. 12D. FIG. 12F shows body weight change as a percentage of initial weight in diet included obese monkeys administered O10 at changing doses and administration frequencies. FIG. 12G shows body weight changes as a percentage of initial in monkeys orally administered O10 (PO) with dose changes or semaglutide. FIG. 12H shows body weight change after removal of O10 administration for the monkeys of FIG. 12G. FIG. 12I shows percent change in body weight as a percentage of initial weight for diet induced obese monkeys orally administered O10 followed by subcutaneous administration. FIG. 12J shows body weight percent change after removal of O10 treatment in monkeys.

FIG. 12K shows body weight percent change at an oral O10 dosing regimen in accordance with the embodiments of the present technology.L(PO: oral administration; SC: subcutaneous administration; QD: once daily; BID: twice daily; BIW: twice weekly).

[0044] FIG. 12L shows changes in body weight as a percentage of day 1 in rats administered saline, a melanocortin 4 receptor (MC4R) selective agonist (A07D (Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2), O7 (Ac-Nle-c[Glu-Pro-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2; SEQ ID NO: 106), or O11 (Ac-Nle-c[Glu-Pro-dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2; SEQ ID NO: 62)), or an equal dose of a melanocortin 3 receptor (MC3R)/MC4R coagonist ((O10)(Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2; SEQ ID NO: 43)).

[0045] FIG. 12M shows an average percent change in normalized body weight from baseline in moneys orally administered O10 (Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2; SEQ ID NO: 43) at a starting dose of 10 mg/kg and increased to 20 mg/kg and 30 mg/kg.

[0046] FIGS. 13A-13N show changes in body composition for the diet-induced obese monkeys of FIGS. 10A-10C.

[0047] FIGS. 14A-14D show blood chemistry levels in diet-induced obese monkeys orally administered 10 mg/kg O10 (Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2; SEQ ID NO: 43) once daily for week 1, 20mg/kg O10 once daily for week 2, and 15 mg/kg O10 twice daily weeks 3 and 4.

[0048] FIGS. 15A-15C show measurements of systolic blood pressure (FIG. 15A), diastolic blood pressure (FIG. 15B), and heart rate (FIG. 15C) in rats subcutaneously administered O10 (Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2; SEQ ID NO: 43) at 0.5 mg/kg, 1 mg/kg, or 3 mg/kg.

[0049] FIGS. 16A-16D show measurements of diastolic blood pressure (DBP), systolic blood pressure (SBP), heart rate, and heart rate corrected QT interval (QTc) in rats administered setmelanotide at 0.5 mg/kg, 1.0 mg/kg, 3.0 mg/kg, or 6.0 mg/kg, relative to control rats administered saline.

[0050] FIGS. 17A-17H show measurements of normalized heart rate (FIG. 17A), QTc (FIG. 17B), systolic blood pressure (FIG. 17C), diastolic blood pressure (FIG. 17D), mean blood pressure (FIG. 17E), QT interval (FIG. 17F), QRS internal (FIG. 17G), and RR internal (FIG. 17H) in male cynomolgus monkeys orally (PO) administered O10 (Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2; SEQ ID NO: 43) at 3, 10, 30, or 60 mg/kg, relative to those subcutaneously (SC) administered setmelanotide at 3 mg/kg or orally administered saline. (N = 3 to 5 animals per group).

[0051] FIG. 18 shows results of O10 (Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2; SEQ ID NO: 43) screened for binding against a panel of 87 targets at 10μM. X-axis represents the percent inhibition of control at 10μM. (MC1R: melanocortin 1 receptor; MC4R: melanocortin 4 receptor).

[0052] FIG. 19 shows exemplary adipose tissue staining in diet-induced obese monkeys orally administered O10 (Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2; SEQ ID NO: 43) at 10 mg/kg.

[0053] FIG. 20 shows plasma concentration of O10 (Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2; SEQ ID NO: 43) in monkeys orally (PO) administered 3mg/kg, 10 mg/kg, 30 mg/kg, or 60 mg/kg O10.

DETAILED DESCRIPTION

[0054] The present technology comprises methods of treating, preventing, or reducing one or more symptoms or conditions associated with metabolic dysfunction in a subject in need thereof using a non-naturally occurring melanocortin analog. In some embodiments, the non-naturally occurring melanocortin analog is administered orally. In some embodiments, the method comprises suppressing appetite in a subject in need thereof using a non-naturally occurring melanocortin analog in accordance with the present technology. In some embodiments, the method comprises promoting fat loss in a subject in need thereof using a non-naturally occurring melanocortin analog in accordance with the present technology. In some embodiments, the method comprises reducing body weight and/or fat mass in a subject in need thereof using a non-naturally occurring melanocortin analog, or a pharmaceutical composition thereof, of the present technology.

[0055] 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 disclosed 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.

[0056] 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 any description, method, system, or process, may be executed in any order and are not limited to the order presented. Moreover, any of the steps or functions thereof may be outsourced to or performed by one or more third parties.

Definitions

[0057] 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.

[0058] 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.

[0059] 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. Typically, such variation may be as much 10% above and below a reference quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length and such variation may be influenced by standard applicable measurement practices. 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.

[0060] The terms "administering" or "administer" include delivery of therapies (e.g., combination therapies, non-naturally occurring melanocortin analogs (also referred to herein as peptides and synthetic peptides), 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.

[0061] 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.

[0062] 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.

[0063] As used herein, a "pharmaceutically acceptable carrier" of the first or the 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 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.

[0064] The term "weight loss agent" refers to a therapeutic agent useful for the treatment or prevention of metabolic dysfunction or one or more symptoms associated with metabolic dysfunction in a subject. In some embodiments, such weight loss agents may be effective to treat, reduce, prevent, or otherwise be useful for a subject having a disease or condition that is not metabolic dysfunction, or besides metabolic dysfunction. The present technology is expected to be useful for subjects that may receive, have received, or are receiving one or more doses of a weight loss agent regardless of the underlying disease or condition that the subject has or develops.

[0065] 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., metabolic dysfunction), 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 or reduction (e.g. by more than 10%,

20%, 30%, 40%, 50%, or more than 60% of the baseline of glucose levels before administration) of circulating glucose levels (2) inhibiting or reducing rate of fat mass gain, (3) relieving to some extent (or, preferably, eliminating) one or more symptoms associated with a pathology related to or caused in part by metabolic dysfunction, (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) an increase in the oxidation of lipids or carbohydrates by at least by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, or at least 80% relative to the initial oxidation rate, (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 loss rate) in the rate of lean muscle mass loss, (9) an increase in lean muscle mass, (10) a reduction in mortality, (11) an increase in the response rate, the durability of response, or number of patients who respond, (12)) a stabilization or reduction (e.g. by more than 10%, 20%, 30%, 40%, 50%, or more than 60% of the baseline of lactate levels before administration) of circulating lactate levels, (13) a decrease in the need for surgery (e.g. gastric bypass, liposuction, sleeve gastrectomy, bariatric surgery), and (14) preventing or reducing organ burden induced by metabolic dysfunction. 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.

[0066] As used herein, the term "prevent," "preventing," or "prevention" means no disorder or disease development if none had occurred, or no further disorder or disease development if there had already been development of the disorder or disease. Also considered is the ability of one to prevent some or all of the symptoms associated with the disorder or disease.

[0067] 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.

[0068] The term "after administration" refers to any duration of time after the non-naturally occurring melanocortin analog or pharmaceutical composition thereof, and/or the weight loss 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 administration" refers to any duration of time before the non-naturally occurring melanocortin analog or pharmaceutical composition thereof, and/or the weight loss 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.

[0069] 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 (m2) and is expressed in units of "kg/m2". "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/m2 to about 25 kg/m2.

[0070] 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 metabolic dysfunction.

[0071] The term "control subject," as used herein, refers to any subject used as a basis for comparison to the subject (e.g., test subject). A control subject includes, but is not limited to, 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.

[0072] "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.

[0073] 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 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.

[0074] A "melanocortin receptor agonist" or "melanocortin agonist" is a naturally occurring substance or manufactured drug substance or composition that may interact with a melanocortin receptor and initiate a pharmacological response characteristic of the melanocortin receptor.

[0075] The terms "bind," "binding," "complex," and "complexing," refer to all types of physical and chemical binding, reactions, complexing, attraction, chelating, and the like.

[0076] The "peptides" of the present technology 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.

[0077] 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.

[0078] 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.

[0079] "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 *Synthetic Peptides: 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 *Synthetic Peptides: 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.

[0080] 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 disclosed 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.

[0081] 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.

[0082] In the peptides of the present technology, 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.

[0083] 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, beta (β)-amino acids, the carbon atom to which the amino group is attached is separated from the carboxylate group by one carbon atom, Cβ.

[0084] 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. 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 combinations thereof.

[0085] Gamma (γ)-amino acids are amino acids where the carbon atom to which the amino group attaches is separated from the carboxylate moiety by two carbon atoms.

[0086] 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 as "c." "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, i.e., —CO—NH_2.

[0087] Additional abbreviations are used herein as follows: Nle is norleucine; Nal(2') is 2'-naphthylalanine; Nal(1') is 1'-naphthylalanine; Tle is tert-leucine; Orn is ornithine; *cis*Pro(guan) is *cis*-4-guanidyl-proline; *trans*Pro(guan) is *trans*-4-guanidyl-proline; p(Cl)dPhe is para-chloro-phenylalanine; and p(F)dPhe is para-fluoro-phenylalanine.

[0088] 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."

[0089] 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.

[0090] An "amine" includes compounds that contain an amine group (—NH_2).

[0091] 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.

[0092] 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."

[0093] "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 melanocortin peptide by physiological enzymes and other factors, in such a manner or to a degree that side effects appear. According to one aspect, a 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 melanocortin analog that lacks a C-terminal extension.

[0094] As used herein, a "composition" refers to a mixture of the active ingredient with other chemical components.

[0095] 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

[0096] The non-naturally occurring melanocortin analogs of the present technology may comprise a non-naturally occurring melanocortin analog or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. Non-naturally occurring melanocortin analogs of the present technology may be selective for the melanocortin 4 receptor (MC4R) and/or melanocortin 3 receptor (MC3R) over other melanocortin receptors, i.e., the melanocortin 1 receptor (MC1R), the melanocortin 2 receptor (MC2R), and the melanocortin 5 receptor (MC5R). Some of the non-naturally occurring melanocortin analogs may bind the MC4R with greater affinity than the MC3R. Alternatively, some melanocortin analogs may bind the MC3R with the same or generally similar affinity as the MC4R.

[0097] The non-naturally occurring melanocortin analogs of the present technology may be full agonists for one or more melanocortin receptors. A full agonist may comprise a non-naturally occurring melanocortin analog having a maximum effect (E_{max}) agonist value of greater than or equal to 85%.

[0098] The non-naturally occurring melanocortin analogs of the present technology may be partial agonists. A partial agonist may comprise a non-naturally occurring melanocortin analog having a maximum effect E_{max} agonist value of less than 85%.

[0099] If a non-naturally occurring melanocortin analog's E_{max} agonist value is greater than it's E_{max} antagonist value, then the non-naturally occurring melanocortin analog may be classified as an agonist (e.g., a full agonist or a partial agonist).

[0100] The non-naturally occurring melanocortin analogs of the present technology may be one or more of (i) a full MC4R agonist (ii) a full MC3R agonist; and (iii) a partial MC3R agonist with no MC3R antagonist activity. In some embodiments, the non-naturally occurring melanocortin is a full MC4R agonist. In some embodiments, the non-naturally occurring melanocortin agonist is a full MC3R agonist and a full MC3R agonist. In some embodiments, the non-naturally occurring melanocortin analog is a full MC4R agonist and partial MC3R agonist with no MC3R antagonist activity. In some embodiments, the non-naturally occurring melanocortin analogs of the present technology have an MC3R E_{max} agonist value of 50-84%. In some embodiments, the non-naturally occurring melanocortin analogs of the present technology have a MC3R:MC4R half maximal effective concentration (EC_{50}) selectivity ratio of less than or equal to 49. In some embodiments, the non-naturally occurring melanocortin analogs of the present technology comprise non-naturally occurring MC4R agonists or non-naturally occurring MC3R agonists.

[0101] The non-naturally occurring melanocortin analogs in accordance with the present technology may have structural features that impart specific properties on the analogs, such as, for example, degradation resistance, enhanced epithelial, gastrointestinal, and/or blood brain barrier transport, and binding affinity for the MC4R and/or MC3R. For example, in some embodiments, the non-naturally occurring melanocortin analogs comprise one or more of (i) blood brain barrier passage capabilities, (ii) one or more pharmaceutical-like pharmacokinetic measurements (e.g., a pharmacokinetic measurement of a weight loss agent pharmaceutical composition or an oral non-naturally occurring melanocortin analog pharmaceutical), (iii) degradation resistance; (iv) equipotency on MC3R and MC4R activity, or (v) oral potency. In some embodiments, the oral potency is greater than a subcutaneous administration potency for an equivalent dose. In some embodiments, the non-naturally

occurring melanocortin analogs comprise two or more of (i)-(v). In some embodiments, he non-naturally occurring melanocortin analogs comprise each of (i)-(v). Accordingly, in some embodiments, the non-naturally occurring melanocortin analogs 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, Pro, dPro, *trans*Pro(guan), and *cis*Pro(guan), may lead to formation of β-hairpin and/or β-turn structures in the non-naturally occurring melanocortin analog. Additionally, disulfide bridges (e.g., cyclization via disulfide bond) may induce and/or stabilize beta-turn structures of the non-naturally occurring melanocortin analogs. In general, cyclization and D-amino acids may induce and/or stabilize beta-turns. Further, in some embodiments, melanocortin analogs include a D-valine-D-proline (dVal-dPro) chain as their C-terminus, which may provide enhanced transport and resistance to degradation.

[0102] The presence of certain structural features may impart the non-naturally occurring melanocortin analogs of the present technology with specific binding properties. For example, inclusion of p(F)dPhe or dPhe at the R^4 position may result in enhanced binding and activation of the melanocortin 4 receptor. Accordingly, melanocortin analogs having p(F)dPhe or dPhe at the R^4 position may be full agonists on MC4R. Further, inclusion of His at the R^3 position may result in full agonism on MC3R as well. By contrast, inclusion of His at the R^3 position may decrease activity on the melanocortin 3 receptor, resulting in only partial agonism on MC3R.

[0103] Non-naturally occurring melanocortin analogs in accordance with the present technology may induce or increase body weight and/or fat mass loss in a subject in need thereof while reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in the subject. Additionally, the non-naturally occurring melanocortin analogs of the present technology may avoid cardiac activation typically seen in conventional melanocortin peptide and small molecule agonists. For example, a subject may maintain a stable heart rate, systolic blood pressure, and/or diastolic blood pressure following administration of a melanocortin analog of the present technology.

[0104] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence according to Formula (I):

X^1-R^1-R^2-R^3-R^4-R^5-R^6-R^7-R^8-R^9-Y^1-Y^2-Y^3-Y^4 (I),

wherein:

X^1 is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

R^1 is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R^2 is selected from the group consisting of Asp, D-cysteine (dCys), Ala, D-alanine (dAla), proline (Pro), glutamic acid (Glu), and phenylalanine (Phe);

R^3 is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln);

R^4 is selected from the group consisting of D-phenylalanine (dPhe), Pro, para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

R^5 is selected from the group consisting of Arg, His, *cis*-4-guanidyl-proline (*cis*Pro(guan)), and *trans*-4-guanidyl-proline (*trans*Pro(guan));

R^6 is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2')));

R^7 is selected from the group consisting of Arg, Pro, ornithine (Orn), cysteine (Cys) and lysine (Lys);

R^8 is absent, Lys, or Trp;

R^9 is absent or Lys;

Y^1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y^2 is selected from the group consisting of dVal, dPro, and dTle;

Y^3 is absent, dVal, or dPro;

Y^4 is absent or dPro; and

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

a disulfide bond between R^2 and R^7 when R^2 is dCys, R^4 is p(Cl)dPhe, and R^7 is Cys;

a lactam bridge between R^1 or R^2 and any one of R^7-R^9 when R^1 or R^2 is Asp, R^4 is dPhe, or p(F)dPhe, and any one of R^7-R^9 is Lys; and

a lactam bridge between R^2 and R^7 when R^2 is Asp or Glu and R^7 is Orn,

provided that:

when R^3 is Pro, then X^1 and Y^3 are present and R^4 is dPhe,

when R^4 is p(Cl)dPhe, then the non-naturally occurring melanocortin analog is not cyclized through a lactam bond between Asp at R^2 and Lys at R^7,

when R^2 and/or R^3 is Phe, then R^4 is Pro and R^6 is dPhe,

when R^4 is dPhe and R^2 is Pro, then X^1 is present and R^5 is Arg, and

when R^4 is dPhe, R^2 is Ala, and R^3 is His, then R^5 is Arg.

[0105] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence according to Formula (I), wherein:

X^1 is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

R^1 is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R^2 is selected from the group consisting of Asp, D-cysteine (dCys), Ala, D-alanine (dAla), proline (Pro), glutamic acid (Glu), and phenylalanine (Phe);

R^3 is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln);

R^4 is selected from the group consisting of D-phenylalanine (dPhe), Pro, para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

R^5 is selected from the group consisting of Arg, His, *cis*-4-guanidyl-proline (*cisPro*(guan)), and *trans*-4-guanidyl-proline (*trans*Pro(guan));

R^6 is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2'));

R^7 is selected from the group consisting of Arg, Pro, ornithine (Orn), cysteine (Cys) and lysine (Lys);

R^8 is absent, Lys, or Trp;

R^9 is absent or Lys;

Y^1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y^2 is selected from the group consisting of dVal, dPro, and dTle;

Y^3 is absent, dVal, or dPro;

Y^4 is absent or dPro;

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

a disulfide bond between R^2 and R^7 when R^2 is dCys, R^4 is p(Cl)dPhe, and R^7 is Cys;

a lactam bridge between R^1 or R^2 and any one of R^7-R^9 when R^1 or R^2 is Asp, R^4 is dPhe, or p(F)dPhe, and any one of R^7-R^9 is Lys; and

a lactam bridge between R^2 and R^7 when R^2 is Asp or Glu and R^7 is Orn;

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

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 48);

Ac-Ala-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 49);

Ac-dNle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 50);

Ac-dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 51);

His-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 52);

dHis-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 53);

Ac-Arg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 54);

Ac-dLys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 55);

Ac-Lys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 56);

Ac-His-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 57);

Ac-dHis-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 58);

Ac-Nle-c[dCys-Pro-dPhe-Arg-Trp-Cys]-dVal-dPro-NH_2 (SEQ ID NO: 59);

Ac-Nle-c[dCys-Pro-dPhe-Arg-Trp-dCys]-dVal-dPro-NH_2 (SEQ ID NO: 60);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 61);

Ac-Nle-c[Glu-Pro-dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 62);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Gly-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 63);

Ac-Nle-c[Asp-Phe-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 64);

Ac-Nle-c[Asp-His-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 65);

Ac-Nle-c[Asp-Pro-dPhe-His-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 66);

Ac-Nle-c[Asp-Pro-dPhe-Lys-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 67);

Ac-Nle-c[Asp-Pro-dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 68);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Nal(2')-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 69);

Ac-Nle-c[dCys-Pro-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro-NH_2 (SEQ ID NO: 70);

Ac-Ala-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 71);

Ac-dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 72);

Ac-Arg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 73);

Ac-Lys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 74);

Ac-dLys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 75);

Ac-His-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 76);

Ac-dHis-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 77);

Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 78);

Ac-Nle-c[Asp-Pro-p(F)dPhe-His-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 79);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 80);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH_2 (SEQ ID NO: 81);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dVal-dVal-dPro-NH_2 (SEQ ID NO: 82);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH_2 (SEQ ID NO: 83);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 84);

Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 85);

Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH_2 (SEQ ID NO: 86);

Ac-Ala-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 87);

Ac-dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 88);

Ac-Arg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 89);

Ac-Lys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 90);

Ac-dLys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 91);

Ac-His-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 92);

Ac-dHis-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 93);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 94);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dTle-NH_2 (SEQ ID NO: 95);

Ac-dHis-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 96);

Ac-Nle-c[Asp-Pro-dPhe-Arg-dTrp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 97);

Ac-Nle-c[Asp-Pro-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 98);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 99);

Ac-Nle-c[Asp-Pro-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 100);

Ac-Nle-c[Asp-Trp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 101);

Ac-Nle-c[Asp-Pro-dPhe-Pro-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 102);

Ac-Nle-c[Asp-Pro-p(Cl)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 103);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 104);

Ac-Nle-c[Glu-Pro-p(Cl)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 105);

Ac-Nle-c[Glu-Pro-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 106);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-OH (SEQ ID NO: 107);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-NH_2 (SEQ ID NO: 108);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 109);

Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 110);

Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 111);

Ac-Ala-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 112);

Ac-dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 113);

Ac-Arg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 114);

Ac-Lys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 115);

Ac-dLys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 116);

Ac-His-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 117);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dTle-dPro-NH_2 (SEQ ID NO: 118);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH_2 (SEQ ID NO: 119);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dVal-dPro-NH_2 (SEQ ID NO: 120);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH_2 (SEQ ID NO: 121);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dVal-dVal-dPro-NH_2 (SEQ ID NO: 122);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-dVal-dPro-NH_2 (SEQ ID NO: 123);

Ac-Nle-c[Asp-Pro-dPhe-transPro(guan)-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 124);

Ac-Nle-c[Asp-Pro-dPhe-cisPro(guan)-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 125);

Ac-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH_2 (SEQ ID NO: 126);

Ac-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dVal-dVal-dPro-NH_2 (SEQ ID NO: 127);

Ac-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH_2 (SEQ ID NO: 128);

Ac-Nle-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH_2 (SEQ ID NO: 129);

Ac-Ala-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 130);

Ac-dArg-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 131);

Ac-Arg-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 132);

Ac-Lys-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 133);

Ac-dLys-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 134);

Ac-His-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 135);

Ac-dHis-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 136);

Ac-Nle-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 137);

Ac-Nle-c[Asp-His-p(Cl)dPhe-His-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 138);

Ac-Nle-c[Asp-His-p(Cl)dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 139);

Ac-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 140);

Ac-Nle-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 141);

Ac-Ala-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 142);

Ac-dArg-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 143);

Ac-Arg-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 144);

Ac-dLys-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 145);

Ac-dHis-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 146);

Ac-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 147);

Ac-Nle-c[Asp-dHis-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 148);

Ac-Nle-c[Asp-Phe-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 149);

Ac-Nle-c[Asp-Gln-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 150);

Ac-Lys-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 151);

Ac-His-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 152);

Ac-Nle-c[Asp-Phe-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 153);

Ac-Nle-c[Asp-Phe-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 154);

Ac-Nle-c[Asp-Phe-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 155);

Ac-Nle-c[Asp-Phe-Phe-Pro-His-dNal(2')-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 156);

Ac-Nle-c[Asp-Phe-His-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 157);

Ac-Nle-c[Asp-Pro-His-dPhe-His-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 158);

Ac-Arg-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 159); and

Ac-dArg-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 160).

[0106] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (I) wherein R^4 is dPhe or p(F)dPhe. When R^4 is dPhe or p(F)dPhe in the sequence of Formula (I), then R^9 is absent. Accordingly, in some embodiments, the sequence of Formula (I) is a sequence of Formula (IA):

$$X^1\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}R^8\text{-}Y^1\text{-}Y^2\text{-}Y^3\text{-}Y^4 \text{ (IA)},$$

wherein:

X^1 is absent or is selected from the group consisting of Nle, Arg, and dArg;

R^1 is selected from the group consisting of Nle, Arg, dArg, Asp, Ala, Lys, dLys, His, and dHis;

R^2 is selected from the group consisting of Asp, Ala, dAla, Pro, and Glu

R^3 is selected from the group consisting of His, dHis, Pro, and Gln;

R^4 is dPhe or p(F)dPhe;

R^5 is selected from the group consisting of Arg, His, *cisPro*(guan), and *trans*Pro(guan);

R^6 is Trp or dNal(2');

R^7 is selected from the group consisting of Pro, Orn, and Lys;

R^8 is absent or Lys;

Y^1 is selected from the group consisting of dVal, dPro, and dTle;

Y^2 is selected from the group consisting of dVal, dPro, and dTle;

Y^3 is absent, dVal, or dPro;

Y^4 is absent or dPro; and

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

a lactam bridge between R^1 or R^2 and R^7 or R^8 when R^1 or R^2 is Asp and R^7 or R^8 is Lys; and

a lactam bridge between R^2 and R^7 when R^2 is Asp or Glu and R^7 is Orn.

[0107] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IA):

$$X^1\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}R^8\text{-}Y^1\text{-}Y^2\text{-}Y^3\text{-}Y^4 \text{ (IA)},$$

wherein:

X^1 is absent or is selected from the group consisting of Nle, Arg, and dArg;

R^1 is selected from the group consisting of Nle, Arg, dArg, Asp, Ala, Lys, dLys, His, and dHis;

R^2 is selected from the group consisting of Asp, Ala, dAla, Pro, and Glu

R^3 is selected from the group consisting of His, dHis, Pro, and Gln;

R^4 is dPhe or p(F)dPhe;

R^5 is selected from the group consisting of Arg, His, *cisPro*(guan), and *trans*Pro(guan);

R^6 is Trp or dNal(2');

R^7 is selected from the group consisting of Pro, Orn, and Lys;

R^8 is absent or Lys;

Y^1 is selected from the group consisting of dVal, dPro, and dTle;

Y^2 is selected from the group consisting of dVal, dPro, and dTle;

Y^3 is absent, dVal, or dPro;

Y^4 is absent or dPro; and

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

a lactam bridge between R^1 or R^2 and R^7 or R^8 when R^1 or R^2 is Asp and R^7 or R^8 is Lys; and

a lactam bridge between R^2 and R^7 when R^2 is Asp or Glu and R^7 is Orn,

provided that:

when R^3 is Pro, then X^1 and Y^3 are present and R^4 is dPhe,

when R^4 is dPhe and R^2 is Pro, then X^1 is present and R^5 is Arg, and

when R^4 is dPhe, R^2 is Ala, and R^3 is His, then R^5 is Arg.

[0108] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IA), wherein:

X^1 is absent or is selected from the group consisting of Nle, Arg, and dArg;

R^1 is selected from the group consisting of Nle, Arg, dArg, Asp, Ala, Lys, dLys, His, and dHis;

R^2 is selected from the group consisting of Asp, Ala, dAla, Pro, and Glu

R^3 is selected from the group consisting of His, dHis, Pro, and Gln;

R^4 is dPhe or p(F)dPhe;

R^5 is selected from the group consisting of Arg, His, *cisPro*(guan), and *trans*Pro(guan);

R^6 is Trp or dNal(2');

R^7 is selected from the group consisting of Pro, Orn, and Lys;

R^8 is absent or Lys;

Y^1 is selected from the group consisting of dVal, dPro, and dTle;

Y^2 is selected from the group consisting of dVal, dPro, and dTle;

Y^3 is absent, dVal, or dPro;

Y^4 is absent or dPro; and

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

a lactam bridge between R^1 or R^2 and R^7 or R^8 when R^1 or R^2 is Asp and R^7 or R^8 is Lys; and

a lactam bridge between R^2 and R^7 when R^2 is Asp or Glu and R^7 is Orn,

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

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 48);

Ac-Ala-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 49);

Ac-dNle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 50);

Ac-dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 51);

His-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 52);

dHis-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 53);

Ac-Arg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 54);

Ac-dLys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 55);

Ac-Lys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 56);

Ac-His-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 57);

Ac-dHis-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 58);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 61);

Ac-Nle-c[Glu-Pro-dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 62);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Gly-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 63);

Ac-Nle-c[Asp-Pro-dPhe-His-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 66);

Ac-Nle-c[Asp-Pro-dPhe-Lys-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 67);

Ac-Nle-c[Asp-Pro-dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 68);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Nal(2')-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 69);

Ac-Ala-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 71);

Ac-dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 72);

Ac-Arg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 73);

Ac-Lys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 74);

Ac-dLys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 75);

Ac-His-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 76);

Ac-dHis-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 77);

Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 78);

Ac-Nle-c[Asp-Pro-p(F)dPhe-His-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 79);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 80);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH_2 (SEQ ID NO: 81);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dVal-dVal-dPro-NH_2 (SEQ ID NO: 82);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH_2 (SEQ ID NO: 83);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 84);

Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 85);

Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH_2 (SEQ ID NO: 86);

Ac-Ala-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 87);

Ac-dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 88);

Ac-Arg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 89);

Ac-Lys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 90);

Ac-dLys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 91);

Ac-His-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 92);

Ac-dHis-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 93);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 94);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dTle-NH_2 (SEQ ID NO: 95);

Ac-dHis-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 96);

Ac-Nle-c[Asp-Pro-dPhe-Arg-dTrp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 97);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 99);

Ac-Nle-c[Asp-Pro-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 100);

Ac-Nle-c[Asp-Pro-dPhe-Pro-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 102);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 104);

Ac-Nle-c[Glu-Pro-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 106);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-OH (SEQ ID NO: 107);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-NH_2 (SEQ ID NO: 108);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 109);

Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 110);

Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 111);

Ac-Ala-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 112);

Ac-dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 113);

Ac-Arg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 114);

Ac-Lys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 115);

Ac-dLys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 116);

Ac-His-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 117);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dTle-dPro-NH_2 (SEQ ID NO: 118);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH_2 (SEQ ID NO: 119);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dVal-dPro-NH_2 (SEQ ID NO: 120);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH_2 (SEQ ID NO: 121);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dVal-dVal-dPro-NH_2 (SEQ ID NO: 122);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-dVal-dPro-NH_2 (SEQ ID NO: 123);

Ac-Nle-c[Asp-Pro-dPhe-transPro(guan)-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 124);

Ac-Nle-c[Asp-Pro-dPhe-cisPro(guan)-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 125);

Ac-Nle-c[Asp-Pro-His-dPhe-His-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 158);

Ac-Arg-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 159); and

Ac-dArg-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 160).

[0109] Further, when the non-naturally occurring melanocortin analog comprises a sequence of Formula (I) or (IA) wherein R^4 is dPhe or p(F)dPhe, then R^8 may also be absent. Additionally, the sequence of Formula (I) or (I) may be cyclized through a lactam bond between R^2 and R^7. Accordingly, in some embodiments, the sequence of Formula (I) or (IA) is a sequence of Formula (IB):

$$X^1\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}Y^1\text{-}Y^2\text{-}Y^3\text{-}Y^4 \text{ (IB)},$$

wherein:

X^1 is absent or Nle;

R^1 is selected from the group consisting of Nle, Arg, dArg, Ala, Lys, dLys, His, and dHis;

R^2 is Asp or Glu;

R^3 is selected from the group consisting of His, dHis, Pro, and Gln;

R^4 is dPhe or p(F)dPhe;

R^5 is selected from the group consisting of Arg, His, *cisPro*(guan), and *trans*Pro(guan);

R^6 is Trp or dNal(2');

R^7 is Orn or Lys;

Y^1 is selected from the group consisting of dVal, dPro, and dTle;

Y^2 is selected from the group consisting of dVal, dPro, and dTle;

Y^3 is absent, dVal, or dPro;

Y^4 is absent or dPro; and

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

a lactam bridge between R^2 and R^7 when R^2 is Asp and R^7 is Lys; and

lactam bridge between Asp or Glu at R^2 and Orn or Lys at R^7.

[0110] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IB):

$$X^1\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}Y^1\text{-}Y^2\text{-}Y^3\text{-}Y^4 \text{ (IB)},$$

wherein:

X^1 is absent or Nle;

R^1 is selected from the group consisting of Nle, Arg, dArg, Ala, Lys, dLys, His, and dHis;

R^2 is Asp or Glu;

R^3 is selected from the group consisting of His, dHis, Pro, and Gln;

R^4 is dPhe or p(F)dPhe;

R^5 is selected from the group consisting of Arg, His, *cisPro*(guan), and *trans*Pro(guan);

R^6 is Trp or dNal(2');

R^7 is Orn or Lys;

Y^1 is selected from the group consisting of dVal, dPro, and dTle;

Y^2 is selected from the group consisting of dVal, dPro, and dTle;

Y^3 is absent, dVal, or dPro;

Y^4 is absent or dPro; and

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

a lactam bridge between R^2 and R^7 when R^2 is Asp and R^7 is Lys; and

a lactam bridge between Asp or Glu at R^2 and Orn or Lys at R^7,

provided that when R^3 is Pro, then X^1 and Y^3 are present and R^4 is dPhe,

[0111] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IB), wherein:

X^1 is absent or Nle;

R^1 is selected from the group consisting of Nle, Arg, dArg, Ala, Lys, dLys, His, and dHis;

R^2 is Asp or Glu;

R^3 is selected from the group consisting of His, dHis, Pro, and Gln;

R^4 is dPhe or p(F)dPhe;

R^5 is selected from the group consisting of Arg, His, *cisPro*(guan), and *trans*Pro(guan);

R^6 is Trp or dNal(2');

R^7 is Orn or Lys;

Y^1 is selected from the group consisting of dVal, dPro, and dTle;

Y^2 is selected from the group consisting of dVal, dPro, and dTle;

Y^3 is absent, dVal, or dPro;

Y^4 is absent or dPro; and

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

a lactam bridge between R^2 and R^7 when R^2 is Asp and R^7 is Lys; and

a lactam bridge between Asp or Glu at R^2 and Orn or Lys at R^7,

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

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 48);

Ac-Ala-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 49);

Ac-dNle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 50);

Ac-dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 51);

His-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 52);

dHis-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 53);

Ac-Arg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 54);

Ac-dLys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 55);

Ac-Lys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 56);

Ac-His-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 57);

Ac-dHis-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 58);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 61);

Ac-Nle-c[Glu-Pro-dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 62);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Gly-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 63);

Ac-Nle-c[Asp-Pro-dPhe-His-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 66);

Ac-Nle-c[Asp-Pro-dPhe-Lys-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 67);

Ac-Nle-c[Asp-Pro-dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 68);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Nal(2')-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 69);

Ac-Ala-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 71);

Ac-dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 72);

Ac-Arg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 73);

Ac-Lys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 74);

Ac-dLys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 75);

Ac-His-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 76);

Ac-dHis-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 77);

Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 78);

Ac-Nle-c[Asp-Pro-p(F)dPhe-His-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 79);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 80);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH_2 (SEQ ID NO: 81);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dVal-dVal-dPro-NH_2 (SEQ ID NO: 82);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH_2 (SEQ ID NO: 83);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 84);

Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 85);

Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH_2 (SEQ ID NO: 86);

Ac-Ala-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 87);

Ac-dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 88);

Ac-Arg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 89);

Ac-Lys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 90);

Ac-dLys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 91);

Ac-His-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 92);

Ac-dHis-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 93);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 94);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dTle-NH_2 (SEQ ID NO: 95);

Ac-dHis-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 96);

Ac-Nle-c[Asp-Pro-dPhe-Arg-dTrp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 97);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 99);

Ac-Nle-c[Asp-Pro-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 100);

Ac-Nle-c[Asp-Pro-dPhe-Pro-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 102);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 104);

Ac-Nle-c[Glu-Pro-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 106);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-OH (SEQ ID NO: 107);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-NH_2 (SEQ ID NO: 108);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 109);

Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 110);

Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 111);

Ac-Ala-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 112);

Ac-dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 113);

Ac-Arg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 114);

Ac-Lys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 115);

Ac-dLys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 116);

Ac-His-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 117);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dTle-dPro-NH_2 (SEQ ID NO: 118);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH_2 (SEQ ID NO: 119);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dVal-dPro-NH_2 (SEQ ID NO: 120);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH_2 (SEQ ID NO: 121);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dVal-dVal-dPro-NH_2 (SEQ ID NO: 122);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-dVal-dPro-NH_2 (SEQ ID NO: 123);

Ac-Nle-c[Asp-Pro-dPhe-transPro(guan)-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 124); and

Ac-Nle-c[Asp-Pro-dPhe-cisPro(guan)-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 125),

[0112] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(IB) wherein R^4 is p(F)dPhe. In further embodiments, R^3 is His, R^5 is Arg, and R^6 is Trp. Accordingly, in some embodiments, the sequence of any one of Formulae (I)-(IB) is a sequence of Formula (IC):

$$X^1\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}Y^1\text{-}Y^2\text{-}Y^3\text{-}Y^4 \text{ (IC)},$$

wherein:

X^1 is absent or Nle;

R^1 is selected from the group consisting of Nle, Arg, dArg, Ala, Lys, dLys, His, and dHis;

R^2 is Asp or Glu;

R^3 is His;

R^4 is p(F)dPhe;

R^5 is Arg;

R^6 is Trp;

R^7 is Orn or Lys;

Y^1 is selected from the group consisting of dVal, dPro, and dTle;

Y^2 is selected from the group consisting of dVal, dPro, and dTle;

Y^3 is absent, dVal, or dPro;

Y^4 is absent or dPro; and

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

a lactam bridge between R^2 and R^7 when R^2 is Asp and R^7 is Lys; and

a lactam bridge between Asp or Glu at R^2 and Orn or Lys at R^7.

[0113] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IC):

$$X^1\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}Y^1\text{-}Y^2\text{-}Y^3\text{-}Y^4 \text{ (IC)},$$

wherein:

X^1 is absent or Nle;

R^1 is selected from the group consisting of Nle, Arg, dArg, Ala, Lys, dLys, His, and dHis;

R^2 is Asp or Glu;

R^3 is His;

R^4 is p(F)dPhe;

R^5 is Arg;

R^6 is Trp;

R^7 is Orn or Lys;

Y^1 is selected from the group consisting of dVal, dPro, and dTle;

Y^2 is selected from the group consisting of dVal, dPro, and dTle;

Y^3 is absent, dVal, or dPro;

Y^4 is absent or dPro; and

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

a lactam bridge between R^2 and R^7 when R^2 is Asp and R^7 is Lys; and

a lactam bridge between Asp or Glu at R^2 and Orn or Lys at R^7.

[0114] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of any one of Formulae (I)-(IB) wherein R^4 is dPhe. Accordingly, in some embodiments, the sequence of any one of Formulae (I)-(IB) is a sequence of Formula (ID):

$$X^1\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}R^8\text{-}Y^1\text{-}Y^2\text{-}Y^3 \text{ (ID)},$$

wherein:

X^1 is absent or norleucine (Nle);

R^1 is Nle or Asp;

R^2 is selected from the group consisting of Asp, Glu, and Pro;

R^3 is selected from the group consisting of His, dHis, Pro, and Gln;

R^4 is dPhe;

R^5 is selected from the group consisting of Arg, His, *cisPro*(guan), and *trans*Pro(guan);

R^6 is Trp;

R^7 is selected from the group consisting of Orn, Lys, and Pro;

R^8 is absent or Lys;

Y^1 is dVal or dPro;

Y^2 is dVal or dPro;

Y^3 is absent or dPro; and

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

a lactam bridge between R^1 or R^2 and R^7 or R^8 when R^1 or R^2 is Asp and R^7 or R^8 is Lys; and

a lactam bridge between R^2 and R^7 when R^2 is Asp or Glu and R^7 is Orn.

[0115] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (ID):

X^1-R^1-R^2-R^3-R^4-R^5-R^6-R^7-R^8-Y^1-Y^2-Y^3 (ID),

wherein:

X^1 is absent or norleucine (Nle);

R^1 is Nle or Asp;

R^2 is selected from the group consisting of Asp, Glu, and Pro;

R^3 is selected from the group consisting of His, dHis, Pro, and Gln;

R^4 is dPhe;

R^5 is selected from the group consisting of Arg, His, *cisPro*(guan), and *trans*Pro(guan);

R^6 is Trp;

R^7 is selected from the group consisting of Orn, Lys, and Pro;

R^8 is absent or Lys;

Y^1 is dVal or dPro;

Y^2 is dVal or dPro;

Y^3 is absent or dPro; and

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

a lactam bridge between R^1 or R^2 and R^7 or R^8 when R^1 or R^2 is Asp and R^7 or R^8 is Lys; and

a lactam bridge between R^2 and R^7 when R^2 is Asp or Glu and R^7 is Orn,

provided that:

when R^3 is Pro, then X^1 and Y^3 are present,

when R^2 is Pro, then X^1 is present and R^5 is Arg.

[0116] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (ID), wherein:

X^1 is absent or norleucine (Nle);

R^1 is Nle or Asp;

R^2 is selected from the group consisting of Asp, Glu, and Pro;

R^3 is selected from the group consisting of His, dHis, Pro, and Gln;

R^4 is dPhe;

R^5 is selected from the group consisting of Arg, His, *cisPro*(guan), and *trans*Pro(guan);

R^6 is Trp;

R^7 is selected from the group consisting of Orn, Lys, and Pro;

R^8 is absent or Lys;

Y^1 is dVal or dPro;

Y^2 is dVal or dPro;

Y^3 is absent or dPro; and

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

a lactam bridge between R^1 or R^2 and R^7 or R^8 when R^1 or R^2 is Asp and R^7 or R^8 is Lys; and

a lactam bridge between R^2 and R^7 when R^2 is Asp or Glu and R^7 is Orn,

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

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 48);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 61);

Ac-Nle-c[Glu-Pro-dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 62);

Ac-Nle-c[Asp-Pro-dPhe-His-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 66);

Ac-Nle-c[Asp-Pro-dPhe-Lys-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 67);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 94);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dTle-NH_2 (SEQ ID NO: 95);

Ac-Nle-c[Asp-Pro-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 100);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-OH (SEQ ID NO: 107);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-NH_2 (SEQ ID NO: 108);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 109);

Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 110);

Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 111);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dTle-dPro-NH_2 (SEQ ID NO: 118);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH_2 (SEQ ID NO: 119);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dVal-dPro-NH_2 (SEQ ID NO: 120);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH_2 (SEQ ID NO: 121);

Ac-Nle-c[Asp-Pro-dPhe-transPro(guan)-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 124); and

Ac-Nle-c[Asp-Pro-dPhe-cisPro(guan)-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 125).

[0117] In some embodiments, when the non-naturally occurring melanocortin analog comprises a sequence of Formula (I) or (IA) wherein R^4 is dPhe or p(F)dPhe, then R^8 is present. In further embodiments, R^4 is dPhe. Accordingly, in some embodiments, the sequence of Formula (I) or (IA) is a sequence of Formula (IE):

$$X^1\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}Y^1\text{-}Y^2 \text{ (IE)},$$

wherein:

X^1 is absent or selected from the group consisting of Nle, Arg, and dArg;

R^1 is Asp;

R^2 is dAla or Ala;

R^3 is His;

R^4 is dPhe;

R^5 is Arg;

R^6 is Trp;

R^7 is Lys;

Y^1 is dVal;

Y^2 is dPro; and

the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between Asp at R^1 and Lys at R^7.

[0118] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IE):

$$X^1\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}Y^1\text{-}Y^2 \text{ (IE)},$$

wherein:

X^1 is absent or selected from the group consisting of Nle, Arg, and dArg;

R^1 is Asp;

R^2 is dAla or Ala;

R^3 is His;

R^4 is dPhe;

R^5 is Arg;

R^6 is Trp;

R^7 is Lys;

Y^1 is dVal;

Y^2 is dPro; and

the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between Asp at R^1 and Lys at R^7.

[0119] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (I) that is cyclized between Asp or Glu at R^2 and Orn at

R7. In further embodiments, R^3 is His and R^4 is p(F)dPhe or p(Cl)dPhe. Accordingly, in some embodiments, the sequence of Formula (I) is a sequence of Formula (IF):

$$R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}Y^1\text{-}Y^2 \text{ (IF)},$$

wherein:

R^1 is Nle;

R^2 is Asp or Glu;

R^3 is His;

R^4 is selected from dPhe, p(F)dPhe, and p(Cl)dPhe;

R^5 is Arg or His;

R^6 is Trp;

R^7 is Orn;

Y^1 is dVal;

Y^2 is dPro; and

the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between Asp or Glu at R^2 and Orn at R^7.

[0120] In some embodiments, the non-naturally occurring melanocortin analog compirses a sequence of Formula (IF):

$$R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}Y^1\text{-}Y^2 \text{ (IF)},$$

wherein:

R^1 is Nle;

R^2 is Asp or Glu;

R^3 is His;

R^4 is selected from dPhe, p(F)dPhe, and p(Cl)dPhe;

R^5 is Arg or His;

R^6 is Trp;

R^7 is Orn;

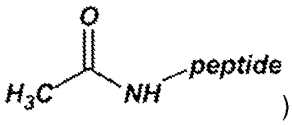
Y^1 is dVal;

Y^2 is dPro; and

the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between Asp or Glu at R^2 and Orn at R^7.

[0121] In some embodiments, the non-naturally occurring melanocortin analog of any one of Formulae (I)-(IF) has one or more beta hairpin (β-hairpin) and/or beta turn (β-turn) structures. In some embodiments, the presence of Pro, dPro, *trans*Pro(guan), and/or *cis*Pro(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.

[0122] As will be appreciated by the skilled artisan, non-naturally occurring melanocortin analogs comprising a sequence of any one of Formulae (I)-(IF), have an N-terminus and a C-terminus. The melanocortin analogs of the present technology are written beginning with the N-terminus at the left-most amino acid residue and ending with the C-terminus at the right most residue. Accordingly, the N-terminus of a non-naturally melanocortin analog comprising a sequence of any one of Formulae (I)-(IF) may be at X^1 or R^1. Analogously, the C-terminus of a non-naturally occurring melanocortin analog comprising a sequence of any one of Formulae (I)-(IF) may be at any of R^7, R^8, R^9, Y^1, Y^2, Y^3, and Y^4.

[0123] 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., 

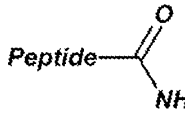
).

[0124] In some embodiments, the N-terminus of the non-naturally occurring melanocortin analog, if present, is not modified.

[0125] In the sequence of any one of Formulae (I)-(IF), $Y^1Y^2Y^3Y^4$ or a fragment thereof represents a C-terminus of the non-naturally occurring melanocortin analog. In some embodiments, Y^1 and Y^2 are present and Y^3-Y^4 are absent. In some embodiments, Y^3-Y^4 are absent, and Y^1 is D-valine and Y^2 is D-proline. In some embodiments, Y^3-Y^4 are absent, and Y^1 is D-proline and Y^2 is D-valine. In some embodiments, Y^3-Y^4 are absent, and Y^1 is D-tert-leucine and Y^2 is D-proline.

[0126] In some embodiments, Y^1-Y^3 are present and Y^4 is absent. In some embodiments, Y^4 is absent and Y^1 is D-proline, Y^2 is D-valine, and Y^3 is D-proline. In some embodiments, Y^4 is absent, and Y^1 is D-tert-leucine, Y^2 is D-tert-leucine, and Y^3 is D-valine.

[0127] In some embodiments, Y^1-Y^4 are present. In some embodiments, Y^1-Y^4 are present and Y^1 is D-valine, Y^2 is D-valine, Y^3 is D-valine, and Y^4 is D-proline.

[0128] 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 any one of Formulae (I)-(IF), a non-naturally occurring melanocortin analog with a C-terminus modified by an amide may be represented by a terminal $-NH_2$.

[0129] In some embodiments, the C-terminus of the non-naturally occurring melanocortin analog is not modified. In the sequence of any one of Formulae (I)-(IF), a non-naturally occurring melanocortin analog with an unmodified C-terminus may be represented by -OH.

[0130] Non-naturally occurring melanocortin analogs comprising a sequence of any one of Formulae (I)-(IF) are 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^2 and R^7 when R^2 is dCys, R^4 is p(Cl)dPhe, and R^7 is Cys; a lactam bridge between R^1 or R^2 and any one of R^7-R^9 when R^1 or R^2 is Asp, R^4 is dPhe, or p(F)dPhe, and any one of R^7-R^9 is Lys; and a lactam bridge between R^2 and R^7 when R^2 is Asp or Glu and R^7 is Orn.

[0131] In some embodiments of the sequence of any one of Formulae (I)-(IF), R^3 is His. In further embodiments, R^3 is His and the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between the Asp at R^2 and the Lys at R^7. In still further embodiments, R^4 is p(F)dPhe or dPhe.

[0132] In some embodiments, X^1, Y^3, and Y^4 are all absent. In further embodiments, R^1 is selected from Nle, Ala, Arg, dArg, Lys, dLys, His, and dHis and R^4 is p(F)dPhe. In still further embodiments, Y^1 is dVal and Y^2 is dPro. In some embodiments, the sequence of any one of Formulae (I)-(IF) is selected from the group consisting of:

Ac-Ala-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 3);

Ac-dArg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 4);

Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 14);

Ac-Arg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 15);

Ac-Lys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 16);

Ac-dLys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 17);

Ac-His-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 18); and

Ac-dHis-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 19),

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

[0133] In other further embodiments, Y^1 is dTle, Y^2 is dPro. In some embodiments, the sequence of any one of Formulae (I)-(IF) is selected from the group consisting of:

Ac-Ala-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 7);

Ac-dArg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 8);

Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 24);

Ac-Arg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 27);

Ac-Lys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 28);

Ac-dLys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 29);

Ac-His-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 30); and

Ac-dHis-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 31),

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

[0134] In some embodiments, R^1 is Nle and R^4 is dPhe. In further embodiments, Y^1 is dVal or dPro, Y^2 is dPro or dVal. In some embodiments, the sequence of any one of Formulae (I)-(IF) is:

Ac-Nle-c[Asp-His-dPhe-Arg-Trp-Lys]-dPro-dVal-NH_2 (SEQ ID NO: 33); or

Ac-Nle-c[Asp-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 42),

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

[0135] Alternatively, in some embodiments, at least one of X^1, Y^3 and Y^4 is present. In further embodiments, R^1 is Nle, and R^4 is p(F)dPhe. In some embodiments, the sequence of any one of Formulae (I)-(IF) is selected from the group consisting of:

Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH_2 (SEQ ID NO: 6);

Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 20);

Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dVal-dVal-dPro-NH_2 (SEQ ID NO: 22);

Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH_2 (SEQ ID NO: 23);

Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 25); and

Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH_2 (SEQ ID NO: 26),

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

[0136] In some embodiments, when R^3 is His, R^4 is p(F)dPhe or dPhe, and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R^2 and Lys at R^7, then R^5 is Arg. Alternatively, in some embodiments, R^5 is an amino acid other than Arg. In further embodiments, R^5 is selected from His, *trans*Pro(guan), *cis*Pro(guan). In some embodiments, the sequence of any one of Formulae (I)-(IF) is selected from the group consisting of:

Ac-Nle-c[Asp-His-p(F)dPhe-His-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 21);

Ac-Nle-c[Asp-His-dPhe-transPro(guan)-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 46); and

Ac-Nle-c[Asp-His-dPhe-cisPro(guan)-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 47),

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

[0137] In some embodiments, when R^3 is His, R^4 is p(F)dPhe or dPhe, and the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R^2 and Lys at R^7, then R^6 is Trp. Alternatively, in some embodiments, R^6 is an amino acid other than Trp. In further embodiments, R^6 is dNal(2'). In some embodiments, the sequence of any one of Formulae (I)-(IF) is: Ac-Nle-c[Asp-His-p(F)dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 5), wherein c represents cyclization through R^2 and R^7 via a lactam bond.

[0138] In some embodiments of the sequence of any one of Formulae (I)-(IF), R^3 is His and the non-naturally occurring melanocortin analog is cyclized through a bond other than a lactam bond between Asp at R^2 and Lys at R^7. In some embodiments, the non-naturally occurring melanocortin analog is cyclized through R^2 and R^7 via a bond other than a lactam bond between Asp at and Lys. For example, the non-naturally occurring melanocortin analog may be cyclized through R^2 and R^7 via a disulfide bond or a lactam formed between amino acids other than Asp and Lys.

[0139] In some embodiments, the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp or Glu at R^2 and Orn at R^7. In further embodiments, R^4 is selected from dPhe, p(Cl)dPhe, and p(F)dPhe. In some embodiments, the sequence of any one of Formulae (I)-(IF) is selected from the group consisting of:

Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 43);

Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 44);

Ac-Nle-c[Glu-His-dPhe-His-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 45);

Ac-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 11); and

Ac-Nle-c[Glu-His-p(Cl)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 12),

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

[0140] In other embodiments, the non-naturally occurring melanocortin analog is cyclized through a disulfide bond between dCys at R^2 and Cys at R^7. In further embodiments, R^4 is p(Cl)dPhe. In some embodiments, the sequence of any one of

Formulae (I)-(IF) is Ac-Nle-c[dCys-His-p(Cl)dPhe-Arg-Trp-Cys]-dVal-dPro-NH_2 (SEQ ID NO: 2), wherein c represents cyclization through R^2 and R^7 via a disulfide bond.

[0141] Alternatively, in some embodiments, the non-naturally occurring melanocortin analog is cyclized through Asp at a residue position other than R^2 and/or Lys at a residue position other than R^7. For example, the non-naturally occurring melanocortin analog may be cyclized through Asp at R^1 and Lys at R^7 or through Asp at R^2 and Lys at R^8.

[0142] In some embodiments, the non-naturally occurring melanocortin analog is cyclized through a lactam bond between Asp at R^2 and Lys at R^8. In further embodiments, the sequence of any one of Formulae (I)-(IF) is: Ac-Nle-c[Asp-His-dPhe-Arg-Trp-Pro-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 35), wherein c represents cyclization through R^2 and R^8 via a lactam bond.

[0143] In some embodiments, the non-naturally occurring melanocortin analog is cyclized between a lactam bond between Asp at R^1 and Lys at R^7. In further embodiments, R^2 is Ala or dAla and R^4 is dPhe. In some embodiments, the sequence of any one of Formulae (I)-(IF) is selected from the group consisting of:

Ac-Nle-c[Asp-dAla-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 38);

Ac-Arg-c[Asp-dAla-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 39);

Ac-dArg-c[Asp-dAla-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 40); and

Ac-Nle-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 41),

wherein c represents cyclization through R^1 and R^7 via a lactam bond.

[0144] In other further embodiments, R^2 is Pro, and R^4 is Phe. In some embodiments, the sequence of any one of Formulae (I)-(IF) is: Ac-Nle-c[Asp-Pro-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 13), wherein c represents cyclization through R^1 and R^7 via a lactam bond.

[0145] In some embodiments of the sequence of any one of Formula (I)-(ID), R^3 is an amino acid other than His. In some embodiments, R^3 is selected from dHis, Gln and Pro. In further embodiments, R^2 is Asp, R^4 is dPhe or p(F)dPhe, R^5 is Arg, R^6 is Trp, and R^7 is Lys.

In some embodiments, the sequence of any one of Formulae (I)-(IF) is selected from the group consisting of:

Ac-Nle-c[Asp-Gln-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 9);

Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH_2 (SEQ ID NO: 10);

Ac-Nle-c[Asp-dHis-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 32);

Ac-Nle-c[Asp-dHis-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 36); and

Ac-Nle-c[Asp-Gln-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 37),

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

[0146] In some embodiments of the sequence of Formula (I), R^3 is an amino acid other than His and R^9 is absent. Alternatively, in some embodiments, R^9 is present. In some embodiments, the sequence of any one of Formulae (I)-(IF) is: Ac-Nle-c[Asp-Phe-Phe-Pro-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 34), wherein c represents cyclization through R^1 and R^9 via a lactam bond.

[0147] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (I). In some embodiments, the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 3-10, 13-33, and 35-47.

[0148] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IA). In some embodiments, the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 3-10, 14-33, 36, 37, and 42-47.

[0149] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IB). In some embodiments, the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 3-8, 14-31, 43, and 44.

[0150] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IC). In some embodiments, the non-naturally occurring

melanocortin analog comprises any one of the sequences of SEQ ID NOs: 10, 13, 33, 35-37, 42, and 45-47.

[0151] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (ID). In some embodiments, the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 38-41.

[0152] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IF). In some embodiments, the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 11, 12, and 43-45. In some embodiments, the non-naturally occurring melanocortin analog comprises any one of the sequences of SEQ ID NOs: 43-45.

[0153] Non-naturally occurring melanocortin analogs of any one of Formulae (I)-(IF) may be an agonist of the melanocortin 4 receptor and an agonist of the melanocortin 3 receptor. In some embodiments, non-naturally occurring melanocortin analogs of any one of Formulae (I)-(IF) are full agonists of the melanocortin 4 receptor and full agonists of the melanocortin 3 receptor. In other embodiments, non-naturally occurring melanocortin analogs of any one of Formulae (I)-(IF) are full agonists of the melanocortin 4 receptor and partial agonists of the melanocortin 3 receptor.

Non-Naturally Occurring Melanocortin Analog Synthesis

[0154] The non-naturally occurring melanocortin analogs of the present technology 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 of the present technology 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 of the present technology.

[0155] 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.

[0156] 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 disclosed 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), the disclosure of which is incorporated herein by reference in its entirety.

[0157] 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.

[0158] 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.

[0159] Guanidino groups may be protected by a suitable protecting group, such as nitro, p-toluenesulfonyl (Tosyl), Z, pentamethylchromanesulfonyl (Pmc),

adamantyloxycarbonyl, pentamethyldihydrobenzofuran-5-sulfonyl (Pbf) and Boc. Pmc is a useful protecting group for Arg.

[0160] 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.

[0161] 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.

[0162] 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.

[0163] 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).

[0164] 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 C18 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 chromatograph (HPLC), amino acid analysis, mass spectrometry, and the like.

Salt Forms of Non-Naturally Occurring Melanocortin Analogs

[0165] The non-naturally occurring melanocortin analog peptides of the present technology 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.

[0166] When the non-naturally occurring melanocortin analogs of the present technology 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 of the present technology 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 of the present technology 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.

Conjugates

[0167] The present technology further includes conjugates comprising a non-naturally occurring melanocortin analog. In some embodiments, the non-naturally melanocortin analog is conjugated to a pharmaceutical agent. Non-limiting examples of suitable pharmaceutical agents include peptides, monoclonal antibodies, and small molecules. In some embodiments, the non-naturally occurring melanocortin analog is conjugated to semaglutide. In other embodiments, the non-naturally occurring melanocortin analog is conjugated to setmelanotide. In yet other embodiments, the non-naturally occurring melanocortin analog is conjugated to a small molecule MCR agonist.

[0168] Conjugates of the present technology further comprise a linker connecting the non-naturally occurring melanocortin analog to the pharmaceutical agent. In some embodiments, the linker is rigid. In some embodiments, the linker is flexible. In some

embodiments, the linker is a cleavable linker. In some embodiments, the linker comprises a glycine-serine (Gly/Ser) linker, a proline-threonine-glycine linker, an alanine linker, a lysine linker, a threonine linker, a valine-glycine-serine-threonine linker, an elastin-like peptide linker, a hexahistidine linker, a polyethylene glycol linker, a fatty acid linker, or a hydrocarbon linker.

[0169] In some embodiments, the linker is a peptide linker. The peptide linkers of the present technology may vary from 2 to 31 amino acids of any primary sequence in length and do not impose any constraints on the conformation or interactions of the linked partners. In some embodiments, the linkers vary from about 2-30, 2-29, 2-28, 2-27, 2-26, 2-25, 2-24, 2-23, 2-22, 2-21, 2-20, 2-19, 2-18, 2-17, 2-16, 2-15, 2- 14, 2-13, 2-12, 2-11, 2-10, 2-9, 2-8, 2-7, 2-6, 2-5, 2-4, 2-3, 3-31, 3-30, 3-29, 3-28, 3-27, 3-26, 3-25, 3-24, 3-23, 3-22, 3-21, 3-20, 3-19, 3-18, 3-17, 3-16, 3-15, 3-14, 3-13, 3-12, 3-11, 3-10, 3-9, 3-8, 3-7, 3-6, 3-5, 3-4, 4-31, 4-30, 4-29, 4-28, 4-27, 4-26, 4-25, 4-24, 4-23, 4-22, 4-21, 4- 20, 4-19, 4-18, 4-17, 4-16, 4-15, 4-14, 4-13, 4-12, 4-11, 4-10, 4-9, 4-8, 4-7, 4-6, 4-5, 5-31, 5- 30, 5-29, 5-28, 5-27, 5-26, 5-25, 5-24, 5-23, 5-22, 5-21, 5-20, 5-19, 5-18, 5-17, 5-16, 5-15, 5- 14, 5-13, 5-12, 5-11, 5-10, 5-9, 5-8, 5-7, 5-6, 6-31, 6-30, 6-29, 6-28, 6-27, 6-26, 6-25, 6-24, 6-23, 6-22, 6-21, 6-20, 6-19, 6-18, 6-17, 6-16, 6-15, 6-14, 6-13, 6-12, 6-11, 6-10, 6-9, 6-8, 6- 7, 7-31, 7-30, 7-29, 7-28, 7-27, 7-26, 7-25, 7-24, 7-23, 7-22, 7-21, 7-20, 7-19, 7-18, 7-17, 7- 16, 7-15, 7-14, 7-13, 7-12, 7-11, 7-10, 7-9, 7-8, 8-31, 8-30, 8-29, 8-28, 8-27, 8-26, 8-25, 8-24, 8-23, 8-22, 8-21, 8-20, 8-19, 8-18, 8-17, 8-16, 8-15, 8-14, 8-13, 8-12, 8-11, 8-10, 8-9, 9-31, 9-30, 9-29, 9-28, 9-27, 9-26, 9-25, 9-24, 9-23, 9-22, 9-21, 9-20, 9-19, 9-18, 9-17, 9-16, 9-15, 9-14, 9-13, 9-12, 9-11, 9-10, 10-31, 10-30, 10-29, 10-28, 10-27, 10-26, 10-25, 10-24, 10-23, 10-22, 10-21, 10-20, 10-19, 10-18, 10-17, 10-16, 10-15, 10-14, 10-13, 10-12, 10-11, 11-31, 11-30, 11-29, 11-28, 11-27, 11-26, 11-25, 11-24, 11-23, 11-22, 11-21, 11-20, 11-19, 11-18, 11-17, 11-16, 11-15, 11-14, 11-13, 11-12, 12-31, 12-30, 12-29, 12-28, 12-27, 12-26, 12-25,12-24, 12-23, 12-22, 12-21, 12-20, 12-19, 12-18, 12-17, 12-16, 12-15, 12-14, 12-13, 13-31, 13-30, 13-29, 13-28, 13-27, 13-26, 13-25, 13-24, 13-23, 13-22, 13-21, 13-20, 13-19, 13-18, 13-17, 13-16, 13-15, 13-14, 14-31, 14-30, 14-29, 14-28, 14-27, 14-26, 14-25, 14-24, 14-23, 14-22, 14-21, 14-20, 14-19, 14-18, 14-17, 14-16, 14-15, 15-31, 15-30, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 15-16, 16-31, 16-30, 16-29, 16-28, 16-27, 16-26, 16-25, 16-24, 16-23, 16-22, 16-21, 16-20, 16-19, 16-18, 16-17, 17-31, 17-30, 17-

29, 17-28, 17-27, 17-26, 17-25, 17-24, 17-23, 17-22, 17-21, 17-20, 17-19, 17-18, 18-31, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 18-19, 19-31, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-31, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 21-31, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, 21-22, 22-31, 22-30, 22-29, 22-28, 22-27, 22-26, 22-25, 22-24, 22-23, 23-31, 23-30, 23-29, 23-28, 23-27, 23-26, 23-25, 23-24, 24-31, 24-30, 24-29, 24-28, 24-27, 24-26, 24-25, 25-31, 25-30, 25-29, 25-28, 25-27, 25-26, 26-31, 26-30, 26-29, 26-28, 26-27, 27-31, 27-30, 27-29, 27-28, 28-31, 28-30, 28-29, 29-31, 29-30, or 30-31 amino acids of any primary sequence in length. The peptide linkers may be designed as appropriate for an intended use.

[0170] The peptide linkers may comprise one or more of a Gly-rich linker (e.g., a flexible linker connecting various domains in a single protein without interfering with the function of each domain; a linker forming stable covalently linked dimers; a linker to connect two independent domains that create a ligand-binding site or recognition sequence), a Serine linker (e.g., a coiled structure linker); a coiled structure linker comprising a Gln, Arg, Glu, Ser, and/or Pro amino acids; a rigid space linker comprising one or more of a Pro, Arg, Phe, Thr, Glu, and/or Gln residues; a linker comprising a flexible Gly-rich regions that may may generate loops connecting domains; or a linker comprising a Thr, Ser, Gly, and/or Ala residue.

[0171] In some embodiments, the linker comprises an amino acid sequence about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 100% identical to the amino acid sequence of any one of Linker A, Linker B, Linker C, Linker D, Linker E, Linker F, Linker G, Linker H, Linker I, Linker J, Linker K, Linker L, Linker M, Linker N, Linker O, Linker P, Linker Q, Linker R, or Linker S in Table 0.

[0172] In some embodiments, the linker comprises an amino acid sequence at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 100% identical to the amino acid sequence of any one of Linker A, Linker B, Linker C, Linker D, Linker E, Linker F, Linker G, Linker H, Linker I, Linker J, Linker K, Linker L, Linker M, Linker N, Linker O, Linker P, Linker Q, Linker R, or Linker S in Table 0.

In some embodiments, the linker comprises an amino acid sequence at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 100% identical to the amino acid sequence of any one of Linker A, Linker B, Linker C, Linker D, Linker E, Linker F, Linker G, Linker H, Linker I, Linker J, Linker K, Linker L, Linker M, Linker N, Linker O, Linker P, Linker Q, Linker R, or Linker S in Table 0.

Table 0: Peptide Linker Amino Acid Sequences

Name	Amino Acid	SEQ ID NO
Linker A	$(GGS)_{1-5}$	173
Linker B	GGGGSLVPRGSGGGGS	174
Linker C	GSGSGS	175
Linker D	GS_8	176
Linker E	GGSGGHMGSGG	177
Linker F	GGSGGSGGSGG	178
Linker G	GGSGG	179
Linker H	GGSGGGGG	180
Linker I	GSGSGSGS	181
Linker J	GSGSGSGSGSGSGSGSGSGSGSGSGSGSG	182
Linker K	GGGSEGGGSEGGGSEGGG	183
Linker L	AAGAATAA	184
Linker M	GGGGG	185
Linker N	GGSSG	186
Linker O	GSGGGTGGGSG	187
Linker P	GT	188
Linker Q	GSGSGSGSGGSG	189
Linker R	GSGGSGSGGSGGSG	190
Linker S	SGGGGSRGGGSGGGG**SGGGGSGGGGSGGGG**	191

Pharmaceutical Compositions

[0173] In some embodiments, the non-naturally occurring melanocortin analogs of the present technology are present in a pharmaceutical composition.

[0174] 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 composition. For example, the non-naturally occurring melanocortin analog is present in the pharmaceutical 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 pharmaceutical composition in a concentration of about 50 mg/mL, relative to a total volume of the pharmaceutical composition.

[0175] In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IF), 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. For example, the non-naturally occurring melanocortin analog comprising a sequence of Formula (IF) is present in the pharmaceutical 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 pharmaceutical composition. In some embodiments, the non-naturally occurring melanocortin analog comprising a sequence of Formula (IF) is present in the pharmaceutical composition in a concentration of about 50 mg/mL, relative to a total volume of the pharmaceutical composition.

[0176] In some embodiments, the composition 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 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 Formula (IF).

[0177] The non-naturally occurring melanocortin analogs may be formulated with one or more pharmaceutically acceptable carriers and/or excipients. The carriers and/or

excipients of the present technology facilitate delivery of the non-naturally occurring melanocortin analog to a subject. Other pharmaceutically acceptable carriers and/or excipients may be included in the pharmaceutical composition to enhance dispersion, solubility, and/or stability of the non-naturally occurring melanocortin analog, and/or to reduce adverse injection site reactions.

[0178] In some embodiments, the pharmaceutical composition comprises 0.1 to 99.9999 wt.%, 1 to 99.999 wt.%, 5 to 99.99 wt.%, 10 to 99.9 wt.%, 15 to 99 wt.%, 20 to 90 wt.%, 30 to 85 wt.%, 40 to 80 wt.%, 50 to 75 wt.%, or 60 to 70 wt.% of the pharmaceutically acceptable carrier and/or excipient relative to a total weight of the pharmaceutical composition.

[0179] In some embodiments, the pharmaceutically acceptable carrier and/or excipient of the pharmaceutical composition is 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.

[0180] In some embodiments, the pharmaceutically acceptable carrier and/or excipient of the pharmaceutical composition is water. In some embodiments, the pharmaceutically acceptable carrier and/or excipient of the pharmaceutical composition is a buffer.

[0181] In some embodiments, the pharmaceutical composition contains about 0.1 to about 99.9999 wt.%, about 1 to about 99.999 wt.%, about 5 to about 99.99 wt.%, about 10 to about 99.9 wt.%, about 15 to about 99 wt.%, about 20 to about 90 wt.%, about 30 to about 85 wt.%, about 40 to about 80 wt.%, about 50 to about 75 wt.%, or about 60 to about 70 wt.% of one or more pharmaceutically acceptable carriers and/or excipients relative to a total weight of the pharmaceutical composition.

[0182] In some embodiments, the pharmaceutical composition contains at least 0.1 to at least 99.9999 wt.%, at least 1 to at least 99.999 wt.%, at least 5 to at least 99.99 wt.%, at least 10 to at least 99.9 wt.%, at least 15 to at least 99 wt.%, at least 20 to at least 90 wt.%, at least 30 to at least 85 wt.%, at least 40 to at least 80 wt.%, at least 50 to at least 75 wt.%, or at least 60 to at least 70 wt.% of one or more pharmaceutically acceptable carriers and/or excipients relative to a total weight of the pharmaceutical composition.

[0183] In some embodiments, the pharmaceutical composition contains at least about 0.1 to at least about 99.9999 wt.%, at least about 1 to at least about 99.999 wt.%, at least about 5 to at least about 99.99 wt.%, at least about 10 to at least about 99.9 wt.%, at least about 15 to at least about 99 wt.%, at least about 20 to at least about 90 wt.%, at least about 30 to at least about 85 wt.%, at least about 40 to at least about 80 wt.%, at least about 50 to at least about 75 wt.%, or at least about 60 to at least about 70 wt.% of one or more pharmaceutically acceptable carriers and/or excipients relative to a total weight of the pharmaceutical composition.

[0184] Any pharmaceutically acceptable carriers and/or excipients known in the art may be included in the pharmaceutical composition. Non-limiting examples of pharmaceutically acceptable carriers and/or excipients include buffers, binders, excipients, stabilizers, lubricants, oils, adjuvants, preservatives, lipids, and antioxidants. The pharmaceutical composition may comprise any combination of the one or more pharmaceutically acceptable carriers and/or excipients previously described in relation to the first and pharmaceutical compositions. In some embodiments, the one or more pharmaceutically acceptable carriers and/or excipients comprise water.

[0185] 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.

[0186] In some embodiments, the one or more pharmaceutically acceptable carriers and/or excipients are isotonic. In some embodiments, the carrier and/or excipient is isotonic to nasal fluids.

[0187] In some embodiments, the pharmaceutical composition further comprises a pharmaceutical salt. Any pharmaceutical salt known in the art may be included in the pharmaceutical composition. For examples, to achieve a desirable tonicity, the pharmaceutical composition may include a salt selected from the group consisting of sodium

chloride, sodium succinate, sodium sulfate, potassium chloride, magnesium chloride, magnesium sulfate, and calcium chloride.

[0188] In some embodiments, the salt is present in the pharmaceutical composition in a concentration of about 0.1 mg/mL to about 50 mg/mL, about 1 mg/mL to about 25 mg/mL, or about 5 mg/mL to about 10 mg/mL, relative to a total volume of the composition.

[0189] In some embodiments, the salt is present in the pharmaceutical composition in a concentration of at least 0.1 mg/mL to at least 50 mg/mL, at least 1 mg/mL to at least 25 mg/mL, or at least 5 mg/mL to at least 10 mg/mL, relative to a total volume of the composition.

[0190] In some embodiments, the salt is present in the pharmaceutical composition in a concentration of at least about 0.1 mg/mL to at least about 50 mg/mL, at least about 1 mg/mL to at least about 25 mg/mL, or at least about 5 mg/mL to at least about 10 mg/mL, relative to a total volume of the composition.

[0191] Pharmaceutically acceptable carriers and/or excipients that may be included in the pharmaceutical composition generally include a pH buffered aqueous solution comprising one or more of the following components: (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.

[0192] In the pH buffered solution of the pharmaceutical composition, the water 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.

[0193] In some embodiments, the pharmaceutical 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.

[0194] In some embodiments, the pharmaceutical composition includes water in an amount of at least 1 wt% to at least 90 wt%, at least 10 wt% to at least 75 wt%, or at least 25 wt% to at least 50 wt%, relative to a total weight of the composition.

[0195] In some embodiments, the pharmaceutical composition includes water in an amount of at least about 1 wt% to at least about 90 wt%, at least about 10 wt% to at least about 75 wt%, or at least about 25 wt% to at least about 50 wt%, relative to a total weight of the composition.

[0196] In some embodiments, sodium acetate is present in the pharmaceutical 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 may be present in the pharmaceutical 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.

[0197] In some embodiments, sodium acetate is present in the pharmaceutical 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 may be present in the pharmaceutical 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.

[0198] In some embodiments, sodium acetate is present in the pharmaceutical composition in a molar concentration of 5 mM to 700 mM, relative to a total volume of the composition. For example, sodium acetate may be present in the pharmaceutical 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.

[0199] In some embodiments, sodium acetate is present in the pharmaceutical 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 may be present in the pharmaceutical 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.

[0200] The term "Tris" refers to tris(hydroxymethyl)aminomethane, which is 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 pharmaceutical composition in a concentration of 0.5 mg/mL to 50 mg/mL, relative to a total volume of the composition. For example, Tris may be present in the pharmaceutical 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.

[0201] In some embodiments, Tris is present in the pharmaceutical 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 may be present in the pharmaceutical 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.

[0202] In some embodiments, Tris is present in the pharmaceutical composition in a molar concentration of 2 mM to 500 mM, relative to a total volume of the composition. For example, Tris may be present in the pharmaceutical 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.

[0203] In some embodiments, Tris is present in the pharmaceutical composition in a molar concentration of about 50 mM to about 70 mM, relative to a total volume of the composition. For example, Tris may be present in the pharmaceutical 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.

[0204] In some embodiments, the pH buffered aqueous solution provides the pharmaceutical 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.

[0205] In some embodiments, a weight ratio of sodium acetate to Tris is about 1:4 to about 4:1, about 2:7 to about 7:2, about 1:3 to about 3:1, about 2:5 to about 5:2, about 1:2 to about 2:1, about 2:3 to about 3:2, or about 1:1. In some embodiments, the weight ratio of sodium acetate to Tris is about 1:1.

[0206] In some embodiments, a weight ratio of sodium acetate to Tris is at least 1:4 to at least 4:1, at least 2:7 to at least 7:2, at least 1:3 to at least 3:1, at least 2:5 to at least 5:2, at least 1:2 to at least 2:1, at least 2:3 to at least 3:2, or at least 1:1. In some embodiments, the weight ratio of sodium acetate to Tris is at least 1:1.

[0207] In some embodiments, a weight ratio of sodium acetate to Tris is at least about 1:4 to at least about 4:1, at least about 2:7 to at least about 7:2, at least about 1:3 to at least about 3:1, at least about 2:5 to at least about 5:2, at least about 1:2 to at least about 2:1, at least about 2:3 to at least about 3:2, or at least about 1:1. In some embodiments, the weight ratio of sodium acetate to Tris is at least about 1:1.

[0208] In some embodiments, a weight ratio of the non-naturally occurring melanocortin analog to sodium acetate is about 1:1 to about 20:1, about 3:2 to about 15:1, about 2:1 to about 12:1, about 3:1 to about 10:1, about 4:1 to about 9:1, about 5:1 to about 8:1, or about 6:1 to about 7:1. In some embodiments, the weight ratio of the non-naturally occurring melanocortin analog to sodium acetate is about 7:1.

[0209] In some embodiments, a weight ratio of the non-naturally occurring melanocortin analog to sodium acetate is at least 1:1 to at least 20:1, at least 3:2 to at least 15:1, at least 2:1 to at least 12:1, at least 3:1 to at least 10:1, at least 4:1 to at least 9:1, at least 5:1 to at least 8:1, or at least 6:1 to at least 7:1. In some embodiments, the weight ratio of the non-naturally occurring melanocortin analog to sodium acetate is at least 7:1.

[0210] In some embodiments, a weight ratio of the non-naturally occurring melanocortin analog to sodium acetate is at least about 1:1 to at least about 20:1, at least about 3:2 to at least about 15:1, at least about 2:1 to at least about 12:1, at least about 3:1 to at least about 10:1, at least about 4:1 to at least about 9:1, at least about 5:1 to at least about 8:1, or at least about 6:1 to at least about 7:1. In some embodiments, the weight ratio of the non-naturally occurring melanocortin analog to sodium acetate is at least about 7:1.

[0211] In some embodiments, a weight ratio of the non-naturally occurring melanocortin analog to Tris is about 1:1 to about 20:1, about 3:2 to about 15:1, about 2:1 to about 12:1, about 3:1 to about 10:1, about 4:1 to about 9:1, about 5:1 to about 8:1, or about 6:1 to about 7:1. In some embodiments, the weight ratio of the non-naturally occurring melanocortin analog to Tris is about 7:1.

[0212] In some embodiments, a weight ratio of the non-naturally occurring melanocortin analog to Tris is at least 1:1 to at least 20:1, at least 3:2 to at least 15:1, at least 2:1 to at least 12:1, at least 3:1 to at least 10:1, at least 4:1 to at least 9:1, at least 5:1 to at least 8:1, or at least 6:1 to at least 7:1. In some embodiments, the weight ratio of the non-naturally occurring melanocortin analog to Tris is at least 7:1.

[0213] In some embodiments, a weight ratio of the non-naturally occurring melanocortin analog to Tris is at least about 1:1 to at least about 20:1, at least about 3:2 to at least about 15:1, at least about 2:1 to at least about 12:1, at least about 3:1 to at least about 10:1, at least about 4:1 to at least about 9:1, at least about 5:1 to at least about 8:1, or at least about 6:1 to at least about 7:1. In some embodiments, the weight ratio of the non-naturally occurring melanocortin analog to Tris is at least about 7:1.

[0214] In addition to sodium acetate and Tris, the pharmaceutical 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 pharmaceutical composition comprises acetic acid as an additional buffering agent.

[0215] The pharmaceutical composition may further comprise one or more chelating agents. Suitable chelating agents include, but are not limited to edetate disodium dihydrate, calcium disodium edetate, sodium edetate, calcium versetamide sodium, calteridol, and diethylenetriaminepentaacetic acid. In some embodiments, the pharmaceutical composition further comprises edetate disodium dihydrate.

[0216] The pharmaceutical composition may further 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. In some embodiments, when the pharmaceutical composition comprises a preservative agent, the preservative agent is phenol, benzyl alcohol, or a combination thereof.

[0217] If present in the pharmaceutical composition, 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.

[0218] The pharmaceutical composition may further comprise an emulsifier. Non-limiting examples of emulsifiers that may be included in the pharmaceutical composition include sodium carboxymethylcellulose, cetyl alcohol, glycerol monostearate, methylcellulose, and stearic acid. In some embodiments, when the pharmaceutical composition comprises an emulsifier, the emulsifier is sodium carboxymethylcellulose.

[0219] The pharmaceutical composition may further comprise a lipid. Lipids may enhance solubility and/or improve permeability of the non-naturally occurring melanocortin analog. In some embodiments, the lipid is a phospholipid. Non-limiting examples of phospholipids that may be included in the pharmaceutical composition include egg phosphatidylcholine, hydrogenated soybean phoshphaditylcholine, glycerophosphocholine, lecithin, and N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-glycero-3-phosphoethanolamine sodium salt. In some embodiments, when the pharmaceutical composition comprises a lipid, the lipid is N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-glycero-3-phosphoethanolamine sodium salt

[0220] The pharmaceutical composition may further comprise a bulking agent. Inclusion of a bulking agent may increase the stability of the pharmaceutical composition. Non-limiting examples of bulking agents that may be included in the pharmaceutical

composition include sucrose, lactose, trehalose, mannitol, sorbitol, glucose, raffinose, glycine, histidine, and polyvinyl pyrrolidone. In some embodiments, when the pharmaceutical composition comprises a bulking agent, the bulking agent is mannitol.

[0221] In some embodiments, the pharmaceutical composition is in the form of an aqueous solution or a suspension. In some embodiments, the pharmaceutical composition is in the form of an emulsion. In some embodiments, the pharmaceutical composition is in the form of an aqueous solution. In some embodiments, the pharmaceutical composition is in the form of an aqueous solution which is clear, colorless, and/or free of visible foreign matter.

[0222] In some embodiments, the pharmaceutical composition has a pH ranging from about 6.5 to about 8.5. In some embodiments, the pharmaceutical 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.

[0223] In some embodiments, the pharmaceutical composition has a pH ranging from at least 6.5 to at least 8.5. In some embodiments, the pharmaceutical composition has a pH of at least 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.

[0224] In some embodiments, the pharmaceutical composition has a pH ranging from at least about 6.5 to at least about 8.5. In some embodiments, the pharmaceutical composition has a pH of at least 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.

[0225] In some embodiments, the pharmaceutical 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 pharmaceutical composition has a pH ranging from about 7.3 to about 7.4. In some embodiments, the pharmaceutical composition has a pH of 7.3 or 7.4.

[0226] In some embodiments, the pharmaceutical composition is basic and has a pH of at least 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 pharmaceutical composition has a pH ranging from at least 7.3 to at least 7.4. In some embodiments, the pharmaceutical composition has a pH of 7.3 or 7.4.

[0227] In some embodiments, the pharmaceutical composition is basic and has a pH of at least 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 pharmaceutical composition has a pH ranging from at least about 7.3 to at least about 7.4. In some embodiments, the pharmaceutical composition has a pH of 7.3 or 7.4.

[0228] In some embodiments, the pharmaceutical composition has an osmolality ranging from 250 mOsm/kg to 350 mOsm/kg. For example, the pharmaceutical composition may have 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 pharmaceutical 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 pharmaceutical composition has an osmolality ranging from about 275 mOsm/kg to about 330 mOsm/kg. In some embodiments, the pharmaceutical composition has an osmolality of about 279 mOsm/kg, about 314 mOsm/kg, or about 329 mOsm/kg.

[0229] In some embodiments, the pharmaceutical composition has an osmolality ranging from 250 mOsm/kg to 350 mOsm/kg. For example, the pharmaceutical composition may have 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 at least 300 mOsm/kg. In some embodiments, the pharmaceutical composition has an osmolarity of at least 250 mOsm/kg, at least 260 mOsm/kg, at least 270 mOsm/kg, at least 280 mOsm/kg, at least 290 mOsm/kg, at least 300 mOsm/kg, at least 310 mOsm/kg, at least 320 mOsm/kg, at least 330 mOsm/kg, at least 340 mOsm/kg, at least 350 mOsm/kg, or at least 360 mOsm/kg. In some embodiments, the pharmaceutical composition has an osmolality ranging from at least 275 mOsm/kg to at least 330 mOsm/kg. In some embodiments, the pharmaceutical composition has an osmolality of at least 279 mOsm/kg, at least 314 mOsm/kg, or at least 329 mOsm/kg.

[0230] In some embodiments, the pharmaceutical composition has an osmolality ranging from 250 mOsm/kg to 350 mOsm/kg. For example, the pharmaceutical composition may have 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 at least about 300 mOsm/kg. In some embodiments, the pharmaceutical composition has an osmolarity of at least about 250 mOsm/kg, at least about 260 mOsm/kg, at least about 270 mOsm/kg, at least about 280 mOsm/kg, at least about 290 mOsm/kg, at least about 300 mOsm/kg, at least about 310 mOsm/kg, at least about 320 mOsm/kg, at least about 330 mOsm/kg, at least about 340 mOsm/kg, at least about 350 mOsm/kg, or at least about 360 mOsm/kg. In some embodiments, the pharmaceutical composition has an osmolality ranging from at least about 275 mOsm/kg to at least about 330 mOsm/kg. In some embodiments, the pharmaceutical composition has an osmolality of at least about 279 mOsm/kg, at least about 314 mOsm/kg, or at least about 329 mOsm/kg.

[0231] In some embodiments, the pharmaceutical composition has a viscosity ranging from about 0.5 cP to about 5 cP. For example, the pharmaceutical composition may have a viscosity ranging from about 0.5 cP to about 5 cP, about 0.75 cP to about 4.5 cP, about 1.0 cP to about 4 cP, about 1.2 cP to about 3.5 cP, about 1.3 cP to about 3 cP, about 1.4 cP to about 2.5 cP, about 1.5 cP to about 2 cP, or about 1.6 cP to about 1.8 cP. In some embodiments, the pharmaceutical 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 pharmaceutical composition has a viscosity of about 1.4 cP or about 1.6 cP.

[0232] In some embodiments, the pharmaceutical composition has a viscosity ranging from at least 0.5 cP to at least 5 cP. For example, the pharmaceutical composition may have a viscosity ranging from at least 0.5 cP to at least 5 cP, at least 0.75 cP to at least 4.5 cP, at least 1.0 cP to at least 4 cP, at least 1.2 cP to at least 3.5 cP, at least 1.3 cP to at least 3 cP, at least 1.4 cP to at least 2.5 cP, at least 1.5 cP to at least 2 cP, or at least 1.6 cP to at least 1.8 cP. In some embodiments, the pharmaceutical composition has a viscosity of at least 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 pharmaceutical composition has a viscosity of at least 1.4 cP or at least 1.6 cP.

[0233] In some embodiments, the pharmaceutical composition has a viscosity ranging from at least about 0.5 cP to at least about 5 cP. For example, the pharmaceutical composition may have a viscosity ranging from at least about 0.5 cP to at least about 5 cP, at least about 0.75 cP to at least about 4.5 cP, at least about 1.0 cP to at least about 4 cP, at least about 1.2 cP to at least about 3.5 cP, at least about 1.3 cP to at least about 3 cP, at least about 1.4 cP to at least about 2.5 cP, at least about 1.5 cP to at least about 2 cP, or at least about 1.6 cP to at least about 1.8 cP. In some embodiments, the pharmaceutical composition has a viscosity of at least 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 pharmaceutical composition has a viscosity of at least about 1.4 cP or at least about 1.6 cP.

[0234] In some embodiments, the pharmaceutical composition disclosed is 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.

[0235] When the pharmaceutical composition is formulated for parenteral administration (e.g., subcutaneous administration), 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.

[0236] In some embodiments, the pharmaceutical composition is formulated for parenteral administration (e.g., subcutaneous administration) and comprises a non-naturally occurring melanocortin analog in a concentration of 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.

[0237] In some embodiments, the pharmaceutical composition is formulated for parenteral administration (e.g., subcutaneous administration) and comprises sodium acetate in a concentration of 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.

[0238] In some embodiments, the pharmaceutical composition is formulated for parenteral administration (e.g., subcutaneous administration) and comprises Tris in a concentration of 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.

[0239] In some embodiments, the pharmaceutical composition comprises one or more antioxidants. For example, the pharmaceutical composition may comprise ascorbic acid, cysteine, sodium metabisulfite, propyl gallate, butylated hydroxytoluene, and/or butylated hydroxyanisole.

[0240] In some embodiments, the pharmaceutical composition comprises a surfactant, such as a sorbitan ester.

[0241] In some embodiments, the pharmaceutical composition comprises a flavoring or scent, such as an aromatic oil.

[0242] In some embodiments, the non-naturally occurring melanocortin analog is solubilized or suspended in a solvent or vehicle. The solvent or vehicle may be purified water, ethyl alcohol, and/or propylene glycol. In some embodiments, the pharmaceutical composition comprises between 0.03 wt% and 1 wt% melanocortin analog solubilized or suspended in a solvent or vehicle. For example, the pharmaceutical composition may comprise the non-naturally occurring melanocortin analog in an amount of about 0.03 wt%,

about 0.05 wt%, about 0.1 wt%, about 0.15 wt%, about 0.2 wt%, about 0.25 wt%, about 0.3 wt%, about 0.35 wt%, about 0.4 wt%, about 0.45 wt%, about 0.5 wt%, about 0.55 wt%, about 0.6 wt%, about 0.65 wt%, about 0.7 wt%, about 0.75 wt%, about 0.8 wt%, about 0.85 wt%, about 0.9 wt%, about 0.95 wt%, or about 1 wt%.

[0243] In some embodiments, the pharmaceutical composition may comprise the non-naturally occurring melanocortin analog in an amount of at least 0.03 wt%, at least 0.05 wt%, at least 0.1 wt%, at least 0.15 wt%, at least 0.2 wt%, at least 0.25 wt%, at least 0.3 wt%, at least 0.35 wt%, at least 0.4 wt%, at least 0.45 wt%, at least 0.5 wt%, at least 0.55 wt%, at least 0.6 wt%, at least 0.65 wt%, at least 0.7 wt%, at least 0.75 wt%, at least 0.8 wt%, at least 0.85 wt%, at least 0.9 wt%, at least 0.95 wt%, or at least 1 wt%.

[0244] In some embodiments, the pharmaceutical composition may comprise the non-naturally occurring melanocortin analog in an amount of at least about 0.03 wt%, at least about 0.05 wt%, at least about 0.1 wt%, at least about 0.15 wt%, at least about 0.2 wt%, at least about 0.25 wt%, at least about 0.3 wt%, at least about 0.35 wt%, at least about 0.4 wt%, at least about 0.45 wt%, at least about 0.5 wt%, at least about 0.55 wt%, at least about 0.6 wt%, at least about 0.65 wt%, at least about 0.7 wt%, at least about 0.75 wt%, at least about 0.8 wt%, at least about 0.85 wt%, at least about 0.9 wt%, at least about 0.95 wt%, or at least about 1 wt%.

[0245] The non-naturally occurring melanocortin analogs of the present technology may be formulated for administration 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.

[0246] In some embodiments, the pharmaceutical 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 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.

[0247] In some embodiments, the pharmaceutical composition is formulated for oral administration. For example, the pharmaceutical composition may be in the form of a tablet, capsule, lozenge, pill, sachet, or any other orally deliverable form know in the art.

[0248] 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, or nebulizer. In some embodiments, the pharmaceutical composition includes a propellant, such as hydrofluoroalkane.

[0249] In some embodiments, the pharmaceutical 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.

Dosing

[0250] In some embodiments, the non-naturally occurring melanocortin analog or a pharmaceutical composition thereof (e.g., the pharmaceutical composition) is 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 non-naturally occurring melanocortin analog is administered every morning, every evening, or every afternoon. In some embodiments, the non-naturally occurring melanocortin analog is administered before a meal, after a meal, or with a meal.

[0251] In some embodiments, the non-naturally occurring melanocortin analog or pharmaceutical composition thereof may be administered as a dosing regimen comprising once, twice, or three times daily 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) schedules may be repeated 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 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).

[0252] In some embodiments, the non-naturally occurring melanocortin analog or pharmaceutical composition thereof is 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.

[0253] Administration of the non-naturally occurring melanocortin analog or pharmaceutical composition thereof at any of the dosing frequencies of the present technology may be repeated for a total of about 2 dosages, about 3 dosages, about 4 dosages, about 5 dosages, about 10 dosages, about 15 dosages, about 20 dosages, about 30 dosages, about 40 dosages, about 50 dosages or more.

[0254] Administration of the non-naturally occurring melanocortin analog or pharmaceutical composition thereof 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.

[0255] Administration of the non-naturally occurring melanocortin analog or pharmaceutical composition thereof at any of the dosing frequencies of the present technology may be repeated for a total of at least about 2 dosages, at least about 3 dosages, at least about 4 dosages, at least about 5 dosages, at least about 10 dosages, at least about 15 dosages, at least about 20 dosages, at least about 30 dosages, at least about 40 dosages, at least about 50 dosages or more.

[0256] In some embodiments, the frequency of dosages of the non-naturally occurring melanocortin analog or pharmaceutical composition thereof is the same during a treatment regimen. In other embodiments, the frequency of dosages of the non-naturally occurring melanocortin analog or pharmaceutical composition thereof is different during a treatment regimen. The non-naturally occurring melanocortin analog or the pharmaceutical composition thereof 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 is repeated at other intervals.

[0257] 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, 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. 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.

[0258] The methods disclosed herein may be performed on the subject for about 1 day, 1 week, 1 month, 3 months, 6 months, 1 year, or 5 years. In some embodiments, the combination therapy (i.e., pharmaceutical combination) is administered to the subject for about 1 day, about 2 days, about 5 days, about 6 days, about 1 week, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 9 months, about 1 year, about 2 years, about 3 years, about 4 years, or about 5 years.

[0259] The methods disclosed herein may be 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 (i.e., pharmaceutical combination) 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.

[0260] The methods disclosed herein may be performed on the subject for at least about 1 day, 1 week, 1 month, 3 months, 6 months, 1 year, or 5 years. In some embodiments, the combination therapy (i.e., pharmaceutical combination) is administered to the subject for at least about 1 day, at least about 2 days, at least about 5 days, at least about 6 days, at least about 1 week, at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 9 months, at least about 1 year, at least about 2 years, at least about 3 years, at least about 4 years, or at least about 5 years.

[0261] In some embodiments, a method disclosed herein is 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.

[0262] 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.

[0263] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 15 mg/kg to about 100 mg/kg per body weight of the subject once daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 30 mg/kg or 60 mg/kg per body weight of the subject once daily.

[0264] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 0.1 mg to about 100 mg once daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 10 mg or about 50 mg once daily.

[0265] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 5 mg/kg to about 1000 mg/kg per body weight of the subject once daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 10 mg/kg to about 550 mg/kg per body weight of the subject once daily. In some embodiments, non-naturally occurring melanocortin analog is administered at a dose of about 15 mg/kg to about 100 mg/kg per body weight of the subject once daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 20 mg/kg to about 75 mg/kg per body weight of the subject once daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 30 mg/kg or 60 mg/kg per body weight of the subject once daily.

[0266] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 5 mg/kg to at least 1000 mg/kg per body weight of the subject once daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 10 mg/kg to at least 550 mg/kg per body weight of the subject once daily. In some embodiments, non-naturally occurring melanocortin analog is administered at a dose of at least 15 mg/kg to at least 100 mg/kg per body weight of the subject once daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 20 mg/kg to at least 75 mg/kg per body weight of the subject once daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 30 mg/kg or 60 mg/kg per body weight of the subject once daily.

[0267] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 5 mg/kg to at least about 1000 mg/kg per body weight of the subject once daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 10 mg/kg to at least about

550 mg/kg per body weight of the subject once daily. In some embodiments, non-naturally occurring melanocortin analog is administered at a dose of at least about 15 mg/kg to at least about 100 mg/kg per body weight of the subject once daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 20 mg/kg to at least about 75 mg/kg per body weight of the subject once daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 30 mg/kg or 60 mg/kg per body weight of the subject once daily.

[0268] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 50 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, about 100 mg/kg, about 125 mg/kg, about 150 mg/kg, about 175 mg/kg, about 200 mg/kg, about 250 mg/kg, about 300 mg/kg, about 350 mg/kg, about 400 mg/kg, about 450 mg/kg, or about 500 mg/kg, about 550 mg/kg, about 600 mg/kg, about 650 mg/kg, about 700 mg/kg, about 750 mg/kg, about 800 mg/kg, about 850 mg/kg, about 900 mg/kg, about 950 mg/kg, or about 1000 mg/kg per body weight of the subject once daily.

[0269] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 5 mg/kg, at least 10 mg/kg, at least 15 mg/kg, at least 20 mg/kg, at least 25 mg/kg, at least 30 mg/kg, at least 35 mg/kg, at least 40 mg/kg, at least 50 mg/kg, at least 65 mg/kg, at least 70 mg/kg, at least 75 mg/kg, at least 80 mg/kg, at least 85 mg/kg, at least 90 mg/kg, at least 95 mg/kg, at least 100 mg/kg, at least 125 mg/kg, at least 150 mg/kg, at least 175 mg/kg, at least 200 mg/kg, at least 250 mg/kg, at least 300 mg/kg, at least 350 mg/kg, at least 400 mg/kg, at least 450 mg/kg, or at least 500 mg/kg, at least 550 mg/kg, at least 600 mg/kg, at least 650 mg/kg, at least 700 mg/kg, at least 750 mg/kg, at least 800 mg/kg, at least 850 mg/kg, at least 900 mg/kg, at least 950 mg/kg, or at least 1000 mg/kg per body weight of the subject once daily.

[0270] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 5 mg/kg, at least about 10 mg/kg, at least about 15 mg/kg, at least about 20 mg/kg, at least about 25 mg/kg, at least about 30 mg/kg, at least about 35 mg/kg, at least about 40 mg/kg, at least about 50 mg/kg, at least about 65 mg/kg,

at least about 70 mg/kg, at least about 75 mg/kg, at least about 80 mg/kg, at least about 85 mg/kg, at least about 90 mg/kg, at least about 95 mg/kg, at least about 100 mg/kg, at least about 125 mg/kg, at least about 150 mg/kg, at least about 175 mg/kg, at least about 200 mg/kg, at least about 250 mg/kg, at least about 300 mg/kg, at least about 350 mg/kg, at least about 400 mg/kg, at least about 450 mg/kg, or at least about 500 mg/kg, at least about 550 mg/kg, at least about 600 mg/kg, at least about 650 mg/kg, at least about 700 mg/kg, at least about 750 mg/kg, at least about 800 mg/kg, at least about 850 mg/kg, at least about 900 mg/kg, at least about 950 mg/kg, or at least about 1000 mg/kg per body weight of the subject once daily.

[0271] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 5 mg/kg per body weight of the subject once daily.

[0272] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 10 mg/kg per body weight of the subject once daily.

[0273] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 15 mg/kg per body weight of the subject once daily.

[0274] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 20 mg/kg per body weight of the subject once daily.

[0275] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 25 mg/kg per body weight of the subject once daily.

[0276] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 30 mg/kg per body weight of the subject once daily.

[0277] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 35 mg/kg per body weight of the subject once daily.

[0278] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 40 mg/kg per body weight of the subject once daily.

[0279] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 50 mg/kg per body weight of the subject once daily.

[0280] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 5 mg/kg per body weight of the subject once daily.

[0281] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 10 mg/kg per body weight of the subject once daily.

[0282] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 15 mg/kg per body weight of the subject once daily.

[0283] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 20 mg/kg per body weight of the subject once daily.

[0284] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 25 mg/kg per body weight of the subject once daily.

[0285] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 30 mg/kg per body weight of the subject once daily.

[0286] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 35 mg/kg per body weight of the subject once daily.

[0287] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 40 mg/kg per body weight of the subject once daily.

[0288] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least 50 mg/kg per body weight of the subject once daily.

[0289] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 5 mg/kg per body weight of the subject once daily.

[0290] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 10 mg/kg per body weight of the subject once daily.

[0291] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 15 mg/kg per body weight of the subject once daily.

[0292] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 20 mg/kg per body weight of the subject once daily.

[0293] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 25 mg/kg per body weight of the subject once daily.

[0294] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 30 mg/kg per body weight of the subject once daily.

[0295] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 35 mg/kg per body weight of the subject once daily.

[0296] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 40 mg/kg per body weight of the subject once daily.

[0297] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of at least about 50 mg/kg per body weight of the subject once daily.

[0298] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 50 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, about 100 mg/kg, about 125 mg/kg, about 150 mg/kg, about 175 mg/kg, about 200 mg/kg, about 250 mg/kg, about 300 mg/kg, about 350 mg/kg, about 400 mg/kg, about 450 mg/kg, about 500 mg/kg, about 550 mg/kg, about 600 mg/kg, about 650 mg/kg, about 700 mg/kg, about 750 mg/kg, about 800 mg/kg, about 850 mg/kg, about 900 mg/kg, about 950 mg/kg, or about 1000 mg/kg per body weight of the subject twice daily.

[0299] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 5 mg/kg per body weight of the subject twice daily.

[0300] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 10 mg/kg per body weight of the subject twice daily.

[0301] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 15 mg/kg per body weight of the subject twice daily.

[0302] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 20 mg/kg per body weight of the subject twice daily.

[0303] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 25 mg/kg per body weight of the subject twice daily.

[0304] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 30 mg/kg per body weight of the subject twice daily.

[0305] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 35 mg/kg per body weight of the subject twice daily.

[0306] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 40 mg/kg per body weight of the subject twice daily.

[0307] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 50 mg/kg per body weight of the subject twice daily.

[0308] In some embodiments, the non-naturally occurring melanocortin analog is administered at one or more doses. In some embodiments, the non-naturally occurring melanocortin analog is administered at two or more doses.

[0309] In some embodiments, the non-naturally occurring melanocortin analog is administered at a first dose once daily or twice daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a second dose once daily or twice daily.

[0310] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose that is a projected human equivalent dose (HED) based on a nonhuman primate dose. In some embodiments, the HED based on a 10 mg/kg nonhuman primate dose ranges from about 300 mg to about 550 mg.

[0311] In some embodiments, the non-naturally occurring melanocortin analog is administered at a first dose once daily for about 5 days to about 10 days. In some embodiments, the non-naturally occurring melanocortin analog is administered at a second dose once daily for about 5 days to about 10 days, after administration of the first dose. In some embodiments, the non-naturally occurring melanocortin analog is administered at a third dose twice daily for about 7 days to about 21 days, after administration of the second dose. In some embodiments, the second dose is greater than the first dose. In some

embodiments, the third dose comprises a cumulative dose that is greater than the second dose.

[0312] In some embodiments, the non-naturally occurring melanocortin analogs or a pharmaceutical composition thereof (e.g., the pharmaceutical composition) is administered at a second dose that is at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 125%, 150%, 175%, 200%, 250%, 300%, 350%, 400%, 450%, or 500% greater than the first dose.

[0313] In some embodiments, the non-naturally occurring melanocortin analogs or a pharmaceutical composition thereof (e.g., the pharmaceutical composition) is administered at a third dose that is at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 125%, 150%, 175%, 200%, 250%, 300%, 350%, 400%, 450%, or 500% greater than the first dose and/or the second dose.

[0314] In some embodiments, the dosage of the second dose is greater than the dosage of the first dose. In some embodiments, the first dose is administered about once a day and the second dose is administered about twice a day.

[0315] In some embodiments, the dosage of the third dose is greater than the dosage of the first dose and/or the second dose. In some embodiments, the first dose and/or the second dose is administered about once a day, and the third dose is administered about twice a day.

[0316] In some embodiments, the non-naturally occurring melanocortin analog is administered using two or more different administration routes. The two or more different administration routes may comprise an oral administration and a subcutaneous administration. The oral administration may occur before, during, or after the subcutaneous administration.

[0317] In some embodiments, the first dose and the second dose comprise different routes of administration. In some embodiments, the first dose comprises an oral dose and the second dose comprises a subcutaneous dose. In some embodiments, the first dose and/or second dose and the third dose comprise different routes of administration. In some

embodiments, the first dose and/or the second dose comprises an oral dose and the third dose comprises a subcutaneous dose.

[0318] In some embodiments, the second dose is administered at least about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, or about 6 weeks after the first dose.

[0319] In some embodiments, the third dose is administered at least about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, or about 6 weeks after the first dose and/or the second dose.

[0320] In some embodiments, the non-naturally occurring melanocortin analog or a pharmaceutical composition thereof (e.g., the pharmaceutical composition) is administered at two or more dosage amounts, each dosage amount differing from the other. The first dosage amount, the second dosage amount, and the third dosage amount may each be greater than, less than, equal to, or substantially equivalent to another dosage amount. For example, the first dosage amount is less than a second dosage amount which is greater than a third dosage amount also greater than the first dosage amount. The dosage amounts refer to doses administered more than once over a period of time, such as a first dosage amount administered daily, BID, TID, or weekly, a second dosage amount administered daily, BID, TID, or weekly, and a third dosage amount administered daily, BID, TID, or weekly. In some embodiments, the first dosage amount, the second dosage amount, or the third dosage amount may be administered every other day, every second day, every third day, twice per week, or twice per month. For example, the first dosage amount of 10 mg/kg may be administered once a day for 7 days, followed by the second dosage amount of 20 mg/kg once a day for 7 days, followed by the third dosage amount of 15 mg/kg twice a day for at least about 7 days. In some embodiments, the third dosage amount is administered for at least about 7 days, at least about 14 days, or at least about 21 days.

[0321] In some embodiments, the non-naturally occurring melanocortin analog or a pharmaceutical composition thereof (e.g., the pharmaceutical composition) may be administered using more than one route of administration. For example, the first dosage

amount and the second dosage amount may be administered by two different routes of administration. In addition, the first dosage amount and the second dosage amount administered via different routes of administration may be the same or different dosage amounts. In some embodiments, the first dosage amount is administered orally and the second dosage amount is administered subcutaneously. The dosage frequency and/or duration of the dosage amounts may be the same or may be different. For example, the frequency of each dosage amount may be more than once per day, once per day, once every other day, once per week, or once every other week, or once per month. As another example, the duration of each dosage amount may be one day, two days, three days, more than three days, one week, more than one week, two weeks, more than two weeks, one month, or more than one month. For example, a dosing regimen may comprise a first dosage amount administered once a day or twice a day for about 5 weeks, and a second dosage amount administered subcutaneously once a day or twice a day for about 1 week. In some embodiments, the second dosage amount is administered the day after the duration of the first dosage amount is complete, or two days, three days, more than three days, one week, more than one week, two weeks, more than two weeks, one month, or more than one month after the first dosage amount is complete. In some embodiments, the second dosage amount is administered at least about 1 week after administration of the first dosage is complete.

[0322] In some embodiments, the non-naturally occurring melanocortin analog or a pharmaceutical composition thereof (e.g., the pharmaceutical composition) is administered at a dose of (i) 10 mg/kg once a day for 7 days, followed by (ii) 20 mg/kg once a day for 7 days, followed by (iii) 15 mg/kg twice a day for at least about 7 days. In some embodiments, (iii) is administered for at least about 7 days, at least about 14 days, or at least about 21 days.

[0323] In some embodiments, the non-naturally occurring melanocortin analog or a pharmaceutical composition thereof (e.g., the pharmaceutical composition) comprises a (i) first dose administered orally once a day or twice a day for about 5 weeks, and (ii) second dose administered subcutaneously once a day or twice a day for about 1 week. In some embodiments, the second dose is administered at least about 1 week after administration of the first dose is complete.

[0324] In some embodiments, the non-naturally occurring melanocortin analog is administered (i) at a first dose of about 5 mg/kg to about 20 mg/kg administered once a day for about 5 days to about 10 days; (ii) at a second dose of about 10 mg/kg to about 40 mg/kg administered once a day after administration of the first dose for about 5 days to about 10 days; (iii) at a third dose of about 5 mg/kg to about 30 mg/kg administered twice a day after administration of the second dose for at least about 5 days to about 10 days. In some embodiments, the third dose is administered twice a day for at least about 7 days or more.

[0325] In some embodiments, the non-naturally occurring melanocortin analog is administered (i) at a first dose of about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, or about 20 mg/kg administered once a day for about 5 days, about 6 days, about 7 days, about 8 days, about 9 days, or about 10 days; (ii) at a second dose of about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, or about 40 mg/kg administered once a day after administration of the first dose about 5 days, about 6 days, about 7 days, about 8 days, about 9 days, or about 10 days; (iii) at a third dose of about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, or about 30 mg/kg administered twice a day after administration of the second dose for at least about 5 days, about, 6 days, about 7 days, about 8 days, about 9 days, or about 10 days. In some embodiments, the third dose is administered twice a day for at least about 7 days, about 8 days, about 9 days, about 10 days, about 11 days, about 12 days, about 13 days, or about 14 days or more.

[0326] In some embodiments, the non-naturally occurring melanocortin analog is administered (i) at a first dose of about 5 mg/kg administered once a day for about 7 days; (ii) at a second dose of about 15 mg/kg administered once a day after administration of the first dose for about 7 days; (iii) at a third dose of about 10 mg/kg administered twice a day after administration of the second dose for at least about 7 days. In some embodiments, the third dose is administered twice a day for at least about 14 days or more.

[0327] In some embodiments, the non-naturally occurring melanocortin analog is administered (i) at a first dose of about 10 mg/kg administered once a day for about 7 days; (ii) at a second dose of about 20 mg/kg administered once a day after administration of the first dose for about 7 days; (iii) at a third dose of about 15 mg/kg administered twice a day

after administration of the second dose for at least about 7 days. In some embodiments, the third dose is administered twice a day for at least about 14 days or more.

[0328] In some embodiments, the non-naturally occurring melanocortin analog is administered (i) at a first dose of about 15 mg/kg administered once a day for about 7 days; (ii) at a second dose of about 25 mg/kg administered once a day after administration of the first dose for about 7 days; (iii) at a third dose of about 20 mg/kg administered twice a day after administration of the second dose for at least about 7 days. In some embodiments, the third dose is administered twice a day for at least about 14 days or more.

[0329] In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 0.1 mg to about 100 mg once daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 0.5 mg to about 75 mg once daily. In some embodiments, the non-naturally occurring melanocortin analog is administered at a dose of about 5 mg to about 60 mg once daily. In some embodiments, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 10 mg or about 50 mg once daily.

[0330] In some embodiments, the non-naturally occurring melanocortin analog is administered as a single dosage unit. In some embodiments, the non-naturally occurring melanocortin analog dose is administered as multiple dosage units. In some embodiments, the multiple dosage units individually comprise about 2.5 mg/mL to about 100 mg/mL of the non-naturally occurring melanocortin analog. In some embodiments, the multiple dosage units individually comprise about 2.5 mg/mL to about 10 mg/mL of the non-naturally occurring melanocortin analog. In some embodiments, the multiple dosage units individually comprise about 6 mg/mL of the non-naturally occurring melanocortin analog. In some embodiments, the non-naturally occurring melanocortin analog is administered as about 5 dosage units to about 10 dosage units. In some embodiments, the non-naturally occurring melanocortin analog is administered as 5 dosage units. In some embodiments, the non-naturally occurring melanocortin analog is administered as 10 dosage units.

[0331] In some embodiments, 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.

[0332] In some embodiments, the non-naturally occurring melanocortin analog is present in the pharmaceutical composition at a dose of about 5 mg to about 1000 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 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 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.

Methods

[0333] The present technology also provides methods of treating, preventing, reducing, or otherwise ameliorating one or more symptoms or conditions associated with metabolic dysfunction comprising administering a non-naturally occurring melanocortin analog to a subject in need thereof. The methods of the present technology may promote fat loss, prevent muscle loss, decrease body weight, accelerate weight loss, decrease fat mass to lean mass ratio, improve body composition and/or BMI, reduce waist circumference, or any combination thereof.

[0334] The present technology comprises methods of reducing body weight and/or fat mass in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog of the present technology to the subject.

[0335] In some embodiments, the present technology comprises methods of reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass.

[0336] In some embodiments, the present technology comprises methods of treating, preventing, reducing, or otherwise ameliorating glucose intolerance and/or diabetes mellitus in the subject.

[0337] In some embodiments, the present technology comprises a method of reducing body weight and/or fat mass in an obese subject (e.g., an obese subject without diabetes mellitus or an obese subject having diabetes mellitus), comprising administering a non-naturally occurring melanocortin analog to the subject.

[0338] In some embodiments, the methods of the present technology (i) reduce a lipid droplets size (e.g., an average lipid droplet size); (ii) increase an adipose tissue mitochondrial number or adipose tissue mitochondrial concentration; (iii) increase an adipose tissue vascularization level; (iv) increase, maintain, or prevent reduction of a beige or brown adipocyte level; (v) increase a metabolic rate; (vi) increase a calorie burn level; and/or (vii) increase, maintain, or prevent reduction of an insulin sensitivity level, relative to a control.

[0339] In some embodiments, the methods of the present technology comprise reducing a lipid droplet, or an average lipid droplet, size by about 5%, 10%, 20%, 30%, 50%, 60%, 70%, 80%, 90%, or 95%, relative to a control.

[0340] In some embodiments, the methods of the present technology comprise reducing a lipid droplet, or an average lipid droplet, size by at least 5%, 10%, 20%, 30%, 50%, 60%, 70%, 80%, 90%, or 95%, relative to a control.

[0341] In some embodiments, the methods of the present technology comprise reducing a lipid droplet, or an average lipid droplet, size by at least about 5%, 10%, 20%, 30%, 50%, 60%, 70%, 80%, 90%, or 95%, relative to a control.

[0342] In some embodiments, the methods of the present technology comprise one or more of (i) increasing an adipose tissue mitochondrial number; (ii) increasing an adipose tissue mitochondrial concentration; (iii) increasing an adipose tissue vascularization level;

increasing a beige adipocyte level; (iv) increasing a brown adipocyte level; (v) increasing a metabolic rate; (vi) increasing a calorie burn level; or (vii) increasing an insulin sensitivity level, by about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 150%, 200%, 250%, 300%, 350%, 400%, 450%, or 500% or more, relative to a control.

[0343] In some embodiments, the methods of the present technology comprise one or more of (i) increasing an adipose tissue mitochondrial number; (ii) increasing an adipose tissue mitochondrial concentration; (iii) increasing an adipose tissue vascularization level; increasing a beige adipocyte level; (iv) increasing a brown adipocyte level; (v) increasing a metabolic rate; (vi) increasing a calorie burn level; or (vii) increasing an insulin sensitivity level, by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 150%, 200%, 250%, 300%, 350%, 400%, 450%, or 500% or more, relative to a control.

[0344] In some embodiments, the methods of the present technology comprise one or more of (i) increasing an adipose tissue mitochondrial number; (ii) increasing an adipose tissue mitochondrial concentration; (iii) increasing an adipose tissue vascularization level; increasing a beige adipocyte level; (iv) increasing a brown adipocyte level; (v) increasing a metabolic rate; (vi) increasing a calorie burn level; or (vii) increasing an insulin sensitivity level, by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 150%, 200%, 250%, 300%, 350%, 400%, 450%, or 500% or more, relative to a control.

[0345] In some embodiments, the present technology comprises a method of preventing, reducing, or otherwise ameliorating hyperplasia in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject.

[0346] In some embodiments, the present technology comprises a method of preventing, reducing, or otherwise ameliorating hypothalamic obesity (e.g., congenital hypothalamic damage and/or or damage from tumors or trauma) in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject.

[0347] In some embodiments, the present technology comprises a method of preventing, reducing, or otherwise ameliorating a proopiomelanocortin (POMC) deficiency in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject.

[0348] In some embodiments, the present technology comprises a method of preventing, reducing, or otherwise ameliorating a leptin deficiency in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject.

[0349] In some embodiments, the present technology comprises a method of preventing, reducing, or otherwise ameliorating a syndromic obesity in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject. Nonlimiting examples of syndromic obesity include Prader–Willi syndrome, Wilms tumor, Aniridia, Genitourinary, Range of Developmental Delays (WAGR) syndrome, Bardet-Biedl syndrome, Fragile X syndrome, Cohen syndrome, Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1) deficiency, Alstrom syndrome, MC4 haploinsufficiency, 17p11.2 deletion syndrome, and 2q37 deletion syndrome.

[0350] In some embodiments, the present technology comprises a method of preventing, reducing, or otherwise ameliorating non-alcoholic steatohepatitis (NASH) (i.e., metabolic dysfunction-associated steatohepatitis (MASH)), in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject.

[0351] In some embodiments, the present technology comprises a method of preventing, reducing, or otherwise ameliorating hyperinsulinism in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject.

[0352] In some embodiments, the present technology comprises a method of preventing, reducing, or otherwise ameliorating Type 2 Diabetes in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject.

[0353] In some embodiments, the present technology comprises a method of preventing, reducing, or otherwise ameliorating a cardiovascular disease (e.g., stroke and/or heart attack) in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject.

[0354] In some embodiments, the present technology comprises a method of preventing, reducing, or otherwise ameliorating osteoarthritis in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject.

[0355] In some embodiments, the present technology comprises a method of preventing, reducing, or otherwise ameliorating a cancer (e.g., decreasing a risk of cancer) in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject.

[0356] In some embodiments, the present technology comprises a method of preventing, reducing, or otherwise ameliorating erectile dysfunction in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject.

[0357] In some embodiments, the method further comprises reducing obesity-related inflammation in the subject.

[0358] In some embodiments, method further comprises preserving or improving kidney function in the subject.

[0359] The present technology also provides methods of reducing obesity-related inflammation in a subject in need thereof, comprising orally administering a non-naturally occurring melanocortin analog to the subject.

[0360] The present technology further provides methods of preserving or improving kidney function in a subject in need thereof, comprising orally administering a non-naturally occurring melanocortin analog to the subject.

[0361] In some embodiments, the method comprises orally administering a non-naturally occurring melanocortin analog comprising a sequence of Formula (I) to the subject. Any of the sequences of Formula (I) listed above may be used in the methods of the present technology. In some embodiments, the method comprises orally administering a non-naturally occurring melanocortin analog comprising a sequence of Formula (IA) to the subject. Any of the sequences of Formula (IA) listed above may be used in the methods of the present technology.

[0362] The present technology also provides methods of reducing body weight and/or fat mass in a subject in need thereof, comprising orally administering about 15 mg/kg to about 100 mg/kg of a non-naturally occurring melanocortin analog to the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of

Formula (I). In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IA).

[0363] The present technology also provides methods of treating, preventing, or reducing glucose intolerance and/or diabetes mellitus in a subject in need thereof, comprising orally administering about 15 mg/kg to about 100 mg/kg of a non-naturally occurring melanocortin analog to the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (I). In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IA).

[0364] The present technology also provides methods of reducing obesity-related inflammation in a subject in need thereof, comprising orally administering about 15 mg/kg to about 100 mg/kg of a non-naturally occurring melanocortin analog to the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (I). In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IF).

[0365] The present technology also provides methods of preserving or improving kidney function in a subject in need thereof, comprising orally administering about 15 mg/kg to about 100 mg/kg of a non-naturally occurring melanocortin analog to the subject. In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (I). In some embodiments, the non-naturally occurring melanocortin analog comprises a sequence of Formula (IF).

[0366] The present technology also provides methods of reducing body weight and/or fat mass in a subject in need thereof, comprising orally administering a non-naturally occurring melanocortin analog having a sequence selected from the group consisting of SEQ ID NOs: 11, 12, and 43-45 to the subject.

[0367] In some embodiments, the method further comprises reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass.

[0368] In some embodiments, wherein the method further comprises treating, preventing, or reducing glucose intolerance and/or diabetes mellitus in the subject.

[0369] The present technology also provides methods of treating, preventing, or reducing glucose intolerance and/or diabetes mellitus in a subject in need thereof, comprising orally administering a non-naturally occurring melanocortin analog having a sequence selected from the group consisting of SEQ ID NOs: 11, 12, and 43-45 to the subject.

[0370] In some embodiments, the method further comprises reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in the subject. In some embodiments, the lean mass is lean muscle mass. In some embodiments, the method further comprises reducing body weight and/or fat mass in the subject.

[0371] In some embodiments, the method further comprises reducing obesity-related inflammation in the subject. In some embodiments, the method further comprises preserving or improving kidney function in the subject.

[0372] The present technology also provides methods of reducing obesity-related inflammation in a subject in need thereof, comprising orally administering a non-naturally occurring melanocortin analog to the subject.

[0373] The present technology also provides methods of preserving or improving kidney function in a subject in need thereof, comprising orally administering a non-naturally occurring melanocortin analog to the subject.

[0374] In some embodiments of the methods, after administration of the non-naturally occurring melanocortin analog, the subject's body weight is more than 5%, more than 10%, more than 15%, more than 20%, more than 25%, more than 30%, more than 35%, or more than 40% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog.

[0375] In some embodiments of the methods after administration of the non-naturally occurring melanocortin analog, the subject's fat mass is more than 5%, more than 10%, more than 15%, more than 20%, more than 25%, more than 30%, more than 35%, or more than 40% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog.

[0376] In some embodiments of the methods of the present technology, the subject exhibits about a 1%, about a 2%, about a 3%, about a 4%, about a 5%, about a 6%, about a 7%, about an 8%, about a 9%, or about a 10% reduction in body weight about 10 days, about 20 days, or about 30 days after administration of a first dose of a non-naturally occurring melanocortin analog of the present technology.

[0377] In some embodiments of the methods of the present technology, the subject exhibits at least a 1%, at least a 2%, at least a 3%, at least a 4%, at least a 5%, at least a 6%, at least a 7%, at least an 8%, at least a 9%, or at least a 10% reduction in body weight at least 10 days, at least 20 days, or at least 30 days after administration of a first dose of a non-naturally occurring melanocortin analog of the present technology.

[0378] In some embodiments of the methods of the present technology, the subject exhibits at least about a 1%, at least about a 2%, at least about a 3%, at least about a 4%, at least about a 5%, at least about a 6%, at least about a 7%, at least about an 8%, at least about a 9%, or at least about a 10% reduction in body weight at least about 10 days, at least about 20 days, or at least about 30 days after administration of a first dose of a non-naturally occurring melanocortin analog of the present technology.

[0379] In some embodiments of the methods of the present technology, the subject exhibits about a 1%, about a 2%, about a 3%, about a 4%, about a 5%, about a 6%, about a 7%, about an 8%, about a 9%, about a 10%, about a 12.5%, about a 15%, about a 17.5%, about a 20%, about a 25%, or about a 30% reduction in fat mass about 10 days, about 20 days, or about 30 days after administration of a first dose of a non-naturally occurring melanocortin analog of the present technology.

[0380] In some embodiments of the methods of the present technology, the subject exhibits at least a 1%, at least a 2%, at least a 3%, at least a 4%, at least a 5%, at least a 6%, at least a 7%, at least an 8%, at least a 9%, at least a 10%, at least a 12.5%, at least a 15%, at least a 17.5%, at least a 20%, at least a 25%, or at least a 30% reduction in fat mass at least 10 days, at least 20 days, or at least 30 days after administration of a first dose of a non-naturally occurring melanocortin analog of the present technology.

[0381] In some embodiments of the methods of the present technology, the subject exhibits at least about a 1%, at least about a 2%, at least about a 3%, at least about a 4%, at least about a 5%, at least about a 6%, at least about a 7%, at least about an 8%, at least about a 9%, at least about a 10%, at least about a 12.5%, at least about a 15%, at least about a 17.5%, at least about a 20%, at least about a 25%, or at least about a 30% reduction in fat mass at least about 10 days, at least about 20 days, or at least about 30 days after administration of a first dose of a non-naturally occurring melanocortin analog of the present technology.

[0382] In some embodiments of the methods of the present technology, the subject exhibits no change, about a 1%, about a 2%, about a 3%, about a 4%, about a 5%, about a 6%, about a 7%, about an 8%, about a 9%, or about a 10% reduction in lean mass loss about 10 days, about 20 days, or about 30 days after administration of a first dose of a non-naturally occurring melanocortin analog of the present technology.

[0383] In some embodiments of the methods of the present technology, the subject exhibits no change, at least a 1%, at least a 2%, at least a 3%, at least a 4%, at least a 5%, at least a 6%, at least a 7%, at least an 8%, at least a 9%, or at least a 10% reduction in lean mass loss at least 10 days, at least 20 days, or at least 30 days after administration of a first dose of a non-naturally occurring melanocortin analog of the present technology.

[0384] In some embodiments of the methods of the present technology, the subject exhibits no change, at least about a 1%, at least about a 2%, at least about a 3%, at least about a 4%, at least about a 5%, at least about a 6%, at least about a 7%, at least about an 8%, at least about a 9%, or at least about a 10% reduction in lean mass loss at least about 10 days, at least about 20 days, or at least about 30 days after administration of a first dose of a non-naturally occurring melanocortin analog of the present technology.

[0385] In some embodiments of the method of the present technology, the subject exhibits no change, about a 1%, about a 2%, about a 3%, about a 4%, about a 5%, about a 6%, about a 7%, about an 8%, about a 9%, or about a 10% increase in lean mass about 10 days, about 20 days, or about 30 days after administration of a first dose of a non-naturally occurring melanocortin analog of the present technology.

[0386] In some embodiments of the method of the present technology, the subject exhibits no change, at least a 1%, at least a 2%, at least a 3%, at least a 4%, at least a 5%, at least a 6%, at least a 7%, at least an 8%, at least a 9%, or at least a 10% increase in lean mass at least 10 days, at least 20 days, or at least 30 days after administration of a first dose of a non-naturally occurring melanocortin analog of the present technology.

[0387] In some embodiments of the method of the present technology, the subject exhibits no change, at least about a 1%, at least about a 2%, at least about a 3%, at least about a 4%, at least about a 5%, at least about a 6%, at least about a 7%, at least about an 8%, at least about a 9%, or at least about a 10% increase in lean mass at least about 10 days, at least about 20 days, or at least about 30 days after administration of a first dose of a non-naturally occurring melanocortin analog of the present technology.

[0388] In some embodiments, the subject exhibits about a 5%, about a 10%, about a 12.5%, about a 15%, about a 17.5%, about a 20%, about a 25%, about a 30%, about a 35%, about a 40%, about a 45%, about a 50%, about a 60%, or about a 70% reduction in food intake per day about 10 days, about 20 days, or about 30 days after administration of a first dose of the combination therapy. In some embodiments, the reduction in food intake occurs about 0.5 hours, about 1 hours, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 10 hours, about 12 hours, about 16 hours, about 20 hours, about 24 hours, about 36 hours, about 48 hours, about 72 hours, about 4 days, about 5 days, about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, or about 6 weeks after administration of a first dose of a non-naturally occurring melanocortin analog of the present technology.

[0389] Food intake may reflect cumulative food intake, net food intake, or both. Cumulative food intake may represent total food intake. Net food intake may represent the difference between total food intake and energy expenditure. Cumulative and net food intake may represent a food intake measurement from start to end of dosing, from start to an intermediate time point of dosing (i.e., a time point after the start of dosing but prior to the end of dosing), from an intermediate time point to end of dosing, or between two or more intermediate time points.

[0390] The methods of the present technology alter a subject's preference for food having high-fat content or low-fat content or is otherwise calorically dense or less calorically dense. In some embodiments, the methods of the present technology increase a subject's preference for one or more of a lower-fat food or a less calorically dense food relative to the food preference of the subject at baseline or of a control. In some embodiments, the methods of the present technology decrease the subject's preference for one or more of a higher-fat food or a more calorically dense food relative to the food preference of the subject at baseline or of a control.

[0391] In some embodiments of the methods of the present technology, the blood glucose level of the subject is decreased following administration of the combination therapy. In some embodiments, the blood glucose level of the subject is decreased following administration of a first dose of the combination therapy.

[0392] In some embodiments, the subject exhibits at least about a 1%, about a 2%, about a 3%, about a 4%, about a 5%, about a 6%, about a 7%, about an 8%, about a 9%, about a 10%, about a 15%, about a 20%, about a 25%, or about a 30% reduction in a blood glucose level about 1 day, 2 days, 3 days, 4 days, 8 days, 10 days, 12 days, 14 days, 20 days, or about 30 days after administration of a first dose of a non-naturally occurring melanocortin analog, relative to a control.

[0393] In some embodiments, the subject exhibits at least at least a 1%, at least a 2%, at least a 3%, at least a 4%, at least a 5%, at least a 6%, at least a 7%, at least an 8%, at least a 9%, at least a 10%, at least a 15%, at least a 20%, at least a 25%, or at least a 30% reduction in a blood glucose level at least 1 day, 2 days, 3 days, 4 days, 8 days, 10 days, 12 days, 14 days, 20 days, or at least 30 days after administration of a first dose of a non-naturally occurring melanocortin analog, relative to a control.

[0394] In some embodiments, the subject exhibits at least about at least about a 1%, at least about a 2%, at least about a 3%, at least about a 4%, at least about a 5%, at least about a 6%, at least about a 7%, at least about an 8%, at least about a 9%, at least about a 10%, at least about a 15%, at least about a 20%, at least about a 25%, or at least about a 30% reduction in a blood glucose level at least about 1 day, 2 days, 3 days, 4 days, 8 days,

10 days, 12 days, 14 days, 20 days, or at least about 30 days after administration of a first dose of a non-naturally occurring melanocortin analog, relative to a control.

[0395] In some embodiments, the subject of the methods of the present technology may experience no change in or a reduction in one or more of an alkaline phosphatase level, a total protein level, an albumin level, a globulin level, a gamma-glutamyl transferase (GGT), a glucose level, a urea nitrogen level, a creatine level, a urea acid level, or a C-reactive protein level in a biological sample from the subject. Nonlimiting examples of biological samples include a circulatory fluid sample (e.g., blood, serum, lymphatic fluid), a urine sample, or a tissue sample.

[0396] In some embodiments, the subject exhibits at least about a 1%, about a 2%, about a 3%, about a 4%, about a 5%, about a 6%, about a 7%, about an 8%, about a 9%, about a 10%, about a 15%, about a 20%, about a 25%, or about a 30% reduction in an alkaline phosphatase level, a total protein level, an albumin level, a globulin level, a GGT, a glucose level, a urea nitrogen level, a creatine level, a urea acid level, or a C-reactive protein level in the biological sample about 1 day, 2 days, 3 days, 4 days, 8 days, 10 days, 12 days, 14 days, 20 days, or about 30 days after administration of a first dose of a non-naturally occurring melanocortin analog of the present technology, relative to a control.

[0397] In some embodiments, the subject exhibits at least at least a 1%, at least a 2%, at least a 3%, at least a 4%, at least a 5%, at least a 6%, at least a 7%, at least an 8%, at least a 9%, at least a 10%, at least a 15%, at least a 20%, at least a 25%, or at least a 30% reduction in an alkaline phosphatase level, a total protein level, an albumin level, a globulin level, a GGT, a glucose level, a urea nitrogen level, a creatine level, a urea acid level, or a C-reactive protein level in the biological sample at least 1 day, 2 days, 3 days, 4 days, 8 days, 10 days, 12 days, 14 days, 20 days, or at least 30 days after administration of a first dose of a non-naturally occurring melanocortin analog of the present technology, relative to a control.

[0398] In some embodiments, the subject exhibits at least about at least about a 1%, at least about a 2%, at least about a 3%, at least about a 4%, at least about a 5%, at least about a 6%, at least about a 7%, at least about an 8%, at least about a 9%, at least about a 10%, at least about a 15%, at least about a 20%, at least about a 25%, or at least about a

30% reduction in an alkaline phosphatase level, a total protein level, an albumin level, a globulin level, a GGT, a glucose level, a urea nitrogen level, a creatine level, a urea acid level, or a C-reactive protein level in the biological sample at least about 1 day, 2 days, 3 days, 4 days, 8 days, 10 days, 12 days, 14 days, 20 days, or at least about 30 days after administration of a first dose of a non-naturally occurring melanocortin analog of the present technology, relative to a control.

[0399] In some embodiments, the subject of the methods of the present technology experiences no change or a reduction in one or more of a total white blood cell count level, a neutrophil level, a lymphocyte level, a monocyte level, an eosinophil level, a basophil level, a red cell distribution width level, a platelet count level, a mean platelet volume in a biological sample from the subject.

[0400] In some embodiments, the subject exhibits at least about a 1%, about a 2%, about a 3%, about a 4%, about a 5%, about a 6%, about a 7%, about an 8%, about a 9%, about a 10%, about a 15%, about a 20%, about a 25%, or about a 30% reduction in a total white blood cell count level, a neutrophil level, a lymphocyte level, a monocyte level, an eosinophil level, a basophil level, a red cell distribution width level, a platelet count level, a mean platelet volume in a biological sample from the subject. In some embodiments, the reduction occurs about 1 day, 2 days, 3 days, 4 days, 8 days, 10 days, 12 days, 14 days, 20 days, or about 30 days after administration of a first dose of a non-naturally occurring melanocortin analog of the present technology, relative to a control.

[0401] In some embodiments, the subject exhibits at least at least a 1%, at least a 2%, at least a 3%, at least a 4%, at least a 5%, at least a 6%, at least a 7%, at least an 8%, at least a 9%, at least a 10%, at least a 15%, at least a 20%, at least a 25%, or at least a 30% reduction in a total white blood cell count level, a neutrophil level, a lymphocyte level, a monocyte level, an eosinophil level, a basophil level, a red cell distribution width level, a platelet count level, a mean platelet volume in a biological sample from the subject. In some embodiments, the reduction occurs at least 1 day, 2 days, 3 days, 4 days, 8 days, 10 days, 12 days, 14 days, 20 days, or at least 30 days after administration of a first dose of a non-naturally occurring melanocortin analog of the present technology, relative to a control.

[0402] In some embodiments, the subject exhibits at least about at least about a 1%, at least about a 2%, at least about a 3%, at least about a 4%, at least about a 5%, at least about a 6%, at least about a 7%, at least about an 8%, at least about a 9%, at least about a 10%, at least about a 15%, at least about a 20%, at least about a 25%, or at least about a 30% reduction in a total white blood cell count level, a neutrophil level, a lymphocyte level, a monocyte level, an eosinophil level, a basophil level, a red cell distribution width level, a platelet count level, a mean platelet volume in a biological sample from the subject. In some embodiments, the reduction occurs at least about 1 day, 2 days, 3 days, 4 days, 8 days, 10 days, 12 days, 14 days, 20 days, or at least about 30 days after administration of a first dose of a non-naturally occurring melanocortin analog of the present technology, relative to a control.

[0403] In some embodiments, the subject of the methods of the present technology experiences no change or an increase in one or more of a red blood cell count, a hemoglobin level, a hematocrit level, a mean corpuscular volume level, a mean corpuscular hemoglobin level, or a mean corpuscular hemoglobin concentration level in a biological sample from the subject, relative to a control. In some embodiments, the red blood cell count, a hemoglobin level, the hematocrit level, the mean corpuscular volume level, the mean corpuscular hemoglobin level, or the mean corpuscular hemoglobin concentration level is increased in the biological sample by at least about 1%, 2%, 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 200%, or 300%, after administration of a first dose of a non-naturally occurring melanocortin analog, relative to a control.

[0404] In some embodiments, the subject of the methods of the present technology may experience no change in or an increase in an albumin to globulin ratio in a biological sample from the subject, relative to a control. In some embodiments, the albumin to globulin ratio is increased in the biological sample by at least about 1%, 2%, 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 200%, or 300%, after administration of a first dose of a non-naturally occurring melanocortin analog, relative to a control.

[0405] In some embodiments, the subject administered a non-naturally occurring melanocortin analog of the present technology exhibits one or more of:

(a) a reduction in fat mass by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, or 85% relative to baseline or a control;

(b) a reduction in epididymal fat mass at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, or 85% relative to baseline or a control;

(c) a reduction in perirenal fat mass at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, or 85% relative to baseline or a control;

(d) a reduction in body weight at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, or 85% relative to baseline or a control;

(e) a reduction in body mass at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, or 85% relative to baseline or a control;

(f) an increase in lean mass by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 150%, 200%, 250%, 300%, 400%, or 500% relative to baseline or a control;

(g) an increase in muscle mass by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 150%, 200%, 250%, 300%, 400%, or 500% relative to baseline or a control;

(h) an increase in glucose tolerance by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 150%, 200%, 250%, 300%, 400%, or 500% relative to baseline or a control;

(i) a reduction in a fat mass to lean mass ratio at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, or 85% relative to baseline or a control;

(j) a reduction in BMI by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, or 85% relative to baseline or a control;

(k) a reduction in waist circumference at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, or 85% relative to baseline or a control;

(l) a reduction in an adverse cardiovascular event by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% relative to baseline or a control;

(m) a reduction in brain mass loss by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% relative to baseline or a control;

(n) a reduction in a hemoglobin A1c level by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% relative to baseline or a control;

(o) a reduction in nausea by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% relative to baseline or a control;

(p) a reduction in vomiting by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% relative to baseline or a control;

(q) a reduction in diarrhea by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% relative to baseline or a control;

(r) a reduction in inflammation by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% relative to baseline or a control;

(s) a reduction in obesity-related inflammation by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% relative to baseline or a control;

(t) an increase in kidney function by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 150%, 200%, 250%, 300%, 400%, or 500% relative to baseline or a control;

(u) a reduction in hyperplasia by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% relative to baseline or a control;

(v) a reduction in alcohol use by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% relative to baseline or a control;

(w) a reduction in metabolic dysfunction by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% relative to baseline or a control;

(x) a reduction in a symptom associated with metabolic dysfunction by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% relative to baseline or a control;

(y) a reduction in blood sugar by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% relative to baseline or a control;

(z) a reduction in weight gain after treatment with a weight loss agent or a non-naturally occurring melanocortin analog is terminated by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% relative to baseline or a control;

(aa) a reduction in body weight measured in kg by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, or 75%, relative to baseline or a control;

(bb) a reduction in BMI by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, or 75%, relative to baseline or a control;

(cc) a reduction in trunk fat mass by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, or 75%, relative to baseline or a control;

(dd) an increase in a bone mineral content level by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 150%, 200%, or 300%, relative to baseline or a control;

(ee) an increase in a whole-body bone mineral content level by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 150%, 200%, or 300%, relative to baseline or a control;

(ff) an increase in a trunk bone mineral content level by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 150%, 200%, or 300%, relative to baseline or a control;

(gg) an increase in a bone density level by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 150%, 200%, or 300%, relative to baseline or a control;

(hh) an increase in a trunk muscle mass by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 150%, 200%, or 300%, relative to baseline or a control;

(ii) a reduction in food intake by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, or 75%, relative to baseline or a control;

(jj) a reduction in caloric intake by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, or 75%, relative to baseline or a control;

(kk) a reduction in a high-fat food intake by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, or 75%, relative to baseline or a control;

(ll) a reduction in a calorically dense food intake by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, or 75%, relative to baseline or a control;

(mm) an increase in a low-fat food intake by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, or 75%, relative to baseline or a control; or

(nn) an increase in a less calorically dense food intake by at least about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, or 75%, relative to baseline or a control.

[0406] In some embodiments, any one of (a)-(nn) is maintained for at about 2 days, 5 days, 1 week, 2 weeks, 3 weeks, 1 month, 3 months, 6 months, 1 year, or 5 years, after administration of the non-naturally occurring melanocortin analog.

[0407] In some embodiments, any one of (a)-(nn) is maintained for at least 2 days, 5 days, 1 week, 2 weeks, 3 weeks, 1 month, 3 months, 6 months, 1 year, or 5 years, after administration of the non-naturally occurring melanocortin analog.

[0408] In some embodiments, any one of (a)-(nn) is maintained for at least about 2 days, 5 days, 1 week, 2 weeks, 3 weeks, 1 month, 3 months, 6 months, 1 year, or 5 years, after administration of the non-naturally occurring melanocortin analog.

[0409] In some embodiments, any one of (a)-(nn) occurs during or after administration of a first, a second, and/or a third dose of the non-naturally occurring melanocortin analog. In some embodiments, any one of (a)-(nn) is greater during or after administration the second dose relative to during or after administration of the first dose. In some embodiments, any one of (a)-(nn) is greater during or after administration the third dose relative to during or after administration of the first dose or the second dose.

[0410] 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 or nuclear magnetic resonance (NMR).

Weight Loss Agents

[0411] Administration of the non-naturally occurring melanocortin analogs of the present technology may comprise rebound-resistant weight loss (i.e., prevention of weight gain after treatment completion) and/or increased muscle retention, relative to a control (e.g., administration of a conventional weight loss agent alone). The rebound resistant weight loss may comprise a prevention or a reduction in fat mass gain and/or BMI increase, relative to the control. In some embodiments, the non-naturally occurring melanocortin analog is administered as a combination therapy with a weight loss agent, where the combination therapy achieves the same weight loss as administration of the weight loss agent alone, but at a reduced dose or dosing frequency relative to the weight loss agent.

[0412] In some embodiments, the rebound-resistant weight loss is maintained for about 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, or 8 weeks after administration of the non-naturally occurring melanocortin analog is complete and/or discontinued.

[0413] In some embodiments, the rebound-resistant weight loss is maintained for at least 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, or 8 weeks after administration of the non-naturally occurring melanocortin analog is complete and/or discontinued.

[0414] In some embodiments, the rebound-resistant weight loss is maintained for at least about 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, or 8 weeks after administration of the non-naturally occurring melanocortin analog is complete and/or discontinued.

[0415] In other embodiments, the subject's weight increases no more than about 10%, about 9%, about 8%, about 7%, about 6%, about 5%, about 4%, about 3%, about 2%, about 1%, or less than about 1%.

[0416] In some embodiments, the present technology comprises a method of suppressing appetite in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject prior to, during, and/or after administration of the weight loss agent. Administration of the non-naturally occurring melanocortin analog prior to, during, and/or after administration of the weight loss agent may produce an additive or synergistic effect on suppressing the subject's appetite. In some embodiments, the weight loss agent is a GLP-1 receptor agonist and the non-naturally occurring melanocortin analog is a melanocortin agonist and administration of the combination therapy produces an additive effect on suppressing the subject's appetite. In some embodiments, the weight loss agent is a dual GLP-1/GIP receptor agonist and the non-naturally occurring melanocortin analog is a melanocortin agonist and administration of the combination therapy produces a synergistic effect on suppressing the subject's appetite.

[0417] In some embodiments, the method reduces food intake of the subject. Administration of the non-naturally occurring melanocortin analog prior to, during, and/or after administration of the weight loss agent may produce an additive or synergistic effect on reducing the subject's food intake. In some embodiments, the method reduces fat body mass and/or body weight of the subject. In some embodiments, the reduction in food intake is a reduction in caloric intake.

[0418] In other embodiments, the subject's weight increases no more than about 10%, about 9%, about 8%, about 7%, about 6%, about 5%, about 4%, about 3%, about 2%, about 1%, or less than about 1% at least about 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, or 8 weeks after administration of the non-naturally occurring melanocortin analog is complete and/or discontinued.

[0419] In some embodiments, the present technology comprises a method of preventing, reducing, or otherwise ameliorating body weight gain a during or after use of a weight loss in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject.

[0420] In some embodiments, the present technology comprises a method of maintaining body weight after use of a weight loss in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject.

[0421] In some embodiments, the present technology comprises a method of preventing, reducing, or otherwise ameliorating a fat mass gain after a weight loss in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject.

[0422] The methods of the present technology may decrease the risk and/or incidence of adverse cardiovascular events associated with the use of a weight loss agent including, but not limited to, cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, angina, sinus tachycardia, sinus bradycardia, coronary artery bypass grafting, percutaneous coronary intervention, heart failure, carotid endarterectomy, peripheral vascular disease, or any combination thereof.

Cardiac Effects

[0423] The methods of the present technology may prevent or decrease the risk and/or incidence of adverse cardiac effects associated with the use of conventional melanocortin analogs, melanocortin peptides, and/or melanocortin receptor agonists. In some embodiments, the subject of the present technology experiences no or substantially no adverse cardiac effects and/or no change in cardiac outcomes during or after administration of a non-naturally occurring melanocortin analog of the present technology, relative to a control (e.g., a subject administered conventional melanocortin analogs, melanocortin peptides, and/or melanocortin receptor agonists). In some embodiments, the adverse cardiac effect and/or change in cardiac outcomes comprises one or more of a change in blood pressure (e.g., systolic blood pressure, diastolic blood pressure, mean arterial blood pressure), heart rate, QT interval, QRS interval, RR interval, or QTc, relative to a control. In some embodiments, the adverse cardiac effect and/or change in cardiac outcomes is a transient change in blood pressure (e.g., systolic blood pressure, diastolic blood pressure, mean arterial blood pressure), heart rate, QT interval, QRS interval, RR interval, or QTc, relative to a control. In some embodiments, the transient change in blood pressure comprises an increase in blood pressure in the evening, at night, during a sleep cycle, or during a dark cycle after administration of the conventional melanocortin analogs, melanocortin peptides, and/or melanocortin receptor agonists.

Tanning and Hyperpigmentation

[0424] The present technology comprises a method of inducing a tanning effect in a subject during or after administration of a non-naturally occurring melanocortin analog. In some embodiments, the tanning effect comprises skin darkening without hyperpigmentation (e.g., an uneven distribution of melanin) compared to subjects who have not received the non-naturally occurring melanocortin analog or compared to the same subject at baseline (e.g., prior to receiving a dose of the non-naturally occurring melanocortin analog). In some embodiments, the tanning effect is not clinically significant, occurs in response to UV or sun exposure, and/or is not substantially ectopic. The tanning effect may occur in combination with weight loss. The weight loss may comprise a retention in muscle mass (e.g., lean muscle mass) and a loss of fat mass. In some embodiments, the tanning effect is observed about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 20 days after administration of a non-naturally occurring melanocortin analog. In some embodiments, the tanning effect occurs at a dose of greater than 100 mg or at least about 200 mg.

[0425] In some embodiments, the tanning effect is reduced after completion and/or discontinuation of the non-naturally occurring melanocortin analog dosing. In some embodiments, the tanning effect is reduced at least about 1 day, 2 days, 3 days, 4 days, 5 days, 1 week, 2 weeks, 3 week, 4 weeks, 5 weeks, 6 weeks, 8 weeks, 10 weeks, 15 weeks, or 20 weeks after completion and/or discontinuation of the non-naturally occurring melanocortin analog dosing.

[0426] In some embodiments the reduced tanning effect comprises reversal of about 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80% 90%, 95%, 99%, or 100% of the total area of skin darkening. In some embodiments, the tanning effect does not comprise ectopic skin hyperpigmentation and/or tanning effects (e.g., of the palms or gums).

[0427] In some embodiments the reduced tanning effect comprises reversal of at least 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80% 90%, 95%, 99%, or 100% of the total area of skin darkening. In some embodiments, the tanning effect does not comprise ectopic skin hyperpigmentation and/or tanning effects (e.g., of the palms or gums).

[0428] In some embodiments the reduced tanning effect comprises reversal of at least about 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80% 90%, 95%, 99%, or 100% of

the total area of skin darkening. In some embodiments, the tanning effect does not comprise ectopic skin hyperpigmentation and/or tanning effects (e.g., of the palms or gums).

[0429] The non-naturally occurring melanocortin analog may be useful in treating, preventing, or otherwise ameliorating one or more hypopigmentation diseases. Nonlimiting examples of hypopigmentation disease include albinism (e.g., oculocutaneous albinism), vitiligo, piebaldism, nevus depigmentosus, hypomelanosis of Ito, phenylketonuria, tuberous sclerosis, dyschromatosis symmetrica hereditaria, Waardenburg syndrome, Hermansky-Pudlak syndrome, Chediak-Higashi syndrome, Griscelli syndrome, and Tietz syndrome, and acquired hypopigmentary diseases such as leukoderma Sutton, Vogt-Koyanagi Harada syndrome, leukoderma senile, leukoderma after sea bathing, and leukoderma syphiliticum.

[0430] The methods of the present technology may prevent or decrease the risk and/or incidence of hyperpigmentation associated with the use of conventional melanocortin analogs, melanocortin peptides, and/or melanocortin receptor agonists. In some embodiments, the subject of the present technology experiences no or substantially no hyperpigmentation during or after administration of a non-naturally occurring melanocortin analog of the present technology, relative to a control (e.g., a subject administered conventional melanocortin analogs, melanocortin peptides, and/or melanocortin receptor agonists). In some embodiments, the hyperpigmentation comprises one or more of hyperpigmentation of the skin, nose, cheeks, or site of administration of the non-naturally occurring melanocortin analog.

Subjects

[0431] 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 20 kg/m^2. In some embodiments, the subject has a BMI of less than 18.5 kg/m^2.

[0432] In some embodiments, the subject has a BMI of greater than 24.9 kg/m^2. In some embodiments, the subject has a BMI of 25 kg/m^2 to 29.9 kg/m^2. In some embodiments, the subject has a BMI of greater than or equal to 30 kg/m^2.

[0433] In some embodiments, the subject is an overweight subject. Overweight subjects include those having a body weight about 3% or more, 5% or more, 10% or more, 20% or more, or 30% or less, than the upper end of "normal" BMI (e.g., 24.9 kg/m2).

[0434] In some embodiments, the subject is an obese subject. Obese subjects include those having a BMI of greater than or equal to 30 kg/m2.

[0435] In some embodiments, the subject has a metabolic dysfunction. In some embodiments, the metabolic dysfunction is selected from the group consisting of obesity, diabetes mellitus, metabolic syndrome, insulin resistance, non-alcoholic fatty liver disease, polycystic ovarian syndrome, metabolic acidosis, hypothyroidism, hyperlipidemia, Cushing Syndrome, and metabolic myopathies. In other embodiments, the subject has another condition which is not metabolic dysfunction, but administration of the weight loss agent provides therapeutic benefit to the non-metabolic dysfunction condition.

[0436] In some embodiments, the subject with a metabolic dysfunction has previously received treatment with the weight loss agent. A subject who has previously received treatment with the weight loss agent has completed at least one full treatment cycle with the weight loss agent. In other embodiments, the subject with a metabolic dysfunction is currently receiving treatment with the weight loss agent. A subject who is currently receiving treatment with the weight loss has received at least one dose of the weight loss agent. In still other embodiments, the subject with a metabolic dysfunction has not received any treatment with the weight loss agent. A subject who has not received any treatment with the weight loss agent has not received even a single dose of the weight loss agent.

[0437] In accordance with the present technology, a subject who has been treated with a weight loss agent has received a weight loss agent in an amount sufficient to induce at least minimum weight loss. Likewise, a subject how is currently undergoing treatment with a weight loss agent is receiving a weight loss agent in an amount sufficient to induce at least minimum weight loss.

[0438] In some embodiments, the subject has previously received treatment with the weight loss agent and has not lost body weight and/or fat mass. Alternatively, in some embodiments, the subject has previously received treatment with the weight loss agent and

has lost body weight and/or fat mass. In such embodiments, the subject may still be overweight or obese. The subject may have stopped treatment with the weight loss agent because they were unable to continue losing body weight and/or fat mass with the weight loss agent.

[0439] In embodiments in which the subject has previously received treatment with the weight loss agent, the subject's body weight may be more than 5%, more than 10%, more than 15%, more than 20%, more than 25%, more than 30%, more than 35%, or more than 40% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog.

[0440] In embodiments in which the subject has previously received treatment with the weight loss agent, the subject's fat mass may be more than 5%, more than 10%, more than 15%, more than 20%, more than 25%, more than 30%, more than 35%, or more than 40% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog.

[0441] In some embodiments, the subject is currently receiving treatment with the weight loss agent and has not lost any body weight. Alternatively, in some embodiments, the subject is currently receiving treatment with the weight loss agent and has lost body weight and/or fat mass. In some embodiments, the subject is currently receiving treatment with the weight loss agent, has lost body weight and/or fat mass, and has failed to lose sufficient body weight and/or fat mass following administration of the weight loss agent. The subject who is currently receiving treatment with the weight loss agent may still be overweight or obese.

[0442] In embodiments in which the subject is currently receiving treatment with the weight loss agent, the subject's body weight may be more than 5%, more than 10%, more than 15%, more than 20%, more than 25%, more than 30%, more than 35%, or more than 40% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog.

[0443] In embodiments in which the subject is currently receiving treatment with the weight loss agent, the subject's fat mass may be more than 5%, more than 10%, more than

15%, more than 20%, more than 25%, more than 30%, more than 35%, or more than 40% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog.

[0444] In some embodiments, the subject has not received any treatment with the weight loss agent and has failed to lose sufficient or any weight using other weight loss methods. In some embodiments, the subject has not received any treatment with the weight loss agent and has not attempted to lose weight using any other methods. In such embodiments, the subject may begin treatment with non-naturally occurring melanocortin analog and the weight loss agent at the same time. A subject who begins administration of the weight loss agent and the non-naturally occurring melanocortin analog at the same time, and continues with concurrent administration of the two therapies, may experience greater body weight and/or fat mass loss compared to a subject who is administered only one of the therapies, e.g., only the weight loss agent or only the non-naturally occurring melanocortin analog.

[0445] In embodiments in which the subject begins treatment with the non-naturally occurring melanocortin analog and the weight loss agent at the same time, the subject's body weight may be more than 10%, more than 15%, more than 20%, more than 25%, more than 30%, more than 35%, more than 40%, more than 45%, more than 50%, or more than 55% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog.

[0446] In embodiments in which the subject begins treatment with the non-naturally occurring melanocortin analog and the weight loss agent at the same time, the subject's fat mass may be more than 10%, more than 15%, more than 20%, more than 25%, more than 30%, more than 35%, more than 40%, more than 45%, more than 50%, or more than 55% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog.

[0447] In some embodiments, the method prevents or reduces muscle mass loss (e.g., involuntary muscle mass loss) in the subject. In some embodiments, the subject's muscle mass is not more than 5%, not more than 10%, not more than 15%, not more than 20%, not

more than 25%, or not more than 30% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog and/or the weight loss agent.

[0448] In some embodiments, the weight loss agent is administered to the subject for treating or preventing one of one or more metabolic dysfunctions. Nonlimiting examples of metabolic dysfunctions include obesity, diabetes mellitus, metabolic syndrome, insulin resistance, non-alcoholic fatty liver disease, polycystic ovarian syndrome, metabolic acidosis, hypothyroidism, hyperlipidemia, Cushing Syndrome, and metabolic myopathies.

[0449] The subject of the present technology may be 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.

Pharmacokinetics and Pharmacodynamics

[0450] 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.

[0451] 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

[0452] "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).

[0453] 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. In some embodiments, the reduced clearance comprises an intestinal fluid clearance, a gastric fluid clearance, a liver clearance, or a liver microsome clearance.

[0454] 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

[0455] In some embodiments, the non-naturally occurring melanocortin analogs of the present technology comprise an increased tissue, plasma, serum, or aqueous 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. The aqueous concentration may comprise an intestinal fluid concentration or a gastric fluid concentration.

[0456] 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).

[0457] 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}).

[0458] 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}).

[0459] 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.

[0460] 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.

[0461] 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).

[0462] In some embodiments, the increased concentration is reflected by a reduction in a partition coefficient or an increase in a partition coefficient, relative to a control. The reduced partition coefficient may reflect an increase in aqueous solubility (e.g., an intestinal

fluid or a gastric fluid), relative to the control. In some embodiments, the increased partition coefficient may reflect an increase in membrane permeability, relative to the control.

[0463] 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.

[0464] 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.

[0465] 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.

[0466] In some embodiments, the increase in tissue, plasma, and/or serum concentration comprises a measurement during administration of the non-naturally occurring melanocortin analogs.

[0467] 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.

[0468] In some embodiments, the concentration of the non-naturally occurring melanocortin analog in the plasma or a tissue of the subject is at least about 5 ng/mL to at least about 2000 ng/mL about 24 hours after administration of the non-naturally occurring melanocortin analog.

[0469] In some embodiments, the non-naturally occurring melanocortin analog is administered to the subject until the concentration of the non-naturally occurring

melanocortin analog in the plasma or a tissue of the subject is at least about 5 ng/mL to at least about 2000 ng/mL after administration of the non-naturally occurring melanocortin analog. In some embodiments, the concentration is at least about 5 ng/mL after administration of the non-naturally occurring melanocortin analog. In some embodiments, the concentration is at least about 10 ng/mL after administration of the non-naturally occurring melanocortin analog. In some embodiments, the concentration is at least about 50 ng/mL after administration of the non-naturally occurring melanocortin analog. In some embodiments, the concentration is at least about 100 ng/mL after administration of the non-naturally occurring melanocortin analog. In some embodiments, the concentration is at least about 200 ng/mL after administration of the non-naturally occurring melanocortin analog. In some embodiments, the concentration is at least about 300 ng/mL after administration of the non-naturally occurring melanocortin analog. In some embodiments, the concentration is at least about 400 ng/mL after administration of the non-naturally occurring melanocortin analog. In some embodiments, the concentration is at least about 500 ng/mL after administration of the non-naturally occurring melanocortin analog. In some embodiments, the wherein concentration is at least about 750 ng/mL after administration of the non-naturally occurring melanocortin analog. In some embodiments, the concentration is at least about 1000 ng/mL after administration of the non-naturally occurring melanocortin analog. In some embodiments, the is at least about 1500 ng/mL after administration of the non-naturally occurring melanocortin analog. In some embodiments, the concentration is at least about 2000 ng/mL after administration of the non-naturally occurring melanocortin analog. In some embodiments, the concentration is a C_{max}.

Distribution

[0470] 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.

[0471] In some embodiments, the measurement of distribution comprises measuring a volume of distribution at the terminal phase (V_d or $V_{d\beta}$), 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, $V_{d\beta}$, V_z, and/or V_{ss} may suggest large distribution beyond the tissue, plasma, and/or serum compartment, relative to the control.

[0472] 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.

[0473] 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.

[0474] 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.

[0475] In some embodiments, the increase in distribution comprises a measurement during administration of the non-naturally occurring melanocortin analogs.

[0476] 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

[0477] 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.

[0478] 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.

EXAMPLES

[0479] 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

[0480] The non-naturally occurring melanocortin analogs of the present technology 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.

[0481] 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.

[0482] 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.

[0483] 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.

[0484] 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 C18 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

[0485] 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.

[0486] 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.

[0487] 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

[0488] 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.

[0489] 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 (DCCl/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: Biological Data

[0490] The agonist and antagonist activity of exemplary non-naturally occurring melanocortin analogs at the melanocortin receptors (e.g., MC1R, MC3R, MC4R, and MC5R) were measured via cAMP accumulation assay, according to the following procedure. Experimental design and execution were conducted by Epics Therapeutics S.A. EuroscreenFast (Bruxelles, Belgium).

Compound Handing

[0491] Compounds were delivered as powder (1 mg) or 10 mM solutions (100 µl) in 100% DMSO. Powders were solubilized in 100% DMSO at a concentration of 10 mM (master solution) in a solvent volume defined. Serial dilutions were performed from master solution in 100% DMSO to obtain intermediate concentrations 200-, 300- or 400-fold higher than the concentrations to be tested, depending on the assay. Each sample was diluted 100-fold in the assay buffer and dispensed in a test plate. Amounts, solvents, and dilutions were estimated based on standard small-molecule drugs. Cell lines used for functional assays are shown in Table 1.

Table 1. Cell lines

Receptor	Cell Line	Reference agonist	Reference antagonist
MC1R	CHO-K1	NDP-α-MSH	N/A
MC3R	CHO-K1	NDP-α-MSH	SHU9119
MC4R	CHO-K1	NDP-α-MSH	SHU9119
MC5R	CHO-K1	NDP-α-MSH	N/A

Compound Testing

[0492] Compounds were tested for (i) agonist and/or antagonist activity at the human MC3 (FAST-0232C) and MC4 (FAST-0233C) receptors, (ii) agonist activity at the human MC1 (FAST-0230C) receptor, and/or (iii) agonist activity at the human MC5 (FAST-0233C) receptor at the following nanomolar concentrations, in duplicate: 0.0001, 0.001, 0.01, 0.03, 0.1, 0.3, 1, 10, 100, and 1,000.

Testing Protocol

[0493] Cyclic AMP (cAMP) Homogenous Time-Resolved Fluorescence (HTRF) assay for Gs coupled receptor:

[0494] CHO-K1 cells expressing recombinant human receptor grown prior to the test in media without antibiotic were detached by gentle flushing with PBS-EDTA (5 mM EDTA), recovered by centrifugation and resuspended in assay buffer (KRH: 5 mM KCl, 1.25 mM MgSO4, 124 mM NaCl, 25 mM HEPES, 13.3 mM Glucose, 1.25 mM KH2PO4, 1.45 mM CaCl2, 0.5 g/l BSA, supplemented with 1mM IBMX or 25µM Rolipram).

[0495] Dose response curves were performed in parallel with the reference compounds.

[0496] For agonist test (384well): 5 µl of cells were mixed with 5 µl of the test compound at increasing concentrations and then incubated 30 min at room temperature. After addition of the lysis buffer containing cAMP-d2 and anti-cAMP cryptate detection reagents, plates were incubated 1-hour at room temperature, and fluorescence ratios were measured according to the manufacturer specification, with the HTRF kit.

[0497] For antagonist test (384well): 5 µl of cells were mixed in the wells of an assay plate with 5 µl of a mix of test compound at increasing concentrations and reference agonist for a final concentration corresponding to the historical EC80. The plates were then incubated 30 min at room temperature. After addition of the lysis buffer containing cAMP-d2 and anti-cAMP cryptate detection reagents, plates were incubated 1-hour at room temperature, and fluorescence ratios were measured according to the manufacturer specification, with the HTRF kit.

Quality Control for Compound Testing

[0498] On each day of experimentation and prior to the testing of compounds, reference compounds were tested at several concentrations in duplicate (n=2) to obtain a dose-response curve and an estimated EC50 and/or IC50 values.

[0499] Reference values thus obtained for the test were compared to historical values obtained from the same receptor and used to validate the experimental session.

[0500] A session was considered as valid only if the reference value was found to be within a 0.5 logs interval from the historical value.

[0501] For replicate determinations, the maximum variability tolerated in the test was of +/-20% around the average of the replicates.

Non-naturally occurring melanocortin analog grouping

[0502] Group A included non-naturally occurring melanocortin analogs A1 to A4, all of which are cyclic peptides comprising the motif c[Asp-His-p(F)dPhe-Arg-Trp-Lys] (SEQ ID NO: 161). Group A melanocortin analogs also comprise Ala or dArg at the N-terminus and dVal-dPro or dTle-dPro at the C-terminus. Group A non-naturally occurring melanocortin analogs are provided in Table 2.

Table 2. Group A non-naturally occurring melanocortin analogs

Melanocortin analog	SEQ ID NO	Formula
A1	3	Ac-Ala-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2
A2	4	Ac-dArg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2
A3	7	Ac-Ala-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2
A4	8	Ac-dArg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2

[0503] Group B included non-naturally occurring melanocortin analogs B1 to B10, all of which are cyclic peptides comprising the motif c[Asp-His-p(F)dPhe-Arg-Trp-Lys] (SEQ ID NO: 161). Group B melanocortin analogs also comprise Arg, Lys, dLys, His, or dHis at the N-terminus and dVal-dPro or dTle-dPro at the C-terminus. Group B non-naturally occurring melanocortin analogs are provided in Table 3.

Table 3. Group B non-naturally occurring melanocortin analogs

Melanocortin analog	SEQ ID NO	Formula
B1	15	Ac-Arg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2
B2	16	Ac-Lys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2
B3	17	Ac-dLys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2
B4	18	Ac-His-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2
B5	19	Ac-dHis-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2
B6	27	Ac-Arg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2
B7	28	Ac-Lys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2
B8	29	Ac-dLys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2
B9	30	Ac-His-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2
B10	31	Ac-dHis-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2

[0504] Group C included non-naturally occurring melanocortin analogs C1 to C4, all of which are cyclic peptides comprising the motif c[Asp-His-p(F)dPhe-Arg-Trp-Lys] (SEQ ID NO: 161). Group C melanocortin analogs also comprise Nle at the N-terminus. Group C non-naturally occurring melanocortin analogs are provided in Table 4.

Table 4. Group C non-naturally occurring melanocortin analogs

Melanocortin analog	SEQ ID NO	Formula
C1	6	Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH_2
C2	14	Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2
C3	20	Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2
C4	22	Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dVal-dVal-dPro-NH_2
C5	23	Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH_2
C6	24	Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2
C7	25	Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2
C8	26	Ac-Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH_2

[0505] Group D included non-naturally occurring melanocortin analogs D1 to D4, all of which are cyclic peptides comprising a derivative of the motif c[Asp-His-p(F)dPhe-Arg-Trp-Lys] (SEQ ID NO: 161). Derivatives of the motif of SEQ ID NO: 161 may include substitution of His with another amino acid, for example, Gln or dHis, substitution of Arg with another amino acid, for example, His, or substitution of Trp with another amino acid, for example, dNal(2'). Group D non-naturally occurring melanocortin analogs are provided in Table 5.

Table 5. Group D non-naturally occurring melanocortin analogs

Melanocortin analog	SEQ ID NO	Formula
D1	5	Ac-Nle-c[Asp-His-p(F)dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH_2
D2	9	Ac-Nle-c[Asp-Gln-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2
D3	21	Ac-Nle-c[Asp-His-p(F)dPhe-His-Trp-Lys]-dVal-dPro-NH_2
D4	32	Ac-Nle-c[Asp-dHis-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2

[0506] Group E included non-naturally occurring melanocortin analogs E1 to E4, all of which are cyclic peptides comprising the motif c[Asp-His-dPhe-Arg-Trp-Lys] (SEQ ID NO: 164) or a derivative thereof. Derivatives of the motif of SEQ ID NO: 164 included in Group E melanocortin analogs include insertions of a Pro between Asp and His or between Trp and Lys. Group E non-naturally occurring melanocortin analogs are provided in Table 6.

Table 6. Group E non-naturally occurring melanocortin analogs

Melanocortin analog	SEQ ID NO	Formula
E1	33	Ac-Nle-c[Asp-His-dPhe-Arg-Trp-Lys]-dPro-dVal-NH_2
E2	13	Ac-Nle-c[Asp-Pro-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2
E3	35	Ac-Nle-c[Asp-His-dPhe-Arg-Trp-Pro-Lys]-dVal-dPro-NH_2
E4	42	Ac-Nle-c[Asp-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2

[0507] Group F included non-naturally occurring melanocortin analogs F1 to F4, all of which are cyclic peptides comprising a derivative of the motif c[Asp-His-dPhe-Arg-Trp-Lys] (SEQ ID NO: 164). Derivatives of the motif of SEQ ID NO: 164 may include substitution of His with another amino acid, for example, Gln, Pro or dHis, or substitution of Arg with another

amino acid, for example, *cis*Pro(guan) or *trans*Pro(guan). Group F non-naturally occurring melanocortin analogs are provided in Table 7.

Table 7. Group F non-naturally occurring melanocortin analogs

Melanocortin analog	SEQ ID NO	Formula
F1	10	Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH_2
F2	36	Ac-Nle-c[Asp-dHis-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2
F3	37	Ac-Nle-c[Asp-Gln-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2
F4	46	Ac-Nle-c[Asp-His-dPhe-*trans*Pro(guan)-Trp-Lys]-dVal-dPro-NH_2
F5	47	Ac-Nle-c[Asp-His-dPhe-*cis*Pro(guan)-Trp-Lys]-dVal-dPro-NH_2

[0508] Group G included non-naturally occurring melanocortin analogs G1, which is a cyclic peptide comprising a derivative of the motif c[Asp-His-dPhe-Arg-Trp-Lys] (SEQ ID NO: 164). The derivative of the motif of SEQ ID NO: 164 included in the Group G melanocortin analog includes at least one insertion between Asp and His. The Group G non-naturally occurring melanocortin analog is provided in Table 8.

Table 8. Group G non-naturally occurring melanocortin analog

Melanocortin analog	SEQ ID NO	Formula
G1	34	Ac-Nle-c[Asp-Phe-Phe-Pro-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2

[0509] Group H included non-naturally occurring melanocortin analogs H1 to H4, all of which are cyclic peptides comprising the motif dAla-His-dPhe-Arg-Trp (SEQ ID NO: 163), or a derivative thereof. Derivatives of the motif of SEQ ID NO: 163 may include substitution of dAla with a similar amino acid, for example, Ala. Group H non-naturally occurring melanocortin analogs are provided in Table 9.

Table 9. Group H non-naturally occurring melanocortin analogs

Melanocortin analog	SEQ ID NO	Formula
H1	38	Ac-Nle-c[Asp-dAla-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2
H2	39	Ac-Arg-c[Asp-dAla-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2

H3	40	Ac-dArg-c[Asp-dAla-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2
H4	41	Ac-Nle-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2

[0510] Group I included non-naturally occurring melanocortin analogs I1 to I3, all of which are cyclic peptides comprising the motif His-p(Cl)dPhe-Arg-Trp (SEQ ID NO: 165). Group I melanocortin analogs also comprise Nle at the N-terminus. Group I non-naturally occurring melanocortin analogs are provided in Table 10.

Table 10. Group I non-naturally occurring melanocortin analogs

Melanocortin analog	SEQ ID NO	Formula
H1	2	Ac-Nle-c[dCys-His-p(Cl)dPhe-Arg-Trp-Cys]-dVal-dPro-NH_2
H2	11	Ac-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2
H3	12	Ac-Nle-c[Glu-His-p(Cl)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2

[0511] Group O included non-naturally occurring melanocortin analogs O1, O5, and O10, all of which are cyclic peptides comprising the motif His-p(F)dPhe-Arg-Trp-Orn (SEQ ID NO: 162), or a derivative thereof. Derivatives of SEQ ID NO: 162 may include substitution of Arg with a similar amino acid, for example, His. Group O non-naturally occurring melanocortin analogs are provided in Table 11.

Table 11. Group O non-naturally occurring melanocortin analogs

Melanocortin analog	SEQ ID NO	Formula
O1	45	Ac-Nle-c[Glu-His-dPhe-His-Trp-Orn]-dVal-dPro-NH_2
O5	44	Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2
O10	43	Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2

Agonist activity of melanocortin analogs on melanocortin 1 receptor and melanocortin 5 receptor

[0512] Administration of some non-naturally occurring melanocortin analogs activated melanocortin 1 receptor (MC1R) and melanocortin 5 receptor (MC5R) activity, as measured by cAMP levels (Table 12).

Table 12. Dose-response results of melanocortin analogs and control against the melanocortin 1 receptor (MC1R) and the melanocortin 5 receptor

SEQ ID NO	Compound ID	MC1R		MC5R	
		EC50 (nM)	Max Activation (Emax)	EC50 (nM)	Max Activation (Emax)
	NDP-a-MSH	0.39	101.06	0.12	101.44
45	O1	0.02	101.40	0.47	100.51
42	E4	0.02	101.95	0.45	100.19
36	F2	4.48	103.24	23.35	100.71
37	F3	0.01	102.70	0.02	104.56
38	H1	0.01	101.61	15.80	102.64
39	H2	0.06	102.19	659.75	100.00
40	H3	0.12	103.00	625.61	100.00
41	H4	0.24	101.52	572.13	100.00
35	E3	0.03	101.98	154.52	98.73
34	G1	0.59	102.19	504.39	100.00
3	A1	0.02	101.59	0.83	101.07
4	A2	0.01	100.72	1.67	101.64
15	B1	0.01	100.40	0.81	103.20
16	B2	0.01	100.35	0.95	101.71
17	B3	0.02	101.08	3.70	101.05
18	B4	0.03	100.11	3.04	102.66
19	B5	0.04	101.92	8.83	102.60
20	C3	0.01	101.68	0.01	103.49
21	D3	0.07	102.90	0.44	102.60
5	D1	0.01	101.22	0.10	99.79
6	C1	0.11	103.79	1.01	102.62
22	C4	0.01	104.17	0.20	101.71

23	C5	0.01	102.78	0.41	101.46
24	C6	0.00	99.42	0.02	102.04
25	C7	0.01	104.93	0.02	102.90
26	C8	0.01	104.27	0.40	101.87
7	A3	0.01	104.22	1.01	102.27
8	A4	0.00	104.33	1.28	104.22
27	B6	0.01	104.99	0.64	101.02
28	B7	0.00	104.19	1.19	103.47
29	B8	0.02	106.13	4.10	102.13
30	B9	0.01	104.45	1.80	101.83
31	B10	0.01	105.28	4.16	100.50
32	D4	0.89	102.45	6.01	97.19
9	D2	0.03	103.05	0.05	103.74
2	H1	0.14	103.43	0.15	103.18
11	H2	0.00	101.21	0.01	101.90
44	O5	0.01	101.43	0.04	102.82
12	H3	0.00	99.70	0.01	102.94
43	O10	0.00	102.27	0.01	103.60
33	E1	0.01	101.15	0.91	99.10
10	F1	0.37	103.99	0.29	103.67
14	C2	0.01	100.02	0.06	101.26

Agonist activity of melanocortin analogs on melanocortin 3 receptor and melanocortin 4 receptor

[0513] Administration of all the non-naturally occurring melanocortin analogs activated melanocortin 3 receptor (MC3R) and melanocortin 4 receptor (MC4R) activity, as measured by cAMP levels (Table 13).

Table 13. Dose-response results of melanocortin analogs and control against the melanocortin 3 receptor (MC3R) and melanocortin 4 receptor (MC4R) in agonist mode

SEQ ID NO	Compound ID	MC3R		MC4R	
		EC50 (nM)	Max Activation (Emax)	EC50 (nM)	Max Activation (Emax)
	NDP-a-MSH	0.17	106.05	0.07	103.19
45	O1	0.40	99.20	0.57	100.60
42	E4	0.73	92.20	0.67	101.05
36	F2	81.32	89.56	7.84	111.15
37	F3	0.58	95.01	0.03	104.98
38	H1	9.24	95.77	0.50	99.72
39	H2	30.14	92.58	2.89	101.65
40	H3	84.48	88.91	6.50	99.28
41	H4	220.55	100.00	21.14	101.12
35	E3	506.44	97.17	70.13	100.00
34	G1	169.79	100.16	28.96	100.41
3	A1	2.76	74.68	0.26	99.57
4	A2	2.34	79.03	0.13	99.87
15	B1	0.35	93.45	0.05	100.50
16	B2	0.56	96.34	0.11	100.53
17	B3	5.73	87.71	0.25	100.00
18	B4	2.62	94.55	0.18	100.08
19	B5	5.37	89.51	0.33	100.20
20	C3	0.24	88.43	0.29	101.14
21	D3	2.84	85.73	3.19	100.09
5	D1	1.55	69.22	0.64	96.25
6	C1	3.61	83.65	5.34	100.64
22	C4	0.49	89.54	0.57	100.46
23	C5	1.23	90.14	0.38	100.18

24	C6	0.33	87.59	0.24	100.29
25	C7	0.36	88.52	0.33	99.69
26	C8	0.94	89.45	0.55	100.36
7	A3	3.59	70.53	0.38	99.13
8	A4	4.37	84.38	0.22	100.00
27	B6	0.66	93.72	0.08	100.18
28	B7	1.15	95.32	0.19	99.83
29	B8	6.90	87.63	0.39	100.00
30	B9	4.95	92.62	0.34	99.87
31	B10	5.82	92.54	0.37	99.44
32	D4	329.06	100.00	47.51	101.64
9	D2	5.72	76.99	0.77	99.71
2	H1	46.67	26.32	1.44	99.21
11	H2	0.04	73.36	0.05	98.36
44	O5	0.03	101.64	0.00	103.23
12	H3	0.03	75.99	0.02	96.79
43	O10	0.06	97.30	0.03	101.25
33	E1	4.00	95.75	0.19	100.59
10	F1	450.91	81.01	0.17	101.59
14	C2	0.11	93.66	0.05	101.94

Antagonist activity of melanocortin analogs on melanocortin 3 receptor and melanocortin 4 receptor

[0514] Administration of none of the non-naturally occurring melanocortin analogs substantially inhibited melanocortin 3 receptor (MC3R) and melanocortin 4 receptor (MC4R) activity, as measured by cAMP levels (Table 14).

Table 14. Dose-response results of melanocortin analogs and control against the melanocortin 3 receptor (MC3R) and melanocortin 4 receptor (MC4R) in antagonist mode

SEQ ID NO	Compound ID	MC3R		MC4R	
		EC50 (nM)	Max Activation (Emax)	EC50 (nM)	Max Activation (Emax)
	SHU9119	2.34	97.24	2.56	98.58
45	O1	>1000	nd	>1000	nd
42	E4	>1000	nd	>1000	nd
36	F2	>1000	nd	>1000	nd
37	F3	>1000	nd	>1000	nd
38	H1	>1000	nd	>1000	nd
39	H2	>1000	nd	>1000	nd
40	H3	>1000	nd	>1000	nd
41	H4	>1000	nd	>1000	nd
35	E3	>1000	nd	>1000	nd
34	G1	>1000	nd	>1000	nd
3	A1	>1000	nd	>1000	nd
4	A2	>1000	nd	>1000	nd
15	B1	>1000	nd	>1000	nd
16	B2	>1000	nd	>1000	nd
17	B3	>1000	nd	>1000	nd
18	B4	>1000	nd	>1000	nd
19	B5	>1000	nd	>1000	nd
20	C3	>1000	nd	>1000	nd
21	D3	>1000	nd	>1000	nd
5	D1	>1000	nd	>1000	nd
6	C1	>1000	nd	>1000	nd
22	C4	>1000	nd	>1000	nd
23	C5	>1000	nd	>1000	nd

24	C6	>1000	nd	>1000	nd
25	C7	>1000	nd	>1000	nd
26	C8	>1000	nd	>1000	nd
7	A3	>1000	nd	>1000	nd
8	A4	>1000	nd	>1000	nd
27	B6	>1000	nd	>1000	nd
28	B7	>1000	nd	>1000	nd
29	B8	>1000	nd	>1000	nd
30	B9	>1000	nd	>1000	nd
31	B10	>1000	nd	>1000	nd
32	D4	>1000	nd	>1000	nd
9	D2	>1000	nd	>1000	nd
2	H1	>1000	nd	>1000	nd
11	H2	1.29	35	>1000	nd
44	O5	>1000	nd	>1000	nd
12	H3	0.51	40	>1000	nd
43	O10	>1000	4	>1000	nd
33	E1	>1000	nd	>1000	nd
10	F1	>1000	nd	>1000	nd
14	C2	>1000	nd	>1000	nd

nd = not determined

Comparison of agonist activity of O10 and similar melanocortin analogs

[0515] To determine the impact that certain features of the melanocortin analogs of the present technology had on agonist activity at the different melanocortin receptors, the agonist activity of O10 was compared to the agonist activity of similar sequences. Specifically, O10 was compared to sequences with different lactam cyclization types, different residues at the R^4 and R^3 positions, and different C-terminal residues. The agonist activity of O10 and comparative sequences is provided in Table 15, below.

Table 15. Agonist activity of O10 and melanocortin analogs with point mutations relative to O10

Feature	Sequence	SEQ ID NO	MC3R		MC4R	
			EC50 (nM)	Max Activation	EC50 (nM)	Max Activation
O10	Ac-Nle-[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH2	43	0.058	97	0.032	101
Linkage	Ac-Nle-[Orn-His-p(F)dPhe-Arg-Trp-Glu]-dVal-dPro-NH2	166	0.051	94	0.031	102
	Ac-Nle-[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH2	14	0.106	94	0.047	102
	Ac-Nle-[Lys-His-p(F)dPhe-Arg-Trp-Asp]-dVal-dPro-NH2	167	0.047	100	0.021	101
	Ac-Nle-[Asp-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH2	44	0.026	102	0.004	103
	Ac-Nle-[Glu-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH2	168	0.077	97	0.042	102
R^4	Ac-Nle-[Glu-His-p(Cl)dPhe-Arg-Trp-Orn]-dVal-dPro-NH2	12	0.029	76	0.017	97
	Ac-Nle-[Glu-His-p(Br)dPhe-Arg-Trp-Orn]-dVal-dPro-NH2	170	0.062	49	0.079	72
	Ac-Nle-[Glu-His-dPhe-Arg-Trp-Orn]-dVal-dPro-NH2	169	0.041	100	0.024	102
	Ac-Nle-[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH2	147	0.220	43	0.609	75
	Ac-Nle-[Asp-His-p(Br)dPhe-Arg-Trp-Lys]-dVal-dPro-NH2	171	291.19	28	1.00	37
	Ac-Nle-[Asp-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH2	42	0.728	92	0.675	101
R^3	Ac-Nle-[Glu-Pro-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH2	106	130.896	25	0.351	91
	Ac-Nle-[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH2	99	0.890	28	0.256	92
C-terminus	Ac-Nle-[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH2	7	0.330	88	0.236	100

[0516] As shown in Table 15, the specific cyclization residues have a minor effect on agonist activity, when the His-p(F)dPhe-Arg-Trp (SEQ ID NO: 162) is conserved. On the other hand, a substantial change in agonist activity on the MC3 receptor was observed when His was substituted for Pro (e.g., SEQ ID NO: 43 vs. SEQ ID NOs: 99 and 106). Additionally, substitution of the smaller p(F)dPhe residue with a larger p(Br)dPhe residue resulted in substantially decreased activation and potency on both MC3R and MC4R (e.g., SEQ ID NO: 43 vs. SEQ ID NO: 171).

Residual binding of melanocortin analogs on melanocortin 1 receptor

[0517] The residual binding of some of the non-naturally occurring melanocortin analogs was measured on the melanocortin 1 receptor (MC1R) by RLB assay. Among the non-naturally occurring melanocortin analogs, O10 had the lowest EC_{50} value at 0.19 nM (Table 16).

Table 16. Dose-response binding results of melanocortin analogs and control against the melanocortin 1 receptor (MC1R)

Synthetic Peptide	**Max Residual Binding %**	**EC_{50} (nM)***	**Hill Coefficient**	**Top (%)**
NDP-a-MSH	99.06	0.85	-1.23	-2.35
C2	102.29	0.44	-0.92	0.33
O10	107.33	0.19	-0.89	-2.20

Residual binding of melanocortin analogs on melanocortin 3 receptor

[0518] The residual binding of some of the non-naturally occurring melanocortin analogs was measured on the melanocortin 3 receptor (MC3R) by RLB assay (Table 17).

Table 17. Dose-response binding results of melanocortin analogs and control against the melanocortin 3 receptor (MC3R)

Synthetic Peptide	**Max Residual Binding %**	**EC_{50} (nM)***	**Hill Coefficient**	**Top (%)**
NDP-a-MSH	100.61	1.34	-0.87	-1.08
C2	106.03	1.99	-0.93	4.26
O10	103.74	0.64	-1.12	-0.59

Residual binding of melanocortin analogs on melanocortin 4 receptor

[0519] The residual binding of some of the non-naturally occurring melanocortin analogs was measured on the melanocortin 4 receptor (MC4R) by RLB assay. Among the non-naturally occurring melanocortin analogs, O10 had the lowest EC_{50} value at 0.23 nM, respectively (Table 18).

Table 18. Dose-response binding results of melanocortin analogs and control against the melanocortin 4 receptor (MC4R)

Synthetic Peptide	**Max Residual Binding %**	**EC_{50} (nM)***	**Hill Coefficient**	**Top (%)**
NDP-a-MSH	95.89	1.07	-1.37	1.61
C2	103.32	0.53	-1.17	0.82
O10	97.31	0.23	-1.22	1.24

Residual binding of melanocortin analogs on melanocortin 5 receptor

[0520] The residual binding of some of the non-naturally occurring melanocortin analogs was measured on the melanocortin 5 receptor (MC5R) by RLB assay. Among the non-naturally occurring melanocortin analogs, O10 had the lowest EC_{50} value at 0.19 nM (Table 19).

Table 19. Dose-response binding results of melanocortin analogs and control against the melanocortin 5 receptor (MC5R)

Synthetic Peptide	**Max Residual Binding %**	**EC_{50} (nM)***	**Hill Coefficient**	**Top (%)**
NDP-a-MSH	103.88	2.07	-1.36	2.39
C2	115.62	4.31	-1.07	0.25
O10	101.15	1.52	-0.94	-1.74

Agonist activity on GPR54

[0521] The agonist activity of some of the non-naturally occurring melanocortin analogs was measured on GPR54 by Aequorin assay. Results from this assay are provided in Table 20.

Table 20. Dose-response results of melanocortin analogs and control against GPR54

Synthetic Peptide	**Max Activation %**	**EC_{50} (nM)***	**Hill Coefficient**	**Top (%)**
Kisspeptin	105.10	6.43	1.60	99.83
LY2112688 trifluoroacetate	1.75	>2000	-	-
O10	0.41	>2000	-	-

Antagonist activity on GPR54

[0522] The antagonist activity of some of the non-naturally occurring melanocortin analogs was measured on GPR54 by Aequorin assay. Results from this assay are provided in Table 21.

Table 21. Dose-response results of melanocortin analogs and control against GPR54

Synthetic Peptide	**Max Inhibition %**	**IC_{50} (nM)***	**Hill Coefficient**	**Top (%)**
LY2112688 trifluoroacetate	6.38	>1000	-	-
O10	4.98	>1000	-	-

Agonist activity on QRFP

[0523] The agonist activity of some of the non-naturally occurring melanocortin analogs was measured on QRFP by Aequorin assay. Results from this assay are provided in Table 22.

Table 22. Dose-response results of melanocortin analogs and control against QRFP

Synthetic Peptide	**Max Activation %**	**EC_{50} (nM)***	**Hill Coefficient**	**Top (%)**
P518	105.91	1.44	1.99	100.33
LY2112688 trifluoroacetate	0.80	>2000	-	-
O10	1.88	>2000	-	-

Antagonist activity on QRFP

[0524] The antagonist activity of some of the non-naturally occurring melanocortin analogs was measured on QRFP by Aequorin assay. Results from this assay are provided in Table 23.

Table 23. Dose-response results of melanocortin analogs and control against QRFP

Synthetic Peptide	**Max Inhibition %**	**IC_{50} (nM)***	**Hill Coefficient**	**Top (%)**
LY2112688 trifluoroacetate	25.70	>1000	-	-
O10	17.74	>1000	-	-

Agonist activity on PrRP

[0525] The agonist activity of some of the non-naturally occurring melanocortin analogs was measured on PrRP by Aequorin assay. Results from this assay are provided in Table 24.

Table 24. Dose-response results of melanocortin analogs and control against PrRP

Synthetic Peptide	**Max Activation %**	**EC_{50} (nM)***	**Hill Coefficient**	**Top (%)**
PrRP 31	112.19	0.33	2.11	104.34
LY2112688 trifluoroacetate	2.33	>2000	-	-
O10	0.46	>2000	-	-

Antagonist activity on PrRP

[0526] The antagonist activity of some of the non-naturally occurring melanocortin analogs was measured on PrRP by Aequorin assay. Results from this assay are provided in Table 25.

Table 25. Dose-response results of melanocortin analogs and control against PrRP

Synthetic Peptide	Max Inhibition %	IC_{50} (nM)*	Hill Coefficient	Top (%)
LY2112688 trifluoroacetate	17.52	>1000	-	-
O10	3.66	>1000	-	-

Agonist activity on NPFF2S

[0527] The agonist activity of some of the non-naturally occurring melanocortin analogs was measured on NPFF2S by Aequorin assay. Results from this assay are provided in Table 26.

Table 26. Dose-response results of melanocortin analogs and control against NPFF2S

Synthetic Peptide	Max Activation %	EC_{50} (nM)*	Hill Coefficient	Top (%)
hNPFF	101.15	0.033	1.45	95.41
LY2112688 trifluoroacetate	0.23	>2000	-	-
O10	0.27	>2000	-	-

Antagonist activity on NPFF2S

[0528] The antagonist activity of some of the non-naturally occurring melanocortin analogs was measured on NPFF2S by Aequorin assay. Results from this assay are provided in Table 27.

Table 27. Dose-response results of melanocortin analogs and control against NPFF2S

Synthetic Peptide	Max Inhibition %	IC_{50} (nM)*	Hill Coefficient	Top (%)
LY2112688 trifluoroacetate	17.01	>1000	-	-
O10	17.51	>1000	-	-

Agonist activity on NPY1

[0529] The agonist activity of some of the non-naturally occurring melanocortin analogs was measured on NPY1 by cAMP assay. Results from this assay are provided in Table 28.

Table 28. Dose-response results of melanocortin analogs and control against NPY1

Synthetic Peptide	**Max Activation %**	**EC_{50} (nM)***	**Hill Coefficient**	**Top (%)**
NPY	99.68	9.42	1.26	101.45
O10	1.45	>1000	-	-

Antagonist activity on NPY1

[0530] The antagonist activity of some of the non-naturally occurring melanocortin analogs was measured on NPY1 by cAMP assay. Results from this assay are provided in Table 29.

Table 29. Dose-response results of melanocortin analogs and control against NPY1

Synthetic Peptide	**Max Inhibition %**	**IC_{50} (nM)***	**Hill Coefficient**	**Top (%)**
BVD10	98.1	22.9	0.86	100.72
O10	23.78	>1000	-	-

Agonist activity on NPFF1

[0531] The agonist activity of some of the non-naturally occurring melanocortin analogs was measured on NPFF1 by cAMP assay. Results from this assay are provided in Table 30.

Table 30. Dose-response results of melanocortin analogs and control against NPFF1

Synthetic Peptide	**Max Activation %**	**EC_{50} (nM)***	**Hill Coefficient**	**Top (%)**
hNPFF	91.83	108	0.81	91.52
O10	5.73	>1000	-	-

Antagonist activity on NPFF1

[0532] The antagonist activity of some of the non-naturally occurring melanocortin analogs was measured on NPFF1 by cAMP assay. Results from this assay are provided in Table 31.

Table 31. Dose-response results of melanocortin analogs and control against NPFF1

Synthetic Peptide	Max Inhibition %	IC_{50} (nM)*	Hill Coefficient	Top (%)
O10	12.89	>1000	-	-

Example 5: Pharmacokinetic Assessment of Non-Naturally Occurring Melanocortin Analogs Following Oral Administration to Rats and Cynomolgus Monkeys

Study Objective

[0533] The objective of this study is to determine the pharmacokinetics of non-naturally occurring melanocortin analogs of the present technology following oral gavage administration in male rats and single oral administration to non-naïve male cynomolgus monkeys. In rats, the test article will be monitored in plasma for up to 24 hours post each dose. Study design and sample collection will be conducted as outlined in Table 32 and Table 33.

Table 32. Study Design

Animal	N	Compound	Compound Formula	Target Dose Level (mg/kg)	Target Dose Volume (mL/kg)	Target Dose Concen-tration (mg/mL)	Vehicle	Dose Route
Cynomolgus Monkey	3	C	C2	30	5	6	physiological saline	Oral
Cynomolgus Monkey	3	E	O10	10	5	2	physiological saline	PO

Cynomolgus Monkey	3	E	O10	30	5	6	physiological saline	PO
Rat	3	C	C2	15	10	1.5	physiological saline	PO
Rat	3	C	C2	30	10	3	physiological saline	PO
Rat	3	C	C2	60	10	6	physiological saline	PO
Rat	3	E	O10	1	1	1	physiological saline	SC
Rat	3	E	O10	3	1	3	physiological saline	SC
Rat	3	E	O10	10	1	10	physiological saline	SC
Rat	3	E	O10	1	1	1	physiological saline	IP
Rat	3	E	O10	3	1	3	physiological saline	IP
Rat	3	E	O10	10	1	10	physiological saline	IP
Rat	3	E	O10	10	10	1	physiological saline	PO
Rat	3	E	O10	30	10	3	physiological saline	PO
Rat	3	E	O10	60	10	6	physiological saline	PO

Table 33. Sample Collections

Group	Dosage	Sampling time points (hr)								
	(mg/kg)	0.083	0.25	0.5	1	2	4	6	8	24
Cynomolgus Monkey	10	P	P	P	P	P	P	P	P	P
Cynomolgus Monkey	30	P	P	P	P	P	P	P	P	P
Rat	1	P/C*	P/C*	P/C*	P	P	P	P	P	P
Rat	3	P	P	P	P	P	P	P	P	P
Rat	10	P	P	P	P	P	P	P	P	P/C*
Rat	15	P	P	P	P	P	P	P	P	P
Rat	30	P	P	P	P	P	P	P	P	P
Rat	60	P	P	P	P	P	P	P	P	P

E: Anticoagulant: Potassium (K_2) EDTA;

P: plasma

C: cerebrospinal fluid

*Sampled only for certain compounds

[0534] Dose Solution Analysis Samples: After each dose preparation, remove approximately 0.5 mL aliquots from the formulations, transfer the aliquots into amber HPLC vials and stored at -60°C or lower until assayed in duplicate for dose validation.

[0535] Disposition of Remaining Test Article Formulations: Remaining formulations will be stored at -60°C or lower.

[0536] Disposition of Remaining Test Article (dry powder or solid): Remaining test article will be stored at room temperature desiccated, and protected from light until shipment or discard.

[0537] Animals will be fasted overnight through 4 hours post dosing.

Vehicle and Formulation Preparation:

[0538] Appropriate amount of test article will be accurately weighed and mixed with appropriate volume of vehicle to get a clear solution or suspension.

[0539] Formulation samples will be removed from each of the formulation solutions, transferred into 1.5 mL of polypropylene microcentrifuge tubes and run dose validation by LC/UV or LC-MS/MS.

[0540] Compounds to be assessed are outlined in Table 34.

Table 34. Compounds

Compound ID	Animal Group	MW (g/mol)	FW (g/mol)	Exact Mass	Purity (%)	CF	Storage Condition
C (C2)	Rats	1238.44	1297.67	N/A	98	N/A	-20°C
E (O10)	Rats	1238.44	1358.54	N/A	99.1	N/A	N/A
C (C2)	Cynomolgus Monkeys	1238.44	1298.49	N/A	95	N/A	-20°C
E (O10)	Cynomolgus Monkeys	1238.44	1358.54	N/A	99.1	N/A	N/A

CF: FW/MW/purity

Animal Specifications: Cynomolgus Monkeys

[0541] Cynomolgus Monkey specifications are outlined in Table 35.

Table 35. Cynomolgus Monkey Specifications

Species	Cynomolgus Monkeys
Justification for Species Selection	This is an acceptable species to support PK studies for compounds intended to use in humans.
History of Dosing	Non-naïve animals
Body Weight Range	≥ 2 kg
Age	≥ 1.5 years old
Sex	Male

Method of Identification	Unique skin tattoo on chest
Number of Animals for Acclimation	4 males
Number of Animals for Dosing	3 males
Justification for number of Animals	The number of animals in each group is the minimum number of animals necessary for assessment of interanimal variability.
Selection of Animals	Animals will have undergone a physical examination for general health by a staff veterinarian. 3 males confirmed as being healthy, will be assigned to study.
Acclimation Period	Selected animals will be acclimated at the testing facility prior to the study.

[0542] Environmental Conditions: Environment controls will be set to maintain a temperature range of 20-26°C, a relative humidity range of 40 to 70%, and a 12-hour light/12-hour dark cycle. The light/dark cycle may be interrupted for study-related activities.

[0543] Housing: Animals will be group-housed (up to four animals/sex/cage) in polysulfone cages with certified aspen shaving bedding or corncob bedding during acclimation and study period. While animals may be individually housed after surgery or when there is special requirement in protocol, as well as, for behavioral or health reasons or due to cage mate death.

[0544] Diet and Feeding: Animals were offered certified rodent breeding and growth diet ad libitum every day, unless fasted for study procedures. Each lot of the diet is analyzed for nutrients, chemical contaminant and microorganisms, the results are reviewed and evaluated by veterinarians before provided to animals.

[0545] Drinking Water: Autoclaved RO (reverses osmosis) water will be available to all animals, ad libum.

[0546] Feed and Water Analyses: Autoclaved RO water will be provided ad libitum via water bottle. Water samples are periodically analyzed by a certified laboratory for specified microorganisms and environment contaminants. The diet is routinely analyzed by the manufacturer for specified microorganisms, nutritional components and environmental contaminants.

[0547] Environmental Enrichment: Enrichment toys will be provided.

[0548] Dose Administration: The dose volume will be determined by the animals' body weight collected on the morning of dosing day.

Animal Specifications: Rats

[0549] Rat specifications are outlined in Table 36.

Table 36. Rat Specifications

Species	Rat
Strain	SD
Source	Approved Vendor.
Gender	Male
Body weight	＞200g
Age	7-10 W
Total number of animals	9 male rats
Justification	The SD rat is a standard species used in pharmacokinetic evaluations and is acceptable to regulatory agencies. The number of animals used in this study is, in the judgment of the investigator involved, the minimum necessary to properly perform this plasma pharmacokinetic evaluation.

Observations and Examinations

[0550] Clinical Observations: All animals will be observed at dosing and each scheduled collection. All abnormalities will be recorded.

[0551] Body Weight: All animals will be weighed on the dosing day prior to dosing to determine the dose volume to be administered.

Sample Collection and Processing

[0552] Blood Sample Collection and Process: At least 0.1 mL blood will be collected at each time point. All blood samples will be collected via jugular vein. All blood samples will be transferred into low binding EP tube with anticoagulant (0.5 M Potassium (K2) EDTA will be pre-added as a ratio of 50:1 for blood: anticoagulant), 0.05% Triton X-100 (e.g., 100uL Blood+2uL 2.5% Triton X-100) will be used for desorption the blood samples will be placed on wet ice.

[0553] Blood samples will be centrifuged within 1hr of collection at 3,200 g 4°C for 10 minutes. Following centrifugation, plasma samples will be transferred into their respective pre-labeled low binding EP tube and immediately frozen over dry ice. The plasma samples will be stored lower than -60°C until bioanalysis.

[0554] LC-MS/MS method development:

[0555] A LC-MS/MS method for the quantitative determination of test compound in biological matrix will be developed.

[0556] N in 1 cassette LC-MS/MS method may be developed for samples coming from different studies as long as these studies belong to the same sponsor.

[0557] Cassette administration assay could be performed if the mass difference (ΔMass) among different analytes is ≥4 Da. In this case, interference evaluation is not necessary.

[0558] If ΔMass among different analytes is less than 4 Da, there is a potential risk that interference would occur during LC-MS/MS analysis. If such kind of cassette assay is still requested by client, interference among analytes will not be evaluated but the LC separation of those analytes by using a generic method will be attempted.

[0559] Sample analysis:

[0560] A calibration curve with at least 6 non-zero calibration standards will be applied for each batch including LLOQ.

[0561] If sample number within a batch is ≤ 12, at least one set of standard curve separated with two parts through begin and end of the sequence should be included in the run and QCs are not required. The recommended injection order is C8, C6, C4, C2, study samples, C7, C5, C3, C1.

[0562] If sample number within a batch is > 12, one standard curve and two sets of QCs with low, middle and high concentrations will be applied for bioanalysis. Meanwhile, QCs number should be more than 5% of study sample number.

[0563] Samples, coming from one client with the same type of matrix in different studies, are allowed to be quantified in one analysis run by using the developed N in 1 cassette LC-MS/MS method.

[0564] Acceptance criteria:

[0565] (1) Linearity: At least 75% of the calibration standards should fall within ±20% of their nominal values for biofluid and within ±25% of their nominal values for tissue and feces samples. If the endpoints, such as LLOQ and ULOQ, on the calibration curve are eliminated, the calibration curve will be truncated. The truncated calibration curve should consist of at least 75% of the initial STDs.

[0566] (2) Accuracy: At least 67% of QCs should fall within ±20% of their nominal values for biofluid and within ±25% of their nominal values for tissue and feces samples. At least half of QCs at each concentration should be passed.

[0567] (3) Specificity: The mass response of analyte in the double blank and blank should be ≤ 50% LLOQ.

[0568] (4) Sensitivity: The LLOQ will be tried to target ≤ 3 ng/mL. Any adjustment of LLOQ will be informed to client in advance.

[0569] (5) Carryover: The mean calculated carryover peak area in the double blanks or blanks immediately after the highest standard injection should be less than that of LLOQ.

If the carryover couldn't meet the criteria, the impact of the carryover on unknown samples should be re-evaluated according to the below procedure:

[0570] Carryover should be re-evaluated based on absolute carryover. Absolute carryover is calculated by carryover contribution multiplies carryover impact, where the carryover contribution is calculated by the area ratio of the double blank or blank with the highest carryover (Area max of carryover blank) to the ULOQ with the minimum calculated value (Area min of ULOQ), and the carryover impact is calculated by the area ratio of one injection (Area of one injection) to the following injection (Area of the following injection). The absolute carryover should be below the acceptable accuracy of the studies (e.g., 20% or 25%).

[0571] Carryover contribution = $Area_{max}$ of carryover blank / $Area_{min}$ of ULOQ Carryover impact = Area of one injection / Area of the following injection Absolute carryover = Carryover contribution * Carryover impact

Data Analysis

[0572] Plasma concentration versus time data for Compounds A-C in Rats and Cynomolgus Monkeys will be plotted in graph and analyzed by non-compartmental approaches. Related PK parameters will be calculated according to dosing route, e.g., Cl, V_{dss} and C0 for intravenous administration, C_{max}, T_{max} or %F for extravascular administration, and T½, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}inf)}$, $MRT_{(0\text{-}t)}$, $MRT_{(0\text{-}inf)}$ for all routes. Preliminary plasma results after 24 hours for 60 mg/kg oral administration in Rats and 30mg/kg of Compound C (C2) in Cynomolgus Monkeys are shown in Table 37 and FIG. 1.

Table 37. Plasma Pharmacokinetic Results of Compound C after 24 hours

Com-pound Name	Formula	60 mg/kg PO plasma Rat Data 24 h					30 mg/kg PO plasma Cynomolgus Monkeys data 24 h				
		Cmax (ng/mL)	Tmax (h)	AUC (ng.h/mL)	Tfinal	T1/2 (h)	Cmax (ng/mL)	Tmax (h)	AUC (ng.h/mL)	Tfinal	T1/2 (h)
C	Ac-Nle-c(Asp-His-p(F)dPhe-	46.3	0.194	31.3	1 h -2 h	0.75	606	0.667	1,653	8h - 24h	3.98

	Arg-Trp-Lys)-dVal-dPro-NH2										

[0573] Plasma concentration versus time data for Compound E (O10) (FIGS. 2A-2F) in Cynomolgus Monkeys was plotted in graphs and analyzed by non-compartmental approaches. Related PK parameters were calculated according to dosing route, e.g., Cl, V_{dss} and C0 for intravenous administration, C_{max}, T_{max} or %F for extravascular administration, and T½, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}inf)}$, $MRT_{(0\text{-}t)}$, $MRT_{(0\text{-}inf)}$ for all routes. Preliminary plasma results after 24 hours of 3 mg/kg, 10 mg/kg, 30 mg/kg, or 60 mg/kg PO administration of Compound E (Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2; O10) in Cynomolgus Monkeys are shown in Table 38.

Table 38. Plasma Pharmacokinetic Results of Compound E (O10) in Cynomolgus Monkeys after 24 hours

Comp. Name	Dose (mg/kg)	Cmax (ng/mL)	Tmax (h)	Tfinal	T1/2 (h)	$AUC_{0\text{-}last}$ (ng.h/mL)	$AUC_{0\text{-}inf}$ (ng.h/mL)	$MRT_{0\text{-}last}$ (h)	$MRT_{0\text{-}inf}$ (h)	AUC_{EX} (%)	$AUMC_{EX}$ (%)
E	3	66.00	1.67	1.50	8.00	206.67	216.20	2.75	3.04	3.91	13.2
E	10	133	1.33	8h	1.84	503	552	2.96	3.56	7.64	21.9
E	30	248	2h	8h - 24h	2.47	1006	1041	3.27	3.66	4.75	14.2
E	60	399.33	2.33	4.02	24.00	1985.33	2014.33	5.03	5.43	1.60	8.31

[0574] Preliminary plasma and cerebrospinal fluid (CSF) results after 24 hours of administration of Compound E (Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH2; O10), and in Rats are shown in Table 39 and Table 40. Graphs of plasma concentration and CSF concentration in Rats are shown in FIGS 3A-3C (SC administration), FIGS. 4A-4G (IP administration), and FIGS. 5A-5C (PO administration).

[0575] Plasma and CSF concentrations over 24 hours after administration of Compound E (O10 or setmelanotide were also assessed (FIGS. 4H-4K). It was predicted

that O10 will be efficacious for treating general obesity in part due to the PK values in plasma and CSF and the higher affinity for MC3R and MC4R relative to setmelanotide.

Table 39. Plasma Pharmacokinetic Results of Compound E (O10) in Rats after 24 hours

Comp Name	Dose (mg/kg)	Admin Route	Cmax (ng/mL)	Tmax (h)	Tfinal	T1/2 (h)	$AUC_{0\text{-}last}$ (ng.h/mL)	$AUC_{0\text{-}inf}$ (ng.h/mL)	$MRT_{0\text{-}last}$ (h)	$MRT_{0\text{-}inf}$ (h)	AUC_{Ex} (%)	AUM C_{EX} (%)
E	1	SC	238	2.00	8h-10h	1.29	1090	1124	3.34	3.58	3.19	8.65
E	3	SC	448	2.67	10h	2.74	3002	3450	4.42	5.66	11.9	28.6
E	10	SC	1366	2.00	24h	2.78	10731	10781	6.51	6.61	0.464	1.97
E	1	IP	821	0.500	4h-6h	0.511	1269	1274	1.13	1.15	0.386	1.72
E	3	IP	1901	0.833	6h-8h	0.539	3826	3828	1.40	1.40	0.0291	0.16
E	10	IP	4245	1.00	10h	0.951	13912	13933	2.23	2.24	0.152	0.77
E	10	PO	6.61	0.333	2h	0.723	7.51	9.02	0.789	1.17	16.9	43.8
E	30	PO	35.9	0.333	2h-4h	0.675	39.8	43.4	0.867	1.08	8.77	26.7
E	60	PO	51.7	0.50	6h	1.29	71.2	73.7	1.58	1.78	3.29	14.5

Table 40. CSF Pharmacokinetic Results of Compound E (O10) in Rats after 24 hours

Comp Name	Dose (mg/kg)	Admin Route	Cmax (ng/mL)	Tmax (h)	Tfinal	T1/2 (h)	$AUC_{0\text{-}last}$ (ng.h/mL)	$AUC_{0\text{-}inf}$ (ng.h/mL)	$MRT_{0\text{-}last}$ (h)	$MRT_{0\text{-}inf}$ (h)	AUC_{Ex} (%)	AUM C_{EX} (%)
E	10	SC	21.3	6.00	10h	5.62	121	226	5.99	11.6	46.5	72.4
E	10	IP	71.	2.00	10h	4.05	343	407	3.82	5.71	15.7	43.5
E	60	OP	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

ND = Not determined

[0576] Dose proportionality of Compound E (O10) following a single administration via SC, IP, and PO in Rats is shown in Tables 41-43.

Table 41. Dose Proportionality of Compound E in Rats after a single SC administration

Compound Name	Compare Doses (mg/kg)			Dose Ratio	Cmax Values	Cmax Ratio	$AUC_{0\text{-}last}$ Values	$AUC_{0\text{-}last}$ Ratio
E	3.00	Over	1.00	3.00	448/238	1.88	3002/1090	2.75
E	10.0	Over	1.00	10.0	1366/238	5.74	10731/1090	9.84
E	10.0	Over	3.00	3.33	1366/448	3.05	10731/3002	3.57

Table 42. Dose Proportionality of Compound E in Rats after a single IP administration

Compound Name	Compare Doses (mg/kg)			Dose Ratio	Cmax Values	Cmax Ratio	$AUC_{0\text{-}last}$ Values	$AUC_{0\text{-}last}$ Ratio
E	3.00	Over	1.00	3.00	1901/821	2.32	3826/1269	3.01
E	10.0	Over	1.00	10.0	4245/821	5.17	13912/1269	11.0
E	10.0	Over	3.00	3.33	4245/1901	2.23	13912/3826	3.64

Table 43. Dose Proportionality of Compound E in Rats after a single PO administration

Compound Name	Compare Doses (mg/kg)			Dose Ratio	Cmax Values	Cmax Ratio	$AUC_{0\text{-}last}$ Values	$AUC_{0\text{-}last}$ Ratio
E	30.0	Over	10.0	3.00	35.9/6.61	5.43	39.8/7.51	5.30
E	60.0	Over	10.0	6.00	51.7/6.61	7.82	71.2/7.51	9.48
E	60.0	Over	30.0	2.00	51.7/35.9	1.44	71.2/39.8	1.79

Plasma Concentration

[0577] Plasma pharmacokinetic measurements using 30 mg/kg were assessed in Cynomolgus monkey plasma up to 24 hours. Results are detailed in Table 44.

Table 44: Pharmacokinetic Data

Compound Name	30 mg/kg PO Cynomolgus Monkey	
	Cmax (ng/mL)	AUC (ng.h/mL)
C2	606 ± 576	1653 ± 1589
O10	248	1006

[0578] The antagonist activity of exemplary non-naturally occurring melanocortin analogs at specific ion channels was measured using the Qube electrophysiological platform. The non-naturally occurring melanocortin analogs and specific ion channel targets are provided in Table 45.

Table 45. Ion channel targets and melanocortin analogs

Melanocortin Analog	Ion channel targets	MW + Saly	Condition
O5	Voltage-Gated Potassium: CHO-hERG	1223.64	Dry powder
O10	Voltage-Gated Potassium: CHO-hERG	1237.65	Dry powder

Methods

[0579] The non-naturally occurring melanocortin analogs identified above were tested for antagonist activity at various ion channels at concentrations ranging from 0.1 mM to 30 mM. In each experiment and if applicable, the respective reference compounds were tested concurrently with the test compounds, and the data were compared with known historical values.

hNav1.5 Sodium Channel Assay – Qube APC

[0580] Onset and steady state block of peak Nav1.5 current is measured using a pulse pattern, repeated every 5 sec, consisting of a hyperpolarizing pulse to -120mV for a 200ms duration, depolarization to -15mV amplitude for a 40ms duration, followed by step to 40mV for 200ms and finally a 100ms ramp (1.2 V/s) to a holding potential of -80mV. Peak current is measured during the step to -15mV.

[0581] The parameters measured were difference between the peak inward current on stepping to -15mV (i.e., peak of the current) and the leak current. All data were filtered for seal quality, seal drop, and current amplitude. The peak current amplitude was calculated before and after compound addition and the amount of block was assessed by dividing the Test compound current amplitude by the Control current amplitude. Control is the mean Nav1.5 current amplitude collected 10 seconds at the end of the vehicle control; Test

Compound is the mean Nav1.5 current amplitude collected 10 seconds at the end of test concentration application for each concentration.

hKv4.3/hKChIP2 Potassium Channel Assay – Qube APC

[0582] After whole cell configuration is achieved, the cells are held at -80mV. Onset and steady state block of hKv4.3 current is measured using a pulse pattern from -80mV to 40mV amplitude for a 110ms duration, and finally a 100ms ramp (1.2 V/s) to -80mV. This paradigm is delivered once every 5s to monitor the current amplitude.

[0583] The parameters measured were the maximum outward current evoked on stepping to 40mV from holding potential of -80mV. All data were filtered for seal quality, seal drop, and current amplitude. The peak current amplitude was calculated before and after compound addition and the amount of block was assessed by dividing the Test compound current amplitude by the Control current amplitude. Control data is the mean Kv4.3/KChIP2 current amplitude collected 10 seconds at the end of the vehicle control period; Test compound data is the mean Kv4.3/KChIP2 current amplitude collected 10 seconds at the end of test concentration application for each concentration.

hCav1.2 (L-type) CiPA Calcium Channel Assay – Qube APC

[0584] Onset and steady state block of peak hCav1.2 current is measured using a pulse pattern, repeated every 15 sec. Cells were held at -80mV for a 50ms before stepping to -90mV for 100ms to measure leak current and then stepped back to -80mV for 50ms, depolarization to 0mV amplitude for a 40ms duration, followed by step to 40mV for 200ms and finally a 100ms ramp (1.2 V/s) to a holding potential of -80 mV. Peak current is measured during the step to 0mV. Each concentration is applied for 5 minutes.

[0585] The calcium current amplitude is calculated by measuring the difference between the peak inward current on stepping to 0mV or the peak inward current at the ramp (i.e. peak of the current) and the leak current. The calcium current is assessed in vehicle control conditions and at the end of each five (5) minute compound application.

hNav1.5 Late Current Sodium Channel Assay – Qube APC

[0586] Onset and steady state block of Late Nav1.5 current is measured using a pulse pattern, repeated every 5 sec, consisting of a hyperpolarizing pulse to -120mV for a 200ms duration, depolarization to -15mV amplitude for a 40ms duration, followed by step to 40mV for 200ms and finally a 100ms ramp (1.2 V/s) to a holding potential of -80mV. Late current is measured as charge current elicited during the ramp with 50nM ATXII.

[0587] The parameters measured were the ramp current charge (AUC) evoked on ramping back to -80mV from 40mV test pulse in the presence of 50nM ATXII. All data were filtered for seal quality, seal drop, and current. The peak and ramp current amplitude was calculated before and after compound addition and the amount of current was assessed by dividing the Test compound current by the Control current. Control data is the mean hNav1.5 late current collected 15 seconds at the end of 50nM ATXII application (50nM ATXII control); Test compound data is the mean ramp hNav1.5 current collected 15 seconds at the end of test concentration application for each concentration.

hERG Potassium Channel Assay - Qube APC

[0588] After whole cell configuration is achieved, the cells are held at -80mV. Cells are held at this voltage for 50ms to measure the leak current, which is subtracted from the tail current on-line. The cells are depolarized to +40mV for 500ms and then to -80 mV over a 100ms ramp to elicit the hERG tail current. This paradigm is delivered once every 8s to monitor the current amplitude. All compounds were tested in the presence of 0.1% Pluronic F-68 Non-Ionic Surfactant and at approximately room temperature.

[0589] The parameters measured were the maximum tail current evoked ramping back to -80mV from the test pulse of 40mV. All data were filtered for seal quality, seal drop, and current amplitude. The peak current amplitude was calculated before and after compound addition and the amount of block was assessed by dividing the Test compound current amplitude by the Control current amplitude. Control data is the mean hERG current amplitude collected for three pulses (24 seconds) at the end of the vehicle control; Test compound data is the mean hERG current amplitude collected for three pulses (24 seconds) at the end of test concentration application for each concentration.

hKCNQ1/hminK Potassium Channel Assay – Qube APC

[0590] After whole cell configuration is achieved, the cells are held at -80mV. KCNQ1/minK currents are evoked by a 1000ms pulse from -80mV to 60mV followed by a ramp from 60mV to -80mV over 115ms with the outward peak currents measured upon depolarization of the cell membrane. This paradigm is delivered once every 15s to monitor the current amplitude.

[0591] The parameters measured were the maximum outward current evoked on stepping to +60mV from a holding potential of -80mV. All data were filtered for seal quality, seal drop, and current amplitude. The peak current amplitude was calculated before and after compound addition and the amount of block was assessed by dividing the Test compound current amplitude by the Control current amplitude. Control data is the mean hKCNQ1/hminK current amplitude collected 30 seconds at the end of vehicle control period; Test compound data is the mean hKCNQ1/hminK current amplitude collected 30 seconds at the end of test concentration application for each concentration.

hKir2.1 Potassium Channel Assay – Qube APC

[0592] After whole cell configuration is achieved, the cells are held at -30mV. Kir2.1 currents are evoked by a single 500ms pulse to -120mV before returning to the holding potential of -30mV. This paradigm is delivered once every 20s to monitor the current amplitude.

[0593] The parameters measured were the maximum inward current elicited on stepping to -120mV for 500ms from a holding potential of -30 mV. All data were filtered for seal quality, seal drop, and current amplitude. The peak current amplitude was calculated before and after compound addition. Residual non-Kir2.1 current was eliminated via normalization to residual current after application of 100uM Barium Chloride. The amount of Test compound effect was then assessed by dividing the Test compound current amplitude by the Control current amplitude. Control data is the mean Kir2.1 current amplitude collected 40 seconds at the end of the vehicle control; Test compound data is the mean Kir2.1 current amplitude collected 30 seconds at the end of test concentration application for each concentration.

Results

[0594] Where presented, IC_{50} values were determined by a non-linear, least squares regression analysis. Reference standards were run as an integral part of each assay to ensure the validity of the results obtained. Results from the ion channel assessment of non-naturally occurring melanocortin analogs are provided in Table 46.

Table 46. Dose-response results of melanocortin analogs and reference compounds against ion channels.

Compound	**Ion channel target**	**Max Inhibtion %**	**Estimated IC_{50} (nM)***
Tetracaine	Nav1.5	95.17	2.67
Flecainide	Kv4.3/ChIP2	96.97	7.60
Nifedipine	Cav1.2	88.16	0.127
Ranolazine	Nav1.5 Late Current	92.16	37.1
Verapamil_01	hERG	105.19	0.217
Verapamil_02	hERG	85.05	0.426
Chromanol 293B	KNQ1/mink	75.00	32.2
Barium Chloride	Kir2.1	103.10	9.12
O5	hERG	1.06	N/C
O10	hERG	15.06	N/C

*N/C: Indicates observed mean maximal inhibition was <25%

Example 7: Assessment of physical biological properties of non-naturally occurring melanocortin analogs

[0595] Physical biological properties including solubility, in vitro absorption and in vitro metabolism of nine exemplary non-naturally occurring melanocortin analogs were assessed according to the following procedures. In each experiment and if applicable, the respective reference compound was tested concurrently with the test compounds, and the data were compared with known values. Stock solutions of the tested compounds were prepared at a concentration of 0.01M in DMSO.

Solution Properties

[0596] Solution properties of non-naturally occurring melanocortin analogs and reference compounds in various biological media were assessed according to the conditions provided in Table 47.

Table 47. Assay conditions for in vitro absorption assessment

Assay	**Technique**	**Incubation**	**Detection Method**
Aqueous solubility (simulated intestinal fluid)	shake-flask	24h, RT	HPLC-UV/Vis
Aqueous solubility (PBS, pH 7.4)	shake-flask	24h, RT	HPLC-UV/Vis
Aqueous solubility (simulated gatric fluid)	shake-flask	24h, RT	HPLC-UV/Vis
Protein binding (plasma, human)	Equilibrium dialysis	4h, 37°C	HPLC-MS/MS
Partition coefficient	shake-flask	60 min, RT	HPLC-UV/Vis
Half-life (simulated gastric fluid)		0, 15, 30, 45 and 60 min, 37°C	HPLC-MS/MS
Half-life (simulated intestinal fluid)	Caco-2 cell line	0, 1, 2, 3, and 4h, 37°C	HPLC-MS/MS

Aqueous Solubility

[0597] Aqueous solubility (μM) was determined by comparing the peak area of the principal peak in a calibration standard (200 μM) containing organic solvent (methanol/water, 60/40, v/v) with the peak area of the corresponding peak in a buffer sample. In addition, chromatographic purity (%) was defined as the peak area of the principal peak relative to the total integrated peak area in the HPLC chromatogram of the calibration standard. A chromatogram of the calibration standard of each test compound, along with a UV/VIS spectrum with labeled absorbance maxima, was generated.

[0598] A chromatogram of the test compound (200 μM) along with a UV/VIS spectrum with labeled absorbance maxima, was generated.

Protein Binding

[0599] The peak areas of the test compound in the buffer and test samples were used to calculate percent binding and recovery according to the following formulas:

$$\text{Protein binding}(\%) = ((\text{Area}_p - \text{Area}_b)/\text{Area}_p) \times 100$$

$$\text{Recovery}(\%) = ((\text{Area}_p - \text{Area}_b)/\text{Area}_c) \times 100$$

where: Area_p = peak area of analyte in protein matrix; Area_b = peak area of analyte in buffer; and Area_c = peak area of analyte in control sample.

Partition Coefficient

[0600] The total amount of compound was determined as the peak area of the principal peak in a calibration standard (100 µM) containing organic solvent (methanol/water, 60/40, v/v). The amount of compound in buffer was determined as the combined, volume-corrected, and weighted areas of the corresponding peaks in the aqueous phases of three organic-aqueous samples of different composition. An automated weighting system was used to ensure the preferred use of raw data from those samples with well quantifiable peak signals. The amount of compound in organic was calculated by subtraction. Subsequently, Log D was calculated as the Log10 of the amount of compound in the organic phase divided by the amount of compound in the aqueous phase.

Half-Life Determination

[0601] At the end of the incubation at each of the time points, an equal volume of an organic mixture (acetonitrile/methanol, 50/50, v/v) was added to the incubation mixture. Samples were analyzed by HPLC-MS/MS and corresponding peak areas were recorded for each analyte. The ratio of precursor compound remaining after each time point relative to the amount present at time 0, expressed as percent, is reported as chemical stability. The half-life (T1/2) was estimated from the slope of the initial linear range of the logarithmic curve of compound remaining (%) versus time, assuming first order kinetics.

[0602] Results of the solubility assessment detailed above are provided in Tables 48-51.

Table 48. Protein binding of melanocortin analogs in plasma

Compound	**Test Concentration (M)**	**Average % Protein Bound**	**Average % Recovery**
Acebutolol	1.0E-5	15.17	112.61
Quinidine_01	1.0E-5	54.99	105.22
Quinidine_02	1.0E-5	66.10	114.10
Sertraline_01	1.0E-5	97.52	64.76
Sertraline_02	1.0E-5	98.25	97.34
Warfarin_01	1.0E-5	98.98	91.90
Warfarin_02	1.0E-5	98.58	107.98
C2	1.0E-5	49.75	118.15
O10	1.0E-5	37.73	112.84

Table 49. Half-life of melanocortin analogs in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF)

Compound	**Test Concentration (M)**	**Average Half-life (min)**	
		SGF	**SIF**
Erythromycin	1.0E-6	42.9	-
Propantheline	1.0E-6	>120	113.6
Chlorambucil	1.0E-6	-	20.0
C2	1.0E-6	>120	36.6
O10	1.0E-6	>120	26.8

Table 50. Aqueous solubility of melanocortin analogs in plasma (PBS), simulated gastric fluid (SGF), and simulated intestinal fluid (SIF)

Compound	**Test Concentration (M)**	**Average Solubility (mM)**		
		PBS*	**SGF**	**SIF**
Diethylstilbestrol	2.0E-4	5.21	-	-
Ketoconazole	2.0E-4	133.32	-	-
Metoprolol	2.0E-4	190.93	-	-
Phenytoin	2.0E-4	89.72	-	-
Rifampicin	2.0E-4	174.01	-	-
Simvastatin	2.0E-4	36.04	-	-
Tamoxifen	2.0E-4	4.12	-	-
C2	2.0E-4	>200	>200	49.98
O10	2.0E-4	>200	>200	19.85

*pH = 7.4

Table 51. Partition coefficient of melanocortin analogs and reference compounds

Compound	**Test Concentration (M)**	**Partition Coefficient***
Haloperidol	1.0E-4	2.53
Ketoconazole	1.0E-4	3.35
Metoprolol	1.0E-4	-0.32
Phenytoin	1.0E-4	2.20
Rifampicin	1.0E-4	1.08
Simvastatin	1.0E-4	>4.01
C2	1.0E-4	-0.31
O10	1.0E-4	-0.40

*log D, n-octanol/PBS, pH 7.4

In Vitro Absorption

[0603] *In vitro* absorption of non-naturally occurring melanocortin analogs was determined using permeability assays. Assay conditions are provided in Table 52.

Table 52. Assay conditions for in vitro absorption assessment

Assay	Source	pH	Incubation	Detection Method
A-B permeability	Caco-2 cell line	6.5/7.4	0 and 60 min, 37°C	HPLC-MS/MS
B-A permeability	Caco-2 cell line	6.5/7.4	0 and 60 min, 37°C	HPLC-MS/MS

Permeability

[0604] The apparent permeability coefficient (Papp) of the test compound was calculated as follows:

[0605] $P_{app}(cm/s) = (V_R*C_{R,end}/Dt) \times (1/A*(C_{D,mid}-C_{R,mid})$

[0606] where V_R is the volume of the receiver chamber; $C_{R,end}$ is the concentration of the test compound in the receiver chamber at the end time point; Δt is the incubation time; A is the surface area of the cell monolayer; $C_{D,mid}$ is the calculated mid-point concentration of the test compound in the donor side, which is the mean value of the donor concentration at time 0 minute and the donor concentration at the end time point; and $C_{R,mid}$ is the mid-point concentration of the test compound in the receiver side, which is one half of the receiver concentration at the end time point. Concentrations of the test compound were expressed as peak areas of the test compound.

Recovery of the Test Compound from the Permeability Assay

[0607] The recovery of the test compound was calculated as follows:

[0608] $Recovery(\%) = ((V_D*C_{D,end}+V_R*C_{R,end})/V_D*C_{D0}) \times 100$

[0609] where V_D and V_R are the volumes of the donor and receiver chambers, respectively; $C_{D,end}$ is the concentration of the test compound in the donor sample at the end time point; $C_{R,end}$ is the concentration of the test compound in the receiver sample at the end time point; and C_{D0} is the concentration of the test compound in the donor sample at time zero. Concentrations of the test compound are expressed as peak areas of the test compound.

Fluorescein assessment for Permeability assays

[0610] Fluorescein was used as the cell monolayer integrity marker. Fluorescein permeability assessment (in the A-B direction at pH 7.4 on both sides) was performed after the permeability assay for the test compound. The cell monolayer that had a fluorescein permeability of less than 1.5 x 10^{-6} cm/s for Caco-2 and MDR1-MDCKII cells and 2.5 x 10^{-6} cm/s for MDCKII cells was considered intact, and the permeability result of the test compound from intact cell monolayer is reported.

[0611] Results of the *in vitro* absorption assessments described above are provided in Table 53.

Table 53. *In vitro* absorption of melanocortin analogs and reference compounds

Compound	**Test Concentration (M)**	**A-B permeability**		**B-A permeability**	
		Permeability (10^{-8} cm/s)	**Recovery (%)**	**Permeability (10^{-8} cm/s)**	**Recovery (%)**
Colchicine	1.0E-5	0.2	83	3.4	89
Labetalol	1.0E-5	6.1	100	26.0	93
Propranolol	1.0E-5	26.4	90	28.9	91
Ranitidine	1.0E-5	0.2	96	1.1	99
C2	1.0E-5	<0.012	92	<0.021	83
O10	1.0E-5	<0.013	92	<0.022	77

In Vitro Metabolism

[0612] *In vitro* metabolism of non-naturally occurring melanocortin analogs was determined using the assay conditions provided in Table 54.

Table 54. Assay conditions for in vitro metabolism assessment

Assay	**Source**	**Incubation**	**Detection Method**
Intrinsic clearance	Human liver microsomes (0.1 mg/mL)	0, 15, 30, 45, and 60 min, 37°C	HPLC-MS/MS

[0613] Metabolic stability, expressed as percent of the parent compound remaining, was calculated by comparing the peak area of the compound at the time point relative to that at time-0. The half-life ($T_{1/2}$) was estimated from the slope of the initial linear range of the logarithmic curve of compound remaining (%) vs. time, assuming the first-order kinetics. The apparent intrinsic clearance (CL_{int}, in μL/min/pmol, μL/min/mg or μL/min/Mcell) was calculated according to the following formula:

$$CL_{int} = 0.693/(T_{1/2}*(\text{mg protein/μL or million cells/μL or pmol CYP isoyme/μL}))$$

[0614] Results from the intrinsic clearance assay are provided in Table 55.

Table 55. *In vitro* metabolism of melanocortin analogs and reference compounds

Compound	**Test Concentration (M)**	**Half-life**	**Clint (uL/mi/mg)**
Imipramine	1.0E-7	>120	<57.8
Propranolol	1.0E-7	>120	<57.8
Terfenadine	1.0E-7	13.2	524.9
Verapamil	1.0E-7	33.8	205.1
C2	1.0E-7	>120	<57.8
O10	1.0E-7	>120	<57.8

Physiochemical and ADME Properties

[0615] Physiochemical and Absorption, Distribution, Metabolism, and Excretion (ADME) properties of O10 were assessed (Tables A and B). O10 may be efficiently manufactured using standard solid-phase peptide synthesis (SPPS). B07, a melanocortin antagonist, has high structural homology to O10. B07 has been made in GMP batches up to 1 kg and it is amenable to efficient SPPS with high overall yields. Non-canonical residues and cyclic structure may restricts fermentation-based approaches, and peptide purification is performed using standard RP-HPLC techniques.

[0616] O10 may be amenable to liquid-phase peptide synthesis (LPPS) for late-stage clinical and commercial manufacturing, offering potential for significant reductions in manufacturing cost. It is anticipated that typical scale-up cost reductions (e.g., use of bulk residues, process optimization, captive manufacturing cost setups) will emerge.

Table A: O10 Physicochemical Properties

logD (n-octanol / PBS)	Aqueous solubility in PBS (uM)	% unmodified, proteinogenic amino acids	Calculated isoelectric point (pI)
-0.40	>200	33	>12

Table B: O10 ADME Properties

Plasma Protein Binding (%)	Half-life in solution (min)		% Remaining after 120 min incubation		Half-life, liver microsomes (min)	Stability in liver microsomes (% remaining after 60 mins)
	SGF*	SIF**	SGF*	SIF**		
37.7	>120 (795)	27	88.7	4.8	>120 (810)	91.7

* SGF: simulated gastric fluid

** SIF: simulated intestinal fluid

Example 8: CYP Inhibition of Non-Naturally Occurring Melanocortin Analogs

[0617] The inhibitory potential of exemplary non-naturally occurring melanocortin analogs was tested on seven human Cytochrome P450 (CYP) enzymes: CYP1A, CYP2B6, CYP2C19, CYPC8, CYP2C9, CYP2D6, and CYP3A. Exemplary melanocortin analogs O7 and O10 and comparator melanocortin analog TCMCB07 (Ac-Nle-c[Asp-Pro-dNal(2')-Arg-Trp-Lys]-dVal-dPro-NH2; SEQ ID NO: 172) were tested at concentrations ranging from 0.1 mM to 100 mM for inhibition of the seven CYPs. The CYP inhibition assays were performed using human liver microsomes (HLM) and human recombinant CYP isozymes in 96-well plate format. Direct inhibition (e.g., zero-min incubation) and time-dependent (e.g., 30 min preincubation) inhibition assays were performed. The results of the CYP inhibition assays of

O7 and O10 at 10 mM are shown in Table 56 and the results of the comparator CYP inhibition assays including IC_{50} values at each of the CYP enzymes are shown in Table 57.

Table 56. CYP Inhibition Studies of O10

Assay	Substrate	NADPH+/-	O7 µm	O10 10µ
CYP1A inhibition	phenacetin		15%	11%
CYP2B6 inhibition	bupropion		4%	21%
CYP2C19 inhibition	omeprazole		9%	44%
CYP2C8 inhibition	amodiaquine		23%	19%
CYP2C9 inhibition	diclofenac		-4%	0%
CYP2D6 inhibition	dextromethorphan		18%	73%
CYP3A inhibition	midazolam		21%	5%
CYP3A inhibition	testosterone		21%	12%
Time-dependent CYP1A inhibition	phenacetin	- NADPH	1%	4%
Time-dependent CYP1A inhibition	phenacetin	+ NADPH	17%	15%
Time-dependent CYP2B6 inhibition	bupropion	- NADPH	-9%	4%
Time-dependent CYP2B6 inhibition	bupropion	+ NADPH	0%	7%
Time-dependent CYP2C19 inhibition	omeprazole	- NADPH	-1%	-4%
Time-dependent CYP2C19 inhibition	omeprazole	+ NADPH	0%	-6%
Time-dependent CYP2C8 inhibition	Amodiaquine	- NADPH	-1%	2%
Time-dependent CYP2C8 inhibition	Amodiaquine	+ NADPH	4%	8%
Time-dependent CYP2C9 inhibition	diclofenac	- NADPH	0%	2%
Time-dependent CYP2C9 inhibition	diclofenac	+ NADPH	-1%	2%
Time-dependent CYP2D6 inhibition	dextromethorphan	- NADPH	-6%	0%
Time-dependent CYP2D6 inhibition	dextromethorphan	+ NADPH	0%	5%
Time-dependent CYP3A inhibition	midazolam	- NADPH	2%	3%
Time-dependent CYP3A inhibition	midazolam	+NADPH	3%	-1%

Table 57. CYP Inhibition of TCMCB07

CYP	Marker Substrate (Conc.)	Isoform-Catalyzed Reaction	TCMCB07 IC50 Values (μm)		IC50 Shift Fold[b]
			No Pre-Incubation	30-min Pre-Incubation (IC 50,30min)	
1A2	Phenacetin (50 μM)	O-Deethylation	>100	>100	NA
2B6	Bupropion (50 μM)	Hydroxilation	>100	>100	NA
2C8	Amodiaquine (2 μM)	N-Deethylation	>100	>100	NA
2C9	Diclofenac (5 μM)	4' -Hydroxylation	>100	>100	NA
2C19	S-Mephenytoin (20 μM)	4' -Hydroxylation	>100	>100	NA
2D6	Bufuralol (5 μM)	1' -Hydroxylation	68.3	96.4	0.7
3A	Midazolam (2 μM)	1' -Hydroxylation	>100	>100	NA
3A	Testosterone (50 μM)	6ß' Hydroxylation	>100	>100	NA

Example 9: Weight Loss in an Animal Model

[0618] Preliminary weight loss and food intake results in animals after administration of 3 mg/kg (3mg/kg) O10 for three or four days are shown in FIGS. 9A (weight loss) and 9B (daily food intake). As shown in FIG. 9A, although animals administered 3 mg/kg O10 demonstrated weight loss compared to animals administered saline. Similarly, animals administered 3 mg/kg O10 had a decrease in daily food intake compared to animals administered saline (FIG. 9B).

Example 10: Body Weight, Complete Blood Count, Clinical Chemistry, and Food Intake in an Animal Model

Objective

[0619] The objective of this study was to evaluate the pharmacodynamic (PD) characteristics and effects on food intake, body composition, and clinical chemistry following administration of exemplary non-naturally occurring melanocortin analogs of the present technology. Non-naturally occurring melanocortin analogs were administered to Cynomolgus monkeys via two subcutaneous (s.c.) injections at different doses.

Primate Specifications

[0620] Primate specifications are outlined in Table 58.

Table 58: Primate Specifications

Species:	Cynomolgus monkey
Sex and Number:	Male, 6
Age:	10~25 years old
Body Weight:	>8 kg
Dosing History:	Non-naïve

Animal Husbandry

[0621] Animals were supplied with unlimited Certified Monkey Diet for 72 hours after dosing on days 1, 8, and 11. Otherwise, the animals were supplied with Certified Monkey Diet twice a day. Animals received fruit daily as nutritional enrichment.

[0622] Animals were supplied with fresh reverse-osmosis (RO) water using an automated watering system.

Study Design

[0623] Non-naturally occurring melanocortin analogs were each administered to a group of Cynomolgus monkeys (n=2 per group) via s.c. injections as outlined in Table 59. The start of treatment is designed as Day 1. The end time of dosing was recorded as 0h.

Table 59. Group & Dosing Information

Group	**Test article**	**N**	**1st Dose Level**	**2nd Dose Level**	**Vehicle**	**Dose volume (mL/kg)**	**Dose Frequency**	**Route of Administration (ROA)**
			(mg/kg)	**(mg/kg)**				
1, 2, & 3	Saline	6	N/A	N/A	N/A	0.5	Day 1	s.c.
2	O10	2	1	3	Saline	0.5	Day 8 (Day 11)	s.c.

Examination and Observations

[0624] General physical examinations were completed once in the acclimation period. Cage-side observations for general health and appearance, such as nausea and vomiting, were done every hour for 6 hours after dosing on Days 8 and 11. Otherwise, cage-side clinical observations were done once daily during the pre-study and after dosing period.

[0625] Acclimatization Period (Day 1-7): Each animal was examined at least once during the acclimation period to determine suitability for the study. Body weight, clinical observations, and food intake observations were recorded daily. Measurement of initial body composition using Dual-Energy X-Ray Absorptiometry (DEXA) was recorded at least once during this time. Standard blood markers (e.g., glucose, insulin, HDL-c, LDL-c, triglycerides, total cholesterol, alanine aminotransferase, aspartate aminotransferase) were measured once.

[0626] Treatment Phase (Days 8-49): Body weight was recorded twice a week, clinical observation and food intake were recorded once a day. Standard hematology and clinical chemistry readouts as above were conducted before dosing and at the conclusion of the study on day 49. DEXA measurements of body composition were conducted biweekly.

Food intake measurement

[0627] Food intake was observed at about 0.5 hours, 1 hour, 1.5 hours, 2 hours, 3 hours, 4 hours, 24 hours, 48 hours, and 72 hours after administration of saline or non-naturally occurring melanocortin analogs at 1 mg/kg and 3 mg/kg (Day 8 and Day 11) dosing. On Days 4-7, monkeys were acclimatized to a normal diet of two meals per day. On Day 8, the lower dose of the non-naturally occurring melanocortin analogs were administered, and observations continued through Day 10. On Day 11, the higher dose of the non-naturally occurring melanocortin analogs was administered, and observations continued through Day 13, the conclusion of the study.

Blood collection

[0628] Blood collection according to Table 60 was conducted for the following: clinical chemistry (Serum), hematology (whole blood). Whole blood was collected at each time point with syringe via the cephalic or saphenous veins into labeled polypropylene tubes.

Table 60. Blood Sampling

Animal Group	**Time Point**	**Test Type**	**Blood Sample Type**	**Minimum Volume of Blood Samples**
All Groups	Day -1, Day 8 (2h), Day 11 (2h).	CBC	Whole Blood	~1 mL
	Day -1, Day 8 (2h), Day 11 (2h).	Clinical Chemistry	Serum	~0.5 mL

Sample Measurement and Analysis

[0629] Clinical chemistry and hematology assessments were conducted, assessing the parameters outlined in Tables 61 and 62.

Table 61: Clinical Chemistry

Parameter	**Abbreviation**	**Unit**
Albumin	ALB	g/L
Globulin (calculated)	GLB	g/L
Albumin/Globulin Ratio	A/G	-
Alkaline Phosphatase	ALP	U/L
Alanine Aminotransferase	ALT	U/L
Aspartate Aminotransferase	AST	U/L
Total Bilirubin	TBIL	μmol/L
Direct Bilirubin	DBIL	μmol/L
Total Cholesterol	CHO	mmol/L
Glucose	GLU	mmol/L
Creatinine Kinase	CK	U/L
Creatinine	CREA	μmol/L
Urea Nitrogen	UREA	mmol/L
Uric Acid	UA	μmol/L
Gamma-glutamyl transferase	GGT	U /L
Total Protein	TP	g/L
Triglycerides	TG	mmol/L
Lactate Dehydrogenase	LDH	U/L

C-reactive Protein	CRP	mg/L

Table 62: Hematology

Parameter	**Abbreviation**	**Unit**
Red blood cell count	RBC	10^{12}/L
Hemoglobin	HGB	g/L
Hematocrit	HCT	%
Mean corpuscular volume	MCV	fL
Mean corpuscular hemoglobin	MCH	pg
Mean corpuscular hemoglobin concentration	MCHC	g/L
Red cell distribution width	RDW	%
Platelet count	PLT	10^9 /L
Mean platelet volume	MPV	fL
Total white blood cell count	WBC	10^9/L
Routine CBC Differential		
Neutrophils	#NEUT	10^9/L
Lymphocytes	#LYM	
Monocytes	#MONO	
Eosinophils	#EOS	
Basophils	#BASO	
Neutrophils	%NEUT	%
Lymphocytes	%LYM	
Monocytes	%MONO	
Eosinophils	%EOS	
Basophils	%BASO	

Body Weight

[0630] Body weight was assessed in male Cynomolgus monkeys having diet-induced obesity of age 14-19 years old (n=6). Monkeys were subcutaneously injected with O10 at 1 mg/kg and 3 mg/kg. Monkeys were fasted overnight before dosing. Body weight was measured on days 1, 8, and 15 and percent change in body weight was calculated. Results are shown in Tables 63 and 64, respectively.

Table 63: Body Weight (kg)

Group	Animal ID	Day 1	Day 8	Day 15
Group 2 O10, 1mg/kg, 3mg/kg, SC, two doses, n=2	3	8.45	8.42	8.78
	4	14.48	14.32	14.44
	Mean	11.47	11.37	11.61
	SD	4.26	4.17	4.00

Table 64: Body Weight (% Change)

Group	Animal No.	Day 1	Day 8	Day 15
Group 2 O10, 1mg/kg, 3mg/kg, SC, two doses, n=2	3	0.0	-0.4	3.9
	4	0.0	-1.1	-0.3
	Mean	0.0	-0.7	1.8
	SD	0.0	0.5	3.0

Complete Blood Count

[0631] Complete blood count (CBC) was assessed on days 1, 8, and 12. Results are detailed in Tables 65-70.

Table 65: Complete Blood Count Day 1 (Part 1)

CBC	Measurement	Total white blood cell count	Neutrophils	Lymphocytes	Monocytes	Eosinophils	Basophils	Neutrophils	Lymphocytes	Monocytes	Eosinophils	Basophils
		WBC	%NEUT	%LYMP	%MONO	%EO	%BASO	#NEUT	#LYMP	#MONO	#EO	#BASO
Group (Day 1)		10^9/L	%	%	%	%	%	10^9/L	10^9/L	10^9/L	10^9/L	10^9/L
Group 2 O10, 1mg/kg, 3mg/kg, SC, two doses, n=2	Mean	13.81	51.75	43	4.1	0.7	0.4	7	5.8	1	0.1	0.06
	SD	1.10	23.55	21	1.6	0.6	0.1	4	2.5	0	0.1	0.01

Table 66: Complete Blood Count Day 1 (Part 2)

CBC	Measurement	Red blood cell count	Hemoglobin	Hematocrit	Mean corpuscular volume	Mean corpuscular hemoglobin	Mean corpuscular hemoglobin concentration	Red cell distribution width	Platelet count	Mean platelet volume
		RBC	HGB	HCT	MCV	MCH	MCHC	RDW-CV	PLT	MPV
Group (Day 1)		10^{12}/L	g/L	%	fL	pg	g/L	%	10^9/L	fL
Group 2 O10, 1mg/kg, 3mg/kg, SC, two doses, n=2	Mean	6.33	146.50	47.65	75.55	23.200	307.500	12.950	549.500	10.150
	SD	0.37	6.36	2.90	8.98	2.404	4.950	0.354	98.288	0.354

Table 67: Complete Blood Count Day 8 (Part 1)

CBC	Measurements	Total white blood cell count	Neutrophils	Lymphocytes	Monocytes	Eosinophils	Basophils	Neutrophils	Lymphocytes	Monocytes	Eosinophils	Basophils
		WBC	%NEUT	%LYMP	%MONO	%EO	%BASO	#NEUT	#LYMP	#MONO	#EO	#BASO
Group (Day 8)		10^9/L	%	%	%	%	%	10^9/L	10^9/L	10^9/L	10^9/L	10^9/L
Group 2 O10, 1mg/kg, 3mg/kg, SC, two doses, n=2	Mean	15.10	61.65	33	4.7	0.6	0.4	10	4.4	1	0.1	0.07
	SD	5.93	20.01	19	0.9	0.4	0.0	7	0.9	0	0.0	0.04

Table 68: Complete Blood Count Day 8 (Part 2)

CBC	Measurements	Red blood cell count	Hemoglobin	Hematocrit	Mean corpuscular volume	Mean corpuscular hemoglobin	Mean corpuscular hemoglobin concentration	Red cell distribution width	Platelet count	Mean platelet volume
		RBC	HGB	HCT	MCV	MCH	MCHC	RDW-CV	PLT	MPV
Group (Day 8)		10^{12}/L	g/L	%	fL	pg	g/L	%	10^9/L	fL
Group 2 O10, 1mg/kg, 3mg/kg, SC, two doses, n=2	Mean	6.10	142.50	45.75	75.20	23.400	311.500	12.750	514.000	10.200
	SD	0.33	6.36	2.90	8.77	2.263	6.364	0.354	59.397	0.000

Table 69: Complete Blood Count Day 12 (Part 1)

CBC	Measurements	Total white blood cell count	Neutro-phils	Lymph ocytes	Mono-cytes	Eosino phils	Baso-phils	Neutro-phils	Lym-pho-cytes	Mono-cytes	Eosino phils	Baso-phils
		WBC	%NEUT	%LYMP	%MONO	%EO	%BASO	#NEUT	#LYMP	#MONO	#EO	#BASO
Group (Day 8)		10^9/L	%	%	%	%	%	10^9/L	10^9/L	10^9/L	10^9/L	10^9/L
Group 2 O10, 1mg/kg, 3mg/kg, SC, two doses, n=2	Mean	13.15	53.05	39	6.8	1.3	0.0	7	4.7	1	0.2	0.00
	SD	3.30	21.57	23	1.8	0.4	0.0	5	1.7	0	0.0	0.00

Table 70: Complete Blood Count Day 12 (Part 2)

CBC	Measurements	Red blood cell count	Hemo-globin	Hema-tocrit	Mean corpus-cular volume	Mean corpus-cular hemo-globin	Mean corpus-cular hemo-globin concen-tration	Red cell distribu-tion width	Platelet count	Mean platelet volume
		RBC	HGB	HCT	MCV	MCH	MCHC	RDW-CV	PLT	MPV
Group (Day 8)		10^{12}/L	g/L	%	fL	pg	g/L	%	10^9/L	fL
Group 2 O10, 1mg/kg, 3mg/kg, SC, two doses, n=2	Mean	6.36	136.00	45.00	70.90	21.400	302.000	13.150	537.000	10.700
	SD	0.19	9.90	3.25	7.21	2.263	0.000	0.212	100.409	0.849

Clinical Chemistry

[0632] Clinical chemistry, including triglycerides, creatine kinase, lactate dehydrogenase, alanine amino transferase, aspartate amino transferase, bilirubin, alkaline phosphatase, total protein, albumin, globulin, glucose, urea nitrogen, creatine, urea acid, and C-reactive protein was assessed in monkey serum on days 1, 8 (2h), and 11 (2h). Results of each measurement are outlined in Tables 71-76.

Table 71: Clinical Chemistry Day 1 (Part 1)

Clinical Chemistry	Measurement	Direct bilirubin	(Total) Cholesterol	Triglycerides	Creatinine Kinase	Lactate Dehydrogenase	Alanine Aminotransferase	Aspartate Aminotransferase	Total Bilirubin	Alkaline Phosphatase
		DBIL	CHO	TG	CK	LDH	ALT	AST	BIL	ALP
Group (Day 1)		umol/L	mmol/L	mmol/L	U/L	U/L	U/L	U/L	umol/L	U/L
Group 2 O10, 1mg/kg, 3mg/kg, SC, two doses, n=2	Mean	0.00	36.70	6.60	217.00	284.0	124.0	30.00	2.0	235.0
	SD	0.00	13.22	2.69	107.48	13.44	50.9	1.41	0.00	26.16

Table 72: Clinical Chemistry Day 1 (Part 2)

Clinical Chemistry	Measurement	Total Protein	Albumin	Globulin (calculated)	Albumin/ Globulin Ratio	Gamma-glutamyl transferase	Glucose	Urea Nitrogen	Creatinine	Urea acid	C-reactive Protein
		TP	ALB	G	A/G	GGT	GLU	BUN	Cr	UA	CRP
Group (Day 1)		g/L	g/L	g/L	%	u/L	mmol/L	mmol/L	umol/L	umol/L	mg/L
Group 2 O10, 1mg/kg, 3mg/kg, SC, two doses, n=2	Mean	82.3	40.30	42.00	1.0	53.6	13.10	4.00	63.0	4	1.95
	SD	0.99	1.41	0.42	0.04	125.44	1.13	0.00	16.97	2.12	0.33

Table 73: Clinical Chemistry Day 8 (Part 1)

Clinical Chemistry	Measurement	Direct bilirubin	(Total) Cho-lesterol	Trigly-cerides	Creati-nine Kinase	Lactate Dehy-droge-nase	Alanine Amino-trans-ferase	Aspar-tate Amino-trans-ferase	Total Bilirubin	Alkaline Phos-phatase
		DBIL	CHO	TG	CK	LDH	ALT	AST	BIL	ALP
Group (Day 8)		umol/L	mmol/L	mmol/L	U/L	U/L	U/L	U/L	umol/L	U/L
Group 2 O10, 1mg/kg, 3mg/kg, SC, two doses, n=2	Mean	0.00	24.95	6.05	213.50	279.0	154.0	36.00	2.0	174.0
	SD	0.00	13.36	4.60	77.07	12.7	86.3	15.56	0.0	5.7

Table 74: Clinical Chemistry Day 8 (Part 2)

Clinical Chemistry	Measurement	Total Protein	Albumin	Globulin (calculated)	Albu-min/ Globulin Ratio	Gamma -glu-tamyl trans-ferase	Glu-cose	Urea Nitro-gen	Creati-nine	Urea acid	C-reac-tive Protein
		TP	ALB	G	A/G	GGT	GLU	BUN	Cr	UA	CRP
Group (Day 8)		g/L	g/L	g/L	%	u/L	mmol/L	mmol/L	umol/L	umol/L	mg/L
Group 2 O10, 1mg/kg, 3mg/kg, SC, two doses, n=2	Mean	82.1	40.00	42.05	1.0	136.9	12.70	4.00	75.0	4	2.13
	SD	0.4	2.83	3.18	0.1	121.8	2.12	1.41	18.4	4	0.23

Table 75: Clinical Chemistry Day 12 (Part 1)

Clinical Chemistry	Measurement	Direct bilirubin	(Total) Cho-lesterol	Trigly-cerides	Creati-nine Kinase	Lactate Dehy-droge-nase	Alanine Amino-trans-ferase	Aspar-tate Amino-trans-ferase	Total Bilirubin	Alkaline Phos-phatase
		DBIL	CHO	TG	CK	LDH	ALT	AST	BIL	ALP
Group (Day 8)		umol/L	mmol/L	mmol/L	U/L	U/L	U/L	U/L	umol/L	U/L
Group 2 O10, 1mg/kg, 3mg/kg, SC, two doses, n=2	Mean	0.00	24.65	1.75	262.50	431.0	55.0	33.00	3.0	136.0
	SD	0.00	8.98	1.34	136.47	32.5	22.6	0.00	0.0	7.1

Table 76: Clinical Chemistry Day 12 (Part 2)

Clinical Chemistry	Measurement	Total Protein	Albu-min	Globu-lin (calcu-lated)	Albu-min/ Globu-lin Ratio	Gamma -glu-tamyl trans-ferase	Glu-cose	Urea Nitro-gen	Creati-nine	Urea acid	C-reac-tive Protein
		TP	ALB	G	A/G	GGT	GLU	BUN	Cr	UA	CRP
Group (Day 8)		g/L	g/L	g/L	%	u/L	mmol/L	mmol/L	umol/L	umol/L	mg/L
Group 2 O10, 1mg/kg, 3mg/kg, SC, two doses, n=2	Mean	83.8	39.85	43.95	0.9	119.4	5.95	3.50	72.0	1	1.23
	SD	1.1	1.77	0.64	0.1	98.5	0.05	0.71	18.4	1	0.33

Food Intake

[0633] Food intake (g) was assessed in monkeys on days 2, 3, 4, 9, 10, 11, and 13-15. Results are detailed in Table 77.

Table 77: Food Intake

Group	Animal ID	Day 2	Day 3	Day 4	Day 9	Day 10	Day 11	Day 13	Day 14	Day 15
Group 2 O10, 1mg/kg, 3mg/kg, SC, two doses, n=2	3	120.21	193.47	202.24	64.76	141.20	183.75	0.00	114.70	141.82
	4	39.45	149.08	177.43	0.00	81.26	113.92	11.47	89.58	124.75
	Mean	79.83	171.28	189.84	32.38	111.23	148.84	5.74	102.14	133.29
	SD	57.11	31.39	17.54	45.79	42.38	49.38	8.11	17.76	12.07

[0634] Food intake was also assessed on days 1, 8, and 12 at 0.5-, 1-, 1.5-, 2-, 3-, 4-, 24-, 48-, and 72-hours post-dose. Results are detailed in Tables 78 and 79.

Table 78: Food intake Days 1 and 8

Group		Day 1									Day 8								
		0.5 h	**1 h**	**1.5 h**	**2 h**	**3 h**	**4 h**	**24 h**	**48 h**	**72 h**	**0.5 h**	**1 h**	**1.5 h**	**2 h**	**3 h**	**4 h**	**24 h**	**48 h**	**72 h**
Group 2 O10, 1mg/kg, 3mg/kg, SC, two doses, n=2	Mean	50.72	9.09	0.98	12.04	42.47	27.93	79.83	171.28	189.84	10.12	1.54	0.00	25.28	12.94	29.28	32.38	111.23	148.84
	SD	42.90	6.18	1.38	17.02	11.81	20.04	57.11	31.39	17.54	8.65	2.17	0.00	2.18	10.98	12.85	45.79	42.38	49.38

Table 79: Food Intake Day 12

Group		Day 12								
		0.5 h	**1 h**	**1.5 h**	**2 h**	**3 h**	**4 h**	**24 h**	**48 h**	**72 h**
Group 2 O10, 1mg/kg, 3mg/kg, SC, two doses, n=2	Mean	11.29	14.52	7.72	11.45	9.41	32.34	5.74	102.14	133.29
	SD	15.96	7.81	2.89	16.19	3.16	3.97	8.11	17.76	12.07

Example 11: Acute Food Intake

[0635] Food intake was assessed in 6 diet-induced obese Cynomolgus monkeys (n=6). Monkeys were first administered saline on day 1 (D1) and food intake was measured (FIGS. 7A-7D). On day 8 and day 12, monkeys were administered 1 mg/kg, O10 (Group 2; n=2), (FIGS. 8A-8H). Monkeys were fasted overnight prior to administration. Food was administered 2 hours after each dose and intake was measured at 0.5-, 1-, 1.5-, 2-, 3-, 4-, 24-, 48-, and 72-hours after dosing. Group 2 monkeys demonstrated a decrease in food intake relative to saline dosing (FIGS. 9A and 9B).

Example 12: Caloric Intake, Body Weight, and Body Composition

Food Intake and Body Composition in Monkeys

[0636] Changes in caloric intake and body weight were assessed in diet-induced obese Cynomolgus monkeys (n=6). Monkeys were orally administered O10 (MC3R/MC4R coagonist) once daily. One day 15, dosing changed to 15/mg/kg administered twice daily, and dosing was maintained until at least day 28 and monkeys were assessed until at least day 35. Control monkeys were administered saline. Daily caloric intake (FIGS. 10A), cumulative caloric intake (FIGS. 10B), percent change in caloric consumption, relative to baseline (FIGS. 10C), and caloric intake per body weight were measured in addition to food intake (also see FIGS. 11A-11R; Tables 80-98). Cumulative caloric intake and percent change in caloric intake, relative to baseline, were each reduced in the monkeys administered O10, relative to those administered saline.

[0637] Food preference towards a lower-fat diet in the monkeys administered O10 was also observed, where O10-treated monkeys consumed 50% more reduced-fat feed and 20% less high-fat feed on average compared to monkeys administered saline (FIGS. 11A-11R).

[0638] Body composition was assessed, including body weight (kg), body height (m), BMI (kg/m^2), whole body bone mineral content (g), trunk bone mineral content (g), bone density (g/cm^2), trunk fat mass (g), trunk fat mass (%), trunk muscle mass (g), trunk muscle mass (%), fat mass (g), fat mass (%), muscle mass (g), muscle mass (%), and lean mass (%) (Tables 99-104) (FIGS. 13A-13N). Diet-induced obese monkeys administered O10 showed a 7.5% weight loss in 5 weeks, relative to baseline.

[0639]

Table 80: Animal Pre-screening and Day 1 Food Intake

Food intake (g)										
Group	**Measurement**	**animal pre-screening**			**animal pre-screening**			**Day 1**		
		AM	**PM**	**Fruit**	**AM**	**PM**	**Fruit**	**AM**	**PM**	**Fruit**
Group 1 saline, p.o., QD, n=8	Mean	28.72	129.69	--	9.66	137.21	--	--	101.98	134.85
	SD	20.42	23.14	--	18.57	24.27	--	--	46.60	33.20
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID	Mean	40.54	144.54	--	31.73	144.95	--	--	101.93	122.26
	SD	33.01	13.39	--	36.82	14.51	--	--	45.97	49.12

Table 81: Days 2-4 Food Intake

Food intake (g)										
Group	**Measurement**	**Day 2**			**Day 3**			**Day 4**		
		AM	**PM**	**Fruit**	**AM**	**PM**	**Fruit**	**AM**	**PM**	**Fruit**
Group 1 saline, p.o., QD, n=8	Mean	1.81	137.23	133.89	3.51	132.73	133.32	14.41	122.99	144.17
	SD	2.15	17.31	44.67	5.30	28.92	46.34	16.15	36.95	11.40
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8),	Mean	35.63	102.78	140.95	23.05	87.15	129.25	32.28	85.12	133.71

Food intake (g)										
Group	Measurement	Day 2			Day 3			Day 4		
		AM	PM	Fruit	AM	PM	Fruit	AM	PM	Fruit
QD 20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID	SD	49.42	46.70	27.24	30.59	69.55	48.14	27.15	63.79	35.26

Table 82: Days 5-7 Food Intake

Food intake (g)										
Group	Measurement	Day 5			Day 6			Day 7		
		AM	PM	Fruit	AM	PM	Fruit	AM	PM	Fruit
Group 1 saline, p.o., QD, n=8	Mean	25.21	102.17	149.29	19.46	108.73	150.05	10.91	95.27	148.06
	SD	26.74	43.46	4.08	25.03	41.71	0.97	16.18	49.78	6.52
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID	Mean	37.92	98.93	146.40	34.08	85.90	138.97	39.47	108.68	118.20
	SD	34.17	45.02	13.22	36.56	53.05	22.03	30.31	43.62	52.58

Table 83: Days 8-10 Food Intake

Food intake (g)										
Group	**Measurement**	**Day 8**			**Day 9**			**Day 10**		
		AM	**PM**	**Fruit**	**AM**	**PM**	**Fruit**	**AM**	**PM**	**Fruit**
Group 1 saline, p.o., QD, n=8	Mean	27.26	128.54	148.97	15.15	125.90	149.79	18.03	117.30	150.51
	SD	32.10	22.81	3.49	21.49	25.72	1.99	19.40	41.84	2.50
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID	Mean	43.80	111.59	129.39	34.55	112.90	150.80	36.55	96.14	151.17
	SD	32.62	39.02	38.99	39.67	45.47	3.07	37.48	46.65	2.12
	SD	19.36	29.53	32.98	14.88	20.31	2.45	16.69	15.13	1.57

Table 84: Days 11-13 Food Intake

Food intake (g)										
Group	**Measurement**	**Day 11**			**Day 12**			**Day 13**		
		AM	**PM**	**Fruit**	**AM**	**PM**	**Fruit**	**AM**	**PM**	**Fruit**
Group 1 saline, p.o., QD, n=8	Mean	20.47	116.25	150.87	24.48	127.92	150.63	27.38	119.84	151.49
	SD	26.24	40.09	1.98	26.57	33.06	1.66	26.31	34.66	1.69
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD	Mean	40.98	101.95	149.81	48.99	100.44	150.48	38.04	107.17	150.35

Food intake (g)										
Group	Measurement	Day 11			Day 12			Day 13		
		AM	PM	Fruit	AM	PM	Fruit	AM	PM	Fruit
20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID	SD	33.86	43.59	1.77	36.91	54.60	1.09	33.43	57.21	1.68

Table 85: Day 14 Food Intake

Food intake (g)				
Group	Measurement	Day 14		
		AM	PM	Fruit
Group 1 saline, p.o., QD, n=8	Mean	19.44	111.72	150.31
	SD	26.36	35.18	1.48
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID	Mean	40.25	82.16	146.35
	SD	36.31	60.65	12.67

Table 86: Days 15 and 16 Food Intake

Group	animal measurement	Day 15			Day 16		
		AM	PM	Fruit	AM	PM	Fruit
Group 1 saline, p.o., QD, n=8	Mean	38.5925	113.9	149.4325	25.0475	114.545	150.6875
	SD	31.80052	52.34367	3.785973	31.71758	27.82156	1.56245
Group 2 O10, p.o., n=8 10mg/kg (Day 1-	Mean	45.02125	97.57875	142.2913	41.97	105.5538	121.1363
	SD	34.05088	62.89411	25.36378	34.61016	45.74607	45.70314

8), QD 20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID							

Table 87: Days 17 and 18 Food Intake

Group	animal measurement	Day 17			Day 18		
		AM	PM	Fruit	AM	PM	Fruit
Group 1 saline, p.o., QD, n=8	Mean	21.95375	115.435	137.9788	46.33	94.53875	151.525
	SD	26.0538	49.55535	39.41042	23.94622	34.91529	3.11345
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID	Mean	32.81	95.5925	126.7725	55.31625	79.3	108.5338
	SD	34.15832	63.96158	44.42461	28.40707	65.04028	60.48643

Table 88: Days 19 and 20 Food Intake

Group	animal measurement	Day 19			Day 20		
		AM	PM	Fruit	AM	PM	Fruit
Group 1 saline, p.o., QD, n=8	Mean	33.3325	115.7438	146.6225	16.05625	133.62	122.9888
	SD	32.53471	40.65942	10.73163	23.02026	26.20351	54.93729
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID	Mean	45.58125	91.6875	122.7325	40.835	97.46	104.33
	SD	25.96755	57.27054	40.21774	33.32081	43.72036	64.86716

Table 89: Days 21 and 22 Food Intake

Group	animal measurement	Day 21			Day 22		
		AM	PM	Fruit	AM	PM	Fruit (Apple)
Group 1 saline, p.o., QD, n=8	Mean	28.42875	107.7988	149.7738	14.545	122.4825	149.9025
	SD	28.2244	31.03882	1.900263	19.27357	30.43795	1.79632
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID	Mean	29.96625	87.84625	150.7288	35.69875	98.495	126.065
	SD	32.86274	57.7063	1.572627	36.23464	48.2559	47.83366

Table 90: Days 24 and 25 Food Intake

Group	Measurement	Day 24			Day 25		
		AM	PM	Fruit	AM	PM	Fruit
Group 1 saline, p.o., QD, n=8	Mean	15.1875	125.255	150.7588	18.29875	122.3863	139.4363
	SD	16.80568	27.85392	1.14588	20.85324	43.51322	29.77701
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID	Mean	41.72625	98.20375	125.375	35.34125	110.0938	131.6438
	SD	31.6025	47.6542	37.76767	36.03342	56.82867	29.42827

Table 91: Days 26 and 27 Food Intake

Group	Measurement	Day 26			Day 27			
		AM	PM	Fruit	AM	PM	Fruit	
Group 1 saline, p.o., QD, n=8	Mean	12.57	121.77	149.07	22.03375	98.49875	145.58	
	SD	24.40542	34.99332	4.822779	22.90044	46.41777	12.71348	
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID	Mean	40.09875	92.255	138.2113	42.07375	98.39125	118.6513	
	SD	33.28731	54.87541	25.65097	31.77313	58.46155	53.53374	

Table 92: Days 28 and 29 Food Intake

Group	Measurement	Day 28			Day 29			
		AM	PM	Fruit	AM	PM	Fruit	
Group 1 saline, p.o., QD, n=8	Mean	21.51125	118.5263	150.7088	N/A	56.8875	68.36875	
	SD	23.64851	34.31948	3.056176	N/A	46.25776	60.77436	
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID	Mean	34.295	94.6825	123.7563	N/A	84.38875	77.53375	
	SD	31.95077	51.40519	41.51449	N/A	62.20844	68.60765	

Table 93: Day 30 Food Intake

Group	Measurement	Day 30		
		AM	PM	Fruit
Group 1 saline, p.o., QD, n=8	Mean	11.67375	104.2775	144.1688
	SD	11.46482	50.89431	10.84557
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID	Mean	37.10125	105.085	120.5925
	SD	29.72132	45.54415	52.98185

Table 94: Food Intake (Calorie) Prescreening and Days 1-4

Food intake (calorie)							
Group	**Measurement**	**animal pre-screening**	**animal pre-screening**	**Day 1**	**Day 2**	**Day 3**	**Day 4**
Group 1 saline, p.o., QD, n=8	Mean	659.49	625.15	509.65	667.41	653.67	655.49
	SD	132.80	139.20	194.71	74.58	131.91	192.58
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID	Mean	764.85	735.80	502.87	640.98	523.48	549.38
	SD	117.28	158.90	201.14	352.85	372.06	351.18

Table 95: Days 5-10 Food Intake (Calorie)

Food intake (calorie)							
Group	**Measurement**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Day 10**
Group 1 saline, p.o., QD, n=8	Mean	606.22	614.76	525.76	726.88	634.60	607.80
	SD	251.70	194.12	236.27	146.38	136.17	212.02
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID	Mean	635.23	561.75	668.01	701.54	646.71	581.60
	SD	289.88	337.46	231.94	267.58	307.34	308.91

Table 96: Days 11-14 Food Intake (Calorie)

Food intake (calorie)					
Group	**Measurement**	**Day 11**	**Day 12**	**Day 13**	**Day 14**
Group 1 saline, p.o., QD, n=8	Mean	611.92	676.21	651.73	627.71
	SD	192.20	198.49	207.14	200.32
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID	Mean	621.76	643.49	634.15	571.09
	SD	289.99	333.19	330.88	353.32

Table 97: Days 15-22 Food Intake (Calorie)

Group	Measurement	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22
Group 1 saline, p.o., QD, n=8	Mean	703.6877	659.7127	646.1119	648.41	691.763	696.0532	603.0544	656.7564
	SD	286.849	149.1018	237.1083	181.2112	199.8555	160.5247	178.8588	169.8756
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg/kg (Day 9-14), QD	Mean	652.1302	664.8225	592.7604	591.8274	618.5284	617.2267	522.6887	615.0129
	SD	373.6455	305.9125	379.7661	369.3952	323.735	293.4429	329.8847	292.7874

Table 98: Days 24-30 Food Intake (Calorie)

Group	Measurement	Day 24	Day 25	Day 26	Day 27	Day 28	Day 29	Day 30
Group 1 saline, p.o., QD, n=8	Mean	671.39985	669.8996857	639.0352714	611.6815571	635.8829571	303.0223429	560.8711571
	SD	142.3724953	248.2354969	179.5501003	237.7878076	176.5516399	224.4573731	255.6706537
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID	Mean	634.4950375	666.6531875	609.834525	633.0230625	592.467325	404.0330625	645.478825
	SD	308.3572522	332.830924	328.5675853	317.5290018	321.5047862	275.3078471	262.1208391

Table 99: Body Composition at Baseline (Part 1)

Group	Measurement	Body weight	Body height	BMI	Whole body bone mineral content	Trunk bone mineral content	Bone density	Trunk fat mass
		kg	m	kg/m2	g	g	g/cm^2	g
Group 1 saline, p.o., QD, n=8	Mean	11.3925	0.46875	52.39938907	395.65	135.4875	0.83825	2489
	SD	2.05281514	0.030443155	11.144731312	23.2690475	14.9020073	0.045603101	1268.159972
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID	Mean	11.46	0.46875	52.255993 98	418.675	149.4875	0.871375	2471.875
	SD	2.173318726	0.03642507	8.894992785	57.99021469	23.91433745	0.062227549	1099.08812

Table 100: Body Composition at Baseline (Part 2)

Group	Measurement	Trunk fat mass	Trunk muscle mass	Trunk muscle mass	Fat mass	Fat mass	Muscle mass	Muscle mass
		%	g	%	g	%	g	%
Group 1 saline, p.o., QD, n=8	Mean	38.7625	3605.375	59.83061715	3287	30.75	6970.25	66.5853178
	SD	11.65405356	424.2802098	11.17204892	1583.54557	9.653570768	668.0149164	8.876878753
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD	Mean	38.475	3785.5	60.05691608	3223.125	30.7875	7026	66.39044693
	SD	10.99736982	792.642236	10.69439969	1412.54931	9.726611141	1560.134243	9.127144584

20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID										

Table 101: Body Composition Day 29 (Part 1)

Group	Measurement	Body weight	Body height	BMI	Whole body bone mineral content	Trunk bone mineral content	Bone density	Trunk fat mass
		kg	m	kg/m2	g	g	g/cm^2	g
Group 1 saline, p.o., QD, n=8	Mean	11.45125	0.46875	52.7105316	392.3625	135.825	0.8265	2394.375
	SD	2.01089488	0.03044316	11.3997457	22.1630283	15.0358381	0.02887906	1201.98145
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID	Mean	10.88125	0.46875	49.2328261	412.675	143.3	0.875125	2103.375
	SD	2.39911554	0.03642507	7.46423249	61.5495561	26.3972401	0.07098378	1072.03211

Table 102: Body Composition Day 29 (Part 2)

Group	Measurement	Trunk fat mass	Trunk muscle mass	Trunk muscle mass	Fat mass	Fat mass	Muscle mass	Muscle mass
		%	g	%	g	%	g	%
Group 1 saline, p.o., QD, n=8	Mean	37.5125	3691	61.0799283	3193.5	29.975	7049.25	67.362223
	SD	12.576104	493.147616	12.1271348	1552.15012	10.1629228	752.923777	9.46956517
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID	Mean	35.5375	3583	62.7968455	2826.5	28.5375	6752.875	68.3613215
	SD	12.7292618	866.349319	12.3416197	1417.4723	10.5881251	1620.04201	9.9040825

Table 103: Body Composition Change (Part 1)

Group	Animal Measurement	Body weight	Body height	BMI	Whole body bone mineral content	Trunk bone mineral content	Bone density	Trunk fat mass	Trunk fat mass
		kg	m	kg/m2	g	g	g/cm^2	g	%
Group 1 saline, p.o., QD, n=8	Mean	0.57051	0	0.57051	-0.80188	0.360312	-1.29225	-4.2308	-4.44744
	SD	1.86646	0	1.86646	2.026707	5.248808	2.720152	8.392962	8.322332
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID	Mean	-5.3671	0	-5.3671	-1.52409	-4.31462	0.376968	-15.7171	-7.99745
	SD	6.709028	0	6.709028	2.803072	6.135995	1.729331	24.72561	20.216

Table 104: Body Composition Change (Part 2)

Group	Animal Measurement	Trunk fat mass	Trunk fat mass	Trunk muscle mass	Trunk muscle mass	Fat mass	Fat mass	Muscle mass	Muscle mass
		g	%	g	%	g	%	g	%
Group 1 saline, p.o., QD, n=8	Mean	-4.2308	-4.44744	2.276212	1.982835	-3.36388	-3.36524	1.063805	1.11051

	SD	8.392962	8.322332	5.032953	3.734766	6.670888	6.571613	2.826273	2.272828
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID	Mean	-15.7171	-7.99745	-5.72336	4.732546	-13.0747	-7.62039	-4.18915	3.06466
	SD	24.72561	20.216	6.870753	10.57395	22.87258	18.60992	3.003433	6.562845

[0640] By day 8, the body weight change relative to baseline was most reduced in the monkeys administered O10, compared to monkeys administered saline (FIGS. 12A-12M) (Tables 105 and 106). Monkeys were administered O10 orally for 36 days and abstained from dosing until day 43. From days 43-50, monkeys were subcutaneously administered O10, with dosing discontinued after day 50S (FIG. 12F, 12G, 12I, 12K). A decrease in percent change in body weight was observed in monkeys administered O10, relative to saline. Following dosing discontinuation, body weight was maintained and did not rebound during the day 50-71 observations (FIGS. 12H-12J).

Table 105: Body Weight (kg) (Day 1-22)

		Day 1	Day 8	Day 15	Day 22	Day 29
Group 1 saline, p.o., QD, n=8	Mean	11.44	11.36	11.39	11.46	11.45
	SD	1.99	2.05	2.04	2.00	2.01
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID	Mean	11.50	11.23	11.06	11.00	10.88
	SD	2.18	2.21	2.23	2.37	2.40

Table 106: Body Weight (Percent Change)

Group	Animal Measurement	Day 1	Day 8	Day 15	Day 22	Day 29
Group 1 saline, p.o., QD, n=8	Mean	0.0	-0.8	-0.5	0.2	0.1
	SD	0.0	1.2	1.3	1.7	2.0
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID	Mean	0.0	-2.5	-4.0	-4.7	-5.8
	SD	0.0	2.0	3.1	4.2	5.6

[0641] Blood chemistry, clinical chemistry, gastric impact, and nausea levels were also assessed (FIGS. 18A-18D; Tables 107-118). Blood levels chemistry levels were unchanged

by day 29 from baseline in monkeys orally administered O10 relative to those administered saline. Cage side observations showed no signs of gastric distress (assessed by stool changes) or nausea (assessed by food refusal).

Table 107: Clinical Chemistry Day 1 (Part A)

Clinical Chemistry		Glucose	Alanine Aminotransferase	Aspartate Aminotransferase	Alkaline Phosphatase	Gamma-glutamyl transferase	Total Bilirubin	Total Protein	Triglycerides
		GLU	ALT	AST	ALP	GGT	TBIL	TP	TG
Day 1		mmol/L	U/L	U/L	U/L	u/L	umol/L	g/L	mmol/L
Group 1 saline, p.o., QD, n=8	Mean	3.9287 5	32.125	44	164.0375	90.5375	2.25	79.1125	1.7125
	SD	0.674525	8.576338	5.451081	65.57861	30.35664	0.886405	6.001771	1.418689
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID	Mean	3.84	42.375	55.125	189.375	107.4875	2.125	79.675	1.6
	SD	1.597552	12.65969	5.667892	95.90313	48.84089	0.640 87	2.409357	0.803563

Table 108: Clinical Chemistry Day 1 (Part B)

Clinical Chemistry		(Total) Cholesterol	Albumin	High density lipoprotein cholesterol	Low density lipoprotein cholesterol	Lactate Dehydrogenase	Creatinine	Urea Nitrogen	Creatine Kinase
		CHO	ALB	HDL-C	LDL-C	LDH	CREA	UREA	CK

Day 1		mmol/L	g/L	mmol/L	mmol/L	U/L	umol/L	mmol/L	U/L
Group 1 saline, p.o., QD, n=8	Mean	8	38.225	1.4875	4.65	693.875	102.75	5.125	238.75
	SD	3.824358	2.809744	0.313676	3.061279	231.6318	15.69122	0.991031	86.59553
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID	Mean	11.8	37.9125	1.75	7.7	947.875	94.125	5.25	534.625
	SD	9.022667	4.703931	0.410575	7.364393	310.3751	25.19885	0.886405	520.3386
	SD	3.274141	4.363301	0.286606	2.574462	170.6956	28.29942	1.669046	837.5634

Table 109: Clinical Chemistry Day 15 (Part A)

Clinical Chemistry	Measurement	Glucose	Alanine Aminotransferase	Aspartate Aminotransferase	Alkaline Phosphatase	Gamma-glutamyl transferase	Total Bilirubin	Total Protein	Triglycerides
		GLU	ALT	AST	ALP	GGT	TBIL	TP	TG
Day 15		mmol/L	U/L	U/L	U/L	u/L	umol/L	g/L	mmol/L
Group 1 saline, p.o., QD, n=8	Mean	8.81375	28	25.5	142.5625	84.6125	1.625	76.75	1.75
	SD	4.720654	9.242758	4.6291	47.90019	30.27009	0.517549	5.358838	1.75987
Group 2	Mean	9.0975	41.625	29.625	170.0625	96.5375	2	78.675	1.8375

O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID	SD	4.4593 1	16.99527	4.983903	72.47878	45.73161	0.534522	3.946698	1.697845

Table 110: Clinical Chemistry Day 15 (Part B)

Clinical Chemistry	Measurement	(Total) Cholesterol	Albumin	High density lipoprotein cholesterol	Low density lipoprotein cholesterol	Lactate Dehydrogenase	Creatinine	Urea Nitrogen	Creatinine Kinase
		CHO	ALB	HDL-C	LDL-C	LDH	CREA	UREA	CK
Day 15		mmol/L	g/L	mmol/L	mmol/L	U/L	umol/L	mmol/L	U/L
Group 1 saline, p.o., QD, n=8	Mean	8.8	38.5	1.7	5.4125	266.625	95.875	3.625	129.5
	SD	5.218648	3.685493	0.40708	4.058655	59.62247	15.16987	1.505941	28.15462
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg/kg (Day 9-14),	Mean	11.1625	38.475	1.725	7.3125	432.75	85.25	3.125	134
	SD	8.848719	4.833144	0.384522	6.701479	173.7739	21.78958	0.834523	47.02677

QD 15mg/kg (Started on Day 15), BID									

Table 111: Clinical Chemistry Day 29 (Part A)

Clinical Chemistry	Measurement	Glucose	Alanine Aminotransferase	Aspartate Aminotransferase	Alkaline Phosphatase	Gamma-glutamyl transferase	Total Bilirubin	Total Protein	Triglycerides
		GLU	ALT	AST	ALP	GGT	TBIL	TP	TG
Day 29		mmol/L	U/L	U/L	U/L	u/L	umol/L	g/L	mmol/L
Group 1 saline, p.o., QD, n=8	Mean	8.48125	25.125	28.5	160	88.7125	1.125	73.65	2.375
	SD	4.44434	10.52124	5.682052	42.4937	34.42484	0.64087	4.809811	1.890389
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID	Mean	8.825	40	30	220	123.1	1.625	77.1625	2.1625
	SD	4.593701	24.0238	5.830952	81.00794	73.50392	1.06066	3.552037	1.789603

Table 112: Clinical Chemistry Day 29 (Part B)

Clinical Chemistry	Measurement	(Total) Cholesterol	Albumin	High density lipoprotein cholesterol	Low density lipoprotein cholesterol	Lactate Dehydrogenase	Creatinine	Urea Nitrogen	Creatinine Kinase
		CHO	ALB	HDL-C	LDL-C	LDH	CREA	UREA	CK
Day 29		mmol/L	g/L	mmol/L	mmol/L	U/L	umol/L	mmol/L	U/L
Group 1 saline, p.o., QD, n=8	Mean	9.6375	35.425	1.7	5.9875	399.125	93.625	6	120.825
	SD	5.233119	3.162165	0.414039	4.046317	123.6891	13.75227	2	44.37901
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID	Mean	11.2625	35.7625	1.7	7.1625	440	86.25	4.875	113.6375
	SD	10.24499	5.130006	0.58554	7.183302	178.764	24.04014	0.834523	45.20414

Table 113: Complete Blood Count Day 1 (Part A)

CBC	Measurement	Total white blood cell count	Red blood cell count	Hemoglobin	Hematocrit	Mean corpuscular volume	Mean corpuscular hemoglobin	Mean corpuscular hemoglobin concentration	Red cell distribution width	Platelet count	Mean platelet volume
		WBC	RBC	HGB	HCT	MCV	MCH	MCHC	RDW	PLT	MPV
Day 1		109/L	1012/L	g/L	%	fL	pg	g/L	%	109/L	fL
Group 1 saline, p.o., QD, n=8	Mean	23.52	5.96125	137	46.275	77.4375	22.9375	296.125	13.6125	430.625	11.75
	SD	5.864472	0.604375	18.53953	6.136716	4.133465	1.622113	7.079901	0.865922	36.52763	1.409154
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID	Mean	18.08125	5.87	127.375	42.9625	73.3	21.7625	296.5	13.7125	459.75	11.1375
	SD	3.083655	0.292282	5.78027	1.542667	3.601587	1.355347	5.879747	0.522186	84.11175	0.450198
	SD	1.319066	0.636114	11.47591	3.825478	2.890255	0.790908	5.578978	0.764269	58.50504	1.218826
	SD	3.617786	0.443976	11.24965	3.645325	3.686171	1.268013	7.453427	0.755811	78.89403	0.906721

Table 114: Complete Blood Count Day 1 (Part B)

CBC	Measurement	Neutrophils	Lymphocytes	Monocytes	Eosinophils	Basophils	Neutrophils	Lymphocytes	Monocytes	Eosinophils	Basophils
		#NEUT	#LYMP	#MONO	#EOS	#BASO	%NEUT	%LYMP	%MONO	%EOS	%BASO
Day 1		109/L	109/L	109/L	109/L	109/L	%	%	%	%	%
Group 1 saline, p.o.,	Mean	17.47125	4.53	1.42625	0.0925	0	74.025	19.475	6.1	0.4	0
	SD	4.98689	1.737354	0.5439	0.070051	0	6.980534	6.10708	1.705453	0.282843	0

QD, n=8											
Group 2	Mean	13.6525	3.165	1.16875	0.095	0	75.1125	18	6.2875	0.6	0
O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID	SD	2.44823	2.142705	0.203991	0.089403	0	12.18511	12.21263	0.903861	0.50409	0

Table 115: Complete Blood Count Day 15 (Part A)

CBC	Measurement	Total white blood cell count	Red blood cell count	Hemoglobin	Hematocrit	Mean corpuscular volume	Mean corpuscular hemoglobin	Mean corpuscular hemoglobin concentration	Red cell distribution width	Platelet count	Mean platelet volume
		WBC	RBC	HGB	HCT	MCV	MCH	MCHC	RDW	PLT	MPV
Day 15		109/L	1012/L	g/L	%	fL	pg	g/L	%	109/L	fL
Group 1 saline, p.o., QD, n=8	Mean	15.565	6.0275	138.375	47.15	78.1125	23	293.5	13.8	423.75	11.2125
	SD	2.62518	0.530815	15.59247	5.160288	3.732268	1.600893	8.194075	0.884792	50.56467	1.409597

Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID	Mean	14.7825	5.67625	123.25	42.125	74.1375	21.725	292.375	14.0875	512.375	9.8875
	SD	2.415189	0.460029	13.1448	4.305063	3.470668	1.339243	6.209152	0.559177	155.9633	0.591457
	SD	3.107244	0.558109	10.41633	3.671682	3.057748	0.740536	4.810702	0.854296	56.0994	1.225255

Table 116: Complete Blood Count Day 15 (Part B)

CBC	Measurement	Neutrophils	Lymphocytes	Monocytes	Eosinophils	Basophils	Neutrophils	Lymphocytes	Monocytes	Eosinophils	Basophils
		#NEUT	#LYMP	#MONO	#EOS	#BASO	%NEUT	%LYMP	%MONO	%EOS	%BASO
Day 15		109/L	109/L	109/L	109/L	109/L	%	%	%	%	%
Group 1 saline, p.o., QD, n=8	Mean	6.4775	7.53875	1.24875	0.29125	0.00875	41.7	48.475	8	1.775	0.05
	SD	2.365271	2.116604	0.381143	0.208562	0.00991	13.48947	11.73551	1.797617	1.072714	0.053452
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg	Mean	7.40875	5.96125	1.16875	0.24125	0.0025	49.625	40.6	8.075	1.6875	0.0125
	SD	2.031948	1.598262	0.538395	0.11507	0.007071	9.623298	9.659045	4.155461	0.862616	0.035355

/kg (Day 9-14), QD 15mg /kg (Started on Day 15), BID											

Table 117: Complete Blood Count Day 29 (Part A)

		WBC	RBC	HGB	HCT	MCV	MCH	MCHC	RDW	PLT	MPV
Day 29		109/L	1012/L	g/L	%	fL	pg	g/L	%	109/L	fL
Group 1 saline, p.o., QD, n=8	Mean	15.8825	6.1775	143.25	48.225	78.0125	23.1875	297.25	13.65	418.5	11.9125
	SD	3.156778	0.523416	14.99286	5.10091	3.985845	1.535706	7.025464	0.81416	45.64772	1.453506
Group 2 O10, p.o., n=8 10mg /kg (Day 1-8), QD 20mg /kg (Day 9-14), QD 15mg /kg (Started on Day 15), BID	Mean	15.0475	5.768775	124.25	42.7375	74.1125	21.5625	290.5	13.825	453.375	11.1375
	SD	4.344621	0.353773	11.87735	3.498137	4.089163	1.574745	6.279217	0.483292	149.5755	0.639056

Table 118: Complete Blood Count Day 29 (Part B)

CBC	Measurement	Neutrophils	Lymphocytes	Monocytes	Eosinophils	Basophils	Neutrophils	Lymphocytes	Monocytes	Eosinophils	Basophils
		#NEUT	#LYMP	#MONO	#EOS	#BASO	%NEUT	%LYMP	%MONO	%EOS	%BASO
Day 29		109/L	109/L	109/L	109/L	109/L	%	%	%	%	%
Group 1 saline, p.o., QD, n=8	Mean	5.88875	8.415	1.21875	0.355	0.005	37.9625	52.3875	7.55	2.075	0.025
	SD	1.712729	2.739859	0.417182	0.269603	0.009258	12.21942	11.01498	1.481312	1.309035	0.046291
Group 2 O10, p.o., n=8 10mg/kg (Day 1-8), QD 20mg/kg (Day 9-14), QD 15mg/kg (Started on Day 15), BID	Mean	7.88375	5.77	1.17375	0.22	0	50.1875	40.4	7.8625	1.55	0
	SD	4.358178	1.925914	0.706964	0.121773	0	13.18803	13.31422	3.981722	0.789213	0
	SD	2.043951	1.461826	0.213299	0.329287	0.004082	9.09586	8.594805	1.704993	2.056858	0.040825

Pigmentation Observations

[0642] Changes in pigmentation were observed in the monkeys orally administered O10, where, at high doses of O10, a tanning effect was observed. The tanning effect comprised skin darkening without hyperpigmentation (e.g., an uneven distribution of melanin) compared to baseline. Notably, the tanning effect was only seen in typically sun-exposed skin, with no observation of ectopic tanning (e.g., palms, gums, etc.). Monkeys

were never exposed to sunlight. Pigmentation resolved back to baseline levels rapidly after treatment was discontinued.

[0643] The slope of the O10 weight loss curve (FIG. 16I) suggests that a lower dose of O10 may be employed for the same efficacy. This suggests presence of a therapeutic window between weight loss and pigmentation (i.e., tanning effect). Combinations with weight loss agents may permit usage of lower doses of both agents, limiting side effects, and increasing therapeutic window further.

Food Intake and Body Composition in Rats

[0644] Normalized cumulative food consumption (FIG. 11Q), and percent change in body weight (FIG. 12L) were assessed in rats administered the following MC4R selective agonists: Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 48; A07D), Ac-Nle-c[Glu-Pro-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 106; O7) and Ac-Nle-c[Glu-Pro-dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 62; O11) (n=5) or MC3R/MC4R co-agonist O10 compared to saline controls (n=4). For each treatment group, rats were subcutaneously administered 0.5 mg/kg of A07D, O7, O10, or O11 for days 1-7 and 1 mg/kg for days 8-17. O11 and O7 did not appear to influence food consumption as a percent of food consumption in saline-treated rats, relative to O10 (FIG. 11Q). At 17 days, O10 treated rats gained only about 0.64% of their body weight compared to saline, which gained about 8.98% body weight (**) (FIG. 12L). O10-treated rats gained less weight than O7-treated rats (****), A07D-treated rats (*), and O11-treated rats (p=.066). O10, an MC3R/MC4R coagonist, also exhibited a stronger influence on caloric consumption, as measures by cumulative food consumption) than the MC4R selective agonists. However, both the MC4R selective agonists and the MC3R/MC4R coagonists were each more effective in reducing body weight relative to saline controls.

Example 13: Cardiac Effects

[0645] Changes in cardiac effects were assessed in rats subcutaneously administered O10 at either 0.5 mg/kg, 1 mg/kg, or 3 mg/kg. Control rats were administered saline. Animal specifications are outlined in Table 119.

Table 119: Animal Specifications

Species Level Age	Sprague-Dawley (SD) Rats SPF 6-7 weeks
Sex	Male
Animal Number (N)	30

Animal Housing

[0646] 6-7 week old male SD rats were obtained and housed in a controlled environment (target conditions: temperature 20 to 24°C, relative humidity 30 to 70%). Temperature and relative humidity was monitored daily. An electronic time-controlled lighting system was used to provide a 12-hour light/12-hour dark cycle. Rats were housed in plastic cages. Enrichment toys were provided. During the housing and study period, the rats were fed with normal chow and fresh water, *ad libitum*.

Animal Acclimation

[0647] After arrival, the animals acclimated to environment for at least 5 days.

Study Design

[0648] Before the experiment, the weight of each animal was measured and rats were be separated into different groups based on weight, with 3 rats per group (Table 120).

Table 120: Study Groups

Group	**Treatment**	**Dosage (mg/kg)**	**Route**	**Volume (mL/kg)**	**Concentration (mg/ml)**	**Monitoring time**	**Number of rats**	**Frequency**
1	Control (Saline)	-	SC	5ml/kg	-	3h	3	Single dose
5	O10	0.5mg/kg			0.1	3h	3	
6	O10	1mg/kg			0.2	3h	3	

7	O10	3mg/kg			0.6	3h	3	

Blood Pressure and 2-Lead ECG Monitoring

[0649] After acclimatization, animals were anesthetized with urethane as well as subjected to femoral vein for drug injection and carotid common artery to measure blood pressure. Meanwhile, electrocardiogram (ECG) was detected by subcutaneous puncture needle electrodes. The body temperature of the rats was maintained at about 37°C during assessments and experimentation. The blood pressure (BP) and ECG was recorded for 15 minutes before administration and for 3 hours after administration continuously for each rat.

Readouts

[0650] Systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were recorded with blood pressure measurements.

[0651] QRS, ST, QT, P wave, T wave, and HR were assessed with ECG measurements.

[0652] Recording duration occurred from -15 min (pre-dose) to 180 min (after dosing).

Blood Collection

[0653] After recording, animals were euthanized with CO_2 immediately and blood was collected for *in vitro* analysis, including plasma corticosterone by ELISA Kit.

Data Processing and Analysis

[0654] All values were expressed as mean ± SEM. The significances of the differences among groups and within groups was evaluated by one-way ANOVA followed by Dunnett's test using Graph Pad statistic software. A p value of less than 0.05 was considered statistically significant. Results for the BP analysis are shown for all groups in Tables 121-123 and for groups 1 and 5-7 in FIGS. 15A-15C. ECG results are shown in Tables 124-128.

Table 121: Blood Pressure Analysis (Part 1)

Group	Animal Measurement	SBP(mmHg)								
		0min	5min	15min	30min	60min	90min	120min	150min	180min
G1: Control	Mean	108	112	112	113	104	106	108	107	107
	SEM	5	2	3	3	9	4	9	8	5

	SEM	1	0	2	1	3	1	2	2	2
G5: O10 0.5mg/kg	Mean	105	104	104	103	107	106	106	110	109
	SEM	1	1	1	1	5	1	1	3	2
G6: O10 1mg/kg	Mean	107	111	110	108	111	108	110	107	110
	SEM	1	1	2	1	2	5	4	4	3
G7: O10 3mg/kg	Mean	103	110	107	109	113	112	109	117	113
	SEM	3	3	2	4	3	3	2	5	4
	SEM	1	5	4	1	1	1	4	1	2

Table 122: Blood Pressure Analysis (Part 2)

Group	**Animal Measurement**	**DBP(mmHg)**								
		0min	**5min**	**15min**	**30min**	**60min**	**90min**	**120min**	**150min**	**180min**
G1: Control	Mean	77	83	81	81	72	73	78	75	74
	SEM	6	4	3	4	9	4	9	8	6
	SEM	2	1	2	1	3	2	3	2	3
G5: O10 0.5mg/kg	Mean	76	74	73	73	78	76	77	82	80
	SEM	2	1	1	2	4	1	2	2	1
G6: O10 1mg/kg	Mean	78	81	80	78	80	76	79	75	79
	SEM	2	4	3	3	4	7	5	4	4
G7: O10 3mg/kg	Mean	74	81	77	80	84	83	81	88	84
	SEM	5	6	4	7	5	6	1	7	7
	SEM	4	5	2	5	4	5	5	2	2

Table 123: Blood Pressure Analysis (Part 3)

Group	**Animal Measurement**	**HR(BPM)**								
		0min	**5min**	**15min**	**30min**	**60min**	**90min**	**120min**	**150min**	**180min**
G1: Control	Mean	370	385	367	374	377	354	352	358	353
	SEM	27	20	23	1	26	31	12	4	27
	SEM	21	21	22	8	26	16	9	17	23
G5: O10 0.5mg/kg	Mean	338	333	323	326	368	366	369	381	375
	SEM	28	30	25	22	24	16	15	18	14
	Mean	325	352	345	339	346	362	383	392	386

G6: O10 1mg/kg	SEM	20	32	33	34	42	38	18	19	21
G7: O10 3mg/kg	Mean	319	363	336	325	377	385	345	394	391
	SEM	8	15	11	15	20	16	16	16	14
	SEM	27	15	5	16	35	29	23	23	21

Table 124: ECG Results (Part 1)

Group	**Animal Measurement**	**Heart Rate (BPM)**								
		0min	**5min**	**15min**	**30min**	**60min**	**90min**	**120min**	**150min**	**180min**
G1: Control	Mean	369	385	367	374	377	358	352	358	353
	SEM	28	20	23	1	26	35	12	5	27
	SEM	21	20	22	8	26	16	9	16	23
G5: O10 0.5mg/kg	Mean	338	333	322	326	368	366	361	381	374
	SEM	28	30	25	22	24	16	19	18	14
G6: O10 1mg/kg	Mean	326	352	345	339	346	362	383	391	386
	SEM	20	32	33	34	42	38	18	18	21
G7: O10 3mg/kg	Mean	319	363	336	325	376	385	345	394	390
	SEM	8	15	11	15	20	16	16	16	13
	SEM	27	15	5	16	36	29	23	24	20

Table 125: ECG Results (Part 2)

Group	**Animal Measurement**	**PR Interval (s)**								
		0min	**5min**	**15min**	**30min**	**60min**	**90min**	**120min**	**150min**	**180min**
G1: Control	Mean	0.0494	0.0496	0.0501	0.0502	0.0505	0.0508	0.0543	0.0531	0.0533
	SEM	0.0026	0.0023	0.0021	0.0007	0.0009	0.0027	0.0009	0.0008	0.0020
	SEM	0.0015	0.0011	0.0015	0.0007	0.0018	0.0014	0.0007	0.0006	0.0006
G5: O10 0.5mg/kg	Mean	0.0521	0.0522	0.0535	0.0527	0.0515	0.0511	0.0514	0.0493	0.0485
	SEM	0.0017	0.0020	0.0018	0.0014	0.0007	0.0009	0.0009	0.0005	0.0007
G6: O10 1mg/kg	Mean	0.0546	0.0512	0.0529	0.0541	0.0503	0.0522	0.0515	0.0505	0.0511
	SEM	0.0035	0.0032	0.0033	0.0028	0.0007	0.0042	0.0041	0.0035	0.0031
G7: O10 3mg/kg	Mean	0.0558	0.0515	0.0537	0.0531	0.0508	0.0512	0.0527	0.0496	0.0495
	SEM	0.0031	0.0028	0.0016	0.0023	0.0019	0.0019	0.0035	0.0018	0.0016

	SEM	0.0009	0.0027	0.0030	0.0016	0.0008	0.0005	0.0007	0.0007	0.0011

Table 126: ECG Results (Part 3)

Group	Animal Measurement	QRS Interval (s)								
		0min	5min	15min	30min	60min	90min	120min	150min	180min
G1: Control	Mean	0.0153	0.0157	0.0158	0.0167	0.0166	0.0167	0.0170	0.0167	0.0165
	SEM	0.0020	0.0018	0.0018	0.0020	0.0020	0.0019	0.0021	0.0019	0.0020
	SEM	0.0012	0.0009	0.0011	0.0011	0.0010	0.0010	0.0011	0.0012	0.0011
G5: O10 0.5mg/kg	Mean	0.0157	0.0160	0.0159	0.0167	0.0162	0.0164	0.0166	0.0167	0.0167
	SEM	0.0008	0.0008	0.0007	0.0007	0.0007	0.0008	0.0008	0.0015	0.0013
G6: O10 1mg/kg	Mean	0.0158	0.0160	0.0163	0.0162	0.0166	0.0164	0.0160	0.0160	0.0161
	SEM	0.0008	0.0007	0.0009	0.0007	0.0009	0.0009	0.0008	0.0008	0.0008
G7: O10 3mg/kg	Mean	0.0171	0.0171	0.0169	0.0171	0.0177	0.0171	0.0177	0.0173	0.0168
	SEM	0.0012	0.0008	0.0010	0.0005	0.0010	0.0006	0.0007	0.0011	0.0007
	SEM	0.0010	0.0008	0.0004	0.0010	0.0004	0.0008	0.0006	0.0002	0.0003

Table 127: ECG Results (Part 4)

Group	Animal Measurement	QTc (s)								
		0min	5min	15min	30min	60min	90min	120min	150min	180min
G1: Control	Mean	0.1498	0.1534	0.1489	0.1531	0.1563	0.1528	0.1612	0.1637	0.1618
	SEM	0.0015	0.0029	0.0044	0.0018	0.0050	0.0064	0.0136	0.0112	0.0047
	SEM	0.0318	0.0319	0.0333	0.0347	0.0380	0.0379	0.0379	0.0397	0.0409
G5: O10 0.5mg/kg	Mean	0.1374	0.1414	0.1391	0.1420	0.1532	0.1511	0.1527	0.1595	0.1559
	SEM	0.0085	0.0103	0.0094	0.0103	0.0090	0.0088	0.0078	0.0038	0.0017
G6: O10 1mg/kg	Mean	0.1234	0.1334	0.1343	0.1326	0.1377	0.1436	0.1490	0.1514	0.1503
	SEM	0.0020	0.0062	0.0047	0.0065	0.0083	0.0098	0.0098	0.0129	0.0139
	Mean	0.1339	0.1532	0.1436	0.1421	0.1563	0.1552	0.1451	0.1644	0.1566

G7: O10 3mg/kg	SEM	0.0040	0.0061	0.0030	0.0078	0.0064	0.0058	0.0049	0.0064	0.0072
	SEM	0.0092	0.0036	0.0064	0.0112	0.0111	0.0105	0.0048	0.0048	0.0050

Table 128: ECG Results (Part 5)

Group	Animal Measurement	ST Height								
		0min	5min	15min	30min	60min	90min	120min	150min	180min
G1: Control	Mean	0.2026	0.1896	0.2176	0.3175	0.3091	0.2614	0.3198	0.2771	0.2747
	SEM	0.1758	0.1558	0.1512	0.1324	0.1234	0.1749	0.1303	0.1402	0.1268
	SEM	0.2106	0.3526	0.2888	0.4242	0.4138	0.4416	0.3763	0.3743	0.3979
G5: O10 0.5mg/kg	Mean	0.4430	0.4196	0.4448	0.4356	0.4014	0.3720	0.3410	0.3174	0.3015
	SEM	0.0826	0.0615	0.0682	0.0691	0.0593	0.0536	0.0437	0.0496	0.0621
G6: O10 1mg/kg	Mean	0.5708	0.5389	0.5473	0.5243	0.4959	0.4805	0.4531	0.3919	0.3693
	SEM	0.1687	0.1876	0.1863	0.2198	0.2343	0.2333	0.2165	0.2060	0.1890
G7: O10 3mg/kg	Mean	0.3120	0.2776	0.3217	0.3108	0.3156	0.2888	0.2587	0.2901	0.2936
	SEM	0.1434	0.1294	0.1456	0.1638	0.1484	0.1576	0.2083	0.1746	0.1939
	SEM	0.1178	0.1478	0.1085	0.1467	0.1726	0.1752	0.1830	0.2104	0.2045

[0655] No significant changes in systolic blood pressure (SBP) (FIG. 15A), diastolic blood pressure (DBP) (FIG. 15B), nor heart rate (HR) (FIG. 15C) were observed in rats administered O10 at any dose, relative to controls. Comparably, setmelanotide-treated animals showed at some doses, there were changes in QTc, suggesting altered cardiac repolarization. (FIGS. 16A-16D).

[0656] Normalized heart rate (HR), QTc, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), QT interval, QRS interval, and RR interval were also assessed in male cynomolgus monkeys orally administered 3 mg/kg, 10 mg/kg, 30 mg/kg, or 60 mg/kg O10 (FIGS. 17A-17H). Relative to control cynomolgus monkeys administered saline, no significant cardiac effects were observed in monkeys administered O10 at any dose. In contrast, monkeys administered setmelanotide experienced an increase

in SBP, DBP, and MBP, relative to monkeys administered saline. This increase was also observed during the dark cycle ("lights off" FIGS. 17C-17H). No increase in these parameters were observed at any time point in monkeys administered O10, relative to those administered saline

Example 14: Assessing Off-Target Binding of O10

[0657] O10 was assessed for interaction with RFamide receptors, which are hypothesized to cause cardiac activation in MC4R-targeting small molecules and peptides (Table 129).

Table 129: O10 Assessment for RFamide Receptor Binding

Agonist mode, EC_{50} (nM)						Antagonist mode, IC_{50} (nM)					
GPR54	NPFF1	NPFF2S	NPY1	PrRP	QRFP	GPR54	NPFF1	NPFF2S	NPY1	PrRP	QRFP
>2000	>1000	>2000	>1000	>2000	>2000	>1000	>1000	>1000	>1000	>1000	>1000

[0658] Generally, O10 did not agonize or antagonize RFamide receptors up to 1000 nM (top concentration tested), 1000x-100,000x above their respective EC50s on MC4R. Additionally, no hERG inhibition observed from O10 at concentrations up to 30 µM.

[0659] O10 was next screened for binding against a panel of 87 receptors and channels at 10 µM. Results showing an inhibition or stimulation higher than 50% were considered to represent significant effects of the test compounds. O10 only showed >50% inhibition of control on melanocortin receptors (FIG. 18). O10 was shown to have minimal inhibition at 10 µM for cytochrome P450 (CYP) enzymes (Table 130 and Table 131). O10 showed no meaningful impact on CYP induction or inhibition at physiologically relevant concentrations, demonstrating minimal drug-drug interactions.

Table 130: Assessing Time Dependent CYP Inhibition

CYP	Substrate	O10 Mean (Min, Max)
1A	HLM, phenacetin substrate + NADPH	14.8 (12.6, 17.0)
1A	HLM, phenacetin substrate - NADPH	4.0 (3.9, 4.0)
2B6	HLM, bupropion substrate + NADPH	6.6 (4.6, 8.7)
2B6	HLM, bupropion substrate - NADPH	4.1 (3.0, 5.2)
2C9	HLM, diclofenac substrate + NADPH	1.6 (-1.0, 4.2)
2C9	HLM, diclofenac substrate - NADPH	1.6 (-0.3, 3.6)
2C19	HLM, omeprazole substrate + NADPH	-6.2 (-6.5, -5.9)
2C19	HLM, omeprazole substrate - NADPH	-4.1 (-5.0, -3.1)
2D6	HLM, dextromethorphan substrate + NADPH	5.5 (4.6, 6.4)
2D6	HLM, dextromethorphan substrate - NADPH	0.2 (-3.8, 4.2)
3A	HLM, midazolam substrate + NADPH	-1.2 (-1.7, -0.7)
3A	HLM, midazolam substrate - NADPH	2.8 (0.3, 5.3)

1A	HLM, phenacetin substrate	10.5 (2.0, 19.0)
2B6	HLM, bupropion substrate	21.1 (20.0, 22.1)
2C9	HLM, diclofenac substrate	0.5 (-1.3, 2.2)
2C19	HLM, omeprazole substrate	73.0 (70.1, 76.0)
2D6	HLM, dextromethorphan substrate	4.8 (1.8, 7.8)
3A	HLM, midazolam substrate	12.0 (7.4, 16.6)

Table 131: Assessing O10 and CYP Induction

CYP	Donor	mRNA Fold Induction of Hepatocytes with Different Treatments: Mean (Min, Max)				
		O10 at Nominal Concentrations			Neg Control	Pos Control*
		1 µM	10 µM	100 µM	Flumazenil (30 µM)	*
1A2	1	1.6 (0.97, 2.38)	1.4 (1.3, 1.53)	1.2 (1.09, 1.38)	1.0	29.3
	2	0.7 (0.45, 0.86)	0.6 (0.58, 0.74)	0.7 (0.52, 1.07)	1.1	14.1
	3	1.6 (0.4, 2.71)	0.9 (0.78, 0.99)	0.8 (0.61, 1.03)	0.9	23.8

2B6	1	3.4 (2.26, 4.78)	1.7 (1.41, 1.91)	1.4 (1.16, 1.78)	1.0	8.2
	2	0.7 (0.45, 0.91)	0.8 (0.65, 0.97)	1.6 (1.0, 2.16)	1.8	8.3
	3	NA	1.1 (1.09, 1.14)	0.9 (0.72, 1.09)	1.3	8.7
3A4	1	3.1 (1.97, 5.31)	20.4 (17.6, 23.2)	3.4 (3.42, 3.55)	0.8	30.7
	2	0.4 (0.34, 0.60)	0.6 (0.50, 0.73)	0.5 (0.32, 0.74)	1.1	18.5
	3	NA	0.8 (0.69, 0.98	0.5 (0.30, 0.75)	1.2	23.8

*Positive controls: Omeprazole (50 µM) for CYP1A2; Phenobarbital (1 mM) for CYP2B6; Rifampicin (10 µM) for CYP3A4.

Example 15: Assessing Adipose Tissue Effects of O10

[0660] To assess adipose tissue effects from O10 administration, fat tissue was harvested from diet-induced obese cynomolgus monkeys orally administered 10 mg/kg O10 or saline control. O10-treated monkeys showed (1) smaller lipid droplets, (2) darker, dense staining likely attributed to higher mitochondrial concentrations, and (3) increased vascularization, relative to saline controls (FIG 20; H&E staining, 200x), consistent with beige/brown adipocytes. This suggests that O10 administration may stimulate metabolic remodeling through adipose tissue browning, which in turn may increase metabolic rate and calorie burn and may improve insulin sensitivity.

Example 16: Assessing absorption, distribution, metabolism, and excretion of non-naturally occurring melanocortin analogs

[0661] Non-naturally occurring melanocortin analogs of the present technology, O10 and C2, were assessed for solution properties, in vitro absorption, and in vitro metabolism for absorption, distribution, metabolism, and excretion (ADME) properties. Various ADME outcomes are outlined in Table 132.

Aqueous Solubility

[0662] Aqueous solubility (μM) was determined by comparing the peak area of the principal peak in a calibration standard (200 μM) containing organic solvent (methanol/water, 60/40, v/v) with the peak area of the corresponding peak in a buffer sample. Additionally, chromatographic purity (%) was defined as the peak area of the principal peak relative to the total integrated peak area in the HPLC chromatogram of the calibration standard. A chromatogram of the calibration standard of each test compound, along with a UV/VIS spectrum with labeled absorbance maxima, was generated.

HPLC-UV Screen

[0663] A chromatogram of the test compound (200 μM) along with a UV/VIS spectrum with labeled absorbance maxima, was generated.

Protein Binding

[0664] The peak areas of the test compound in the buffer and test samples were used to calculate percent binding and recovery according to the following formulas:

Protein binding (%)= $(Area_p - Area_b Area_p) * 100$

Recovery (%)=$((Area_p + Area_b)/Area_c) * 100$

where:

$Area_p$ = Peak area of analyte in protein matrix

$Area_b$ = Peak area of analyte in buffer

$Area_c$ = Peak area of analyte in control sample

Partition Coefficient

[0665] The total amount of compound was determined as the peak area of the principal peak in a calibration standard (100 μM) containing organic solvent (methanol/water, 60/40, v/v). The amount of compound in buffer was determined as the combined, volume-corrected, and weighted areas of the corresponding peaks in the aqueous phases of three organic-aqueous samples of different composition. An automated weighting system was used to ensure the preferred use of raw data from those samples with well quantifiable peak signals.

The amount of compound in organic was calculated by subtraction. Subsequently, LogD was calculated as the Log10 of the amount of compound in the organic phase divided by the amount of compound in the aqueous phase.

Half-Life Determination

[0666] At the end of the incubation at each of the time points, an equal volume of an organic mixture (acetonitrile/methanol, 50/50, v/v) was added to the incubation mixture. Samples were analyzed by HPLC-MS/MS and corresponding peak areas were recorded for each analyte. The ratio of precursor compound remaining after each time point relative to the amount present at time 0, expressed as percent, is reported as chemical stability. The half-life ($T_{1/2}$) was estimated from the slope of the initial linear range of the logarithmic curve of compound remaining (%) versus time, assuming first-order kinetics.

ADME-Tox: In Vitro Absorption

Permeability

[0667] The apparent permeability coefficient (Papp) of the test compound was calculated as follows:

$P_{app}(cm/s)=(V_R \cdot C_{R,end}/\Delta t) \cdot (1/A^*(C_{D,mid}-C_{R,mid}))$

where:

V_R is the volume of the receiver chamber.

$C_{R,end}$ is the concentration of the test compound in the receiver chamber at the end time point.

Δt is the incubation time.

A is the surface area of the cell monolayer.

$C_{D,mid}$ is the calculated mid-point concentration of the test compound in the donor side, which is the mean value of the donor concentration at time 0 minute and the donor concentration at the end time point.

$C_{R,mid}$ is the mid-point concentration of the test compound in the receiver side, which is one half of the receiver concentration at the end time point. Concentrations of the test compound were expressed as peak areas of the test

Recovery of the Test Compound from the Permeability Assay

[0668] The recovery of the test compound was calculated as follows:

Recovery (%)=$((V_D \cdot C_{D,end}+V_R \cdot C_{R,end})/(V_D \cdot C_{D0}))*100$

where: V_D and V_R are the volumes of the donor and receiver chambers, respectively.

$C_{D,end}$ is the concentration of the test compound in the donor sample at the end time point.

$C_{R,end}$ is the concentration of the test compound in the receiver sample at the end time point.

C_{D0} is the concentration of the test compound in the donor sample at time zero. Concentrations of the test compound are expressed as peak areas of the test compound.

Fluorescein Assessment for Permeability Assays

[0669] Fluorescein was used as the cell monolayer integrity marker. Fluorescein permeability assessment (in the A-B direction at pH 7.4 on both sides) was performed after the permeability assay for the test compound. The cell monolayer that had a fluorescein permeability of less than 1.5×10^{-6} cm/s for Caco-2 and MDR1-MDCKII cells and 2.5×10^{-6} cm/s for MDCKII cells was considered intact, and the permeability result of the test compound from intact cell monolayer is reported.

ADME-Tox: In Vitro Metabolism

Intrinsic Clearance (microsomes, S9, cryopreserved hepatocytes, recombinant CYP, recombinant UGT)

[0670] Metabolic stability, expressed as percent of the parent compound remaining, was calculated by comparing the peak area of the compound at the time point relative to that at time-0. The half-life ($T_{1/2}$) was estimated from the slope of the initial linear range of the logarithmic curve of compound remaining (%) vs. time, assuming first-order kinetics. The apparent intrinsic clearance (CL_{int}, in µL/min/pmol, µL/min/mg or µL/min/Mcell) was calculated according to the following formula:

$CL_{int} = 0.693/(T_{1/2}$*(mg protein/μL or million cells/μL or pmol CYP isoyme/μL))

Table 132: ADME Assessment of Non-Naturally Occurring Analogs and Reference Compounds

Compound	Test Concentration	Percent Protein Bound (1st replicate)(%)	Percent Protein Bound (2nd replicate)(%)	Percent Protein Bound (mean)(%)	Percent Recovery (1st replicate)(%)	Percent Recovery (2nd replicate)(%)	Percent Recovery (mean)(%)
O10	1.0E-05 M	40.23	35.24	37.73	112.28	113.40	112.84
C2	1.0E-05 M	50.61	48.90	49.75	110.60	125.71	118.15
Acebutolol	1.0E-05 M	16.16	14.18	15.17	116.82	108.4	112.61
Quinidine	1.0E-05 M	45.09	64.89	54.99	107.43	103	105.22
Quinidine	1.0E-05 M	63.03	69.17	66.1	115.06	113.14	114.1
Sertraline	1.0E-05 M	97.2	97.84	97.52	58.41	71.11	64.76
Sertraline	1.0E-05 M	98.01	98.5	98.25	96.63	98.05	97.34
Warfarin	1.0E-05 M	98.94	99.01	98.98	93.13	90.66	91.9
Warfarin	1.0E-05 M	98.11	99.05	98.58	112.92	103.05	107.98

Half Life: simulated gastric fluid

Compound	Test Concentration	Incubation (minutes)	% Compound Remaining (1st replicate)	% Compound Remaining (2nd replicate)	% Compound Remaining (Mean)	Half-Life (minutes) (first replicate)	Half-Life (minutes) (second replicate)	Half-Life (minutes) (mean replicate)
O10	1.0E-06 M	0	100.00	100.00	100.00	935.3	654.1	>120
O10	1.0E-06 M	30	95.57	94.69	95.13			
O10	1.0E-06 M	60	{100.0}	94.55	94.55			
O10	1.0E-06 M	90	92.66	91.88	92.27			
O10	1.0E-06 M	120	90.87	86.60	88.73			
C2	1.0E-06 M	0	100.00	100.00	100.00	514.6	469.8	>120
C2	1.0E-06 M	30	90.27	84.75	87.51			
C2	1.0E-06 M	60	87.32	85.76	86.54			
C2	1.0E-06 M	90	85.50	84.63	85.07			
C2	1.0E-06 M	120	83.95	80.20	82.08			

Erythromycin	1.0E-06 M	--	--	--	--	42.4	43.4	42.9
Propantheline	1.0E-06 M	--	--	--	--	433.7	515.3	>120

Half-life: Simulated intestinal fluid

Compound	**Test Concentration**	**Incubation (minutes)**	**% Compound Remaining (1st)**	**% Compound Remaining (2nd)**	**% Compound Remaining (Mean)**	**Half-Life (minutes) (first replicate)**	**Half-Life (minutes) (second replicate)**	**Half-Life (minutes) (mean replicate)**
O10	1.0E-06 M	0	100.00	100.00	100.00	27.5	26.0	26.8
O10	1.0E-06 M	30	65.15	62.47	63.81			
O10	1.0E-06 M	60	29.22	26.97	28.10			
O10	1.0E-06 M	90	12.04	11.01	11.52			
O10	1.0E-06 M	120	5.32	4.36	4.84			

C2	1.0E-06 M	0	100.00	100.00	100.00	37.1	36.2	36.6
C2	1.0E-06 M	30	71.22	68.20	69.71			
C2	1.0E-06 M	60	38.32	37.48	37.90			
C2	1.0E-06 M	90	18.28	17.76	18.02			
C2	1.0E-06 M	120	11.96	11.06	11.51			
Chlorambucil	1.0E-06 M	--	--	--	--	19.9	20	20
Propantheline	1.0E-06 M	--	--	--	--	123.9	103.3	113.6

Aqueous solubility: simulated intestinal fluid				
Compound	**Test Concentration**	**Solubility (μM, 1st)**	**Solubility (μM, 2nd)**	**Solubility (μM, mean)**
O10	2.0E-04 M	21.33	18.37	19.85
C2	2.0E-04 M	46.69	53.27	49.98
Aqueous solubility: PBS, pH 7.4				
O10	2.0E-04 M	203.88	215.93	>200
C2	2.0E-04 M	199.28	202.82	>200

Aqueous solubility: gastric fluid				
O10	2.0E-04 M	205.21	205.57	>200
C2	2.0E-04 M	197.18	210.67	>200
Diethylstilbesterol	2.0E-04 M	5.13	5.3	5.21
Ketoconazole	2.0E-04 M	140.23	126.41	133.32
Metoprolol	2.0E-04 M	195.25	186.61	190.93
Phenytoin	2.0E-04 M	87.35	92.08	89.72
Rifampicin	2.0E-04 M	172.46	175.57	174.01
Simvastatin	2.0E-04 M	36.93	35.16	36.04
Tamoxifen	2.0E-04 M	1.38	6.86	4.12

Partition coefficient (log D, n-octanol/PBS, pH 7.4)		
Compound	Test Concentration	LogD
O10	1.0E-04 M	-0.40
C2	1.0E-04 M	-0.31
Haloperidol	1.0E-04 M	2.53
Ketoconazole	1.0E-04 M	3.35

Metoprolol	1.0E-04 M	-0.32
Phenytoin	1.0E-04 M	2.2
Rifampicin	1.0E-04 M	1.08
Simvastatin	1.0E-04 M	>4.01

in vitro absorption: A-B permeability (Caco-2, pH 6.5/7.4)								
Compound	**Test Concentration**	**Permeability (10-6 cm/s, 1st replicate)**	**Permeability (10-6 cm/s, 2nd replicate)**	**Permeability (10-6 cm/s, Mean)**	**Flags**	**Percent Recovery (%, 1st replicate)**	**Percent Recovery (%, 2nd replicate)**	**Percent Recovery (%, Mean)**
O10	1.0E-05 M	0.01	0.01	<0.013	BLQ	91	93	92
C2	1.0E-05 M	0.01	0.01	<0.012	BLQ	91	92	92
Colchicine	1.0E-05 M	0.18	0.13	0.2		80	86	83
Labetalol	1.0E-05 M	6.02	6.15	6.1		98	101	100
Propranolol	1.0E-05 M	25.54	27.19	26.4		89	91	90
Ranitidine	1.0E-05 M	0.21	0.18	0.2		91	100	96

in vitro absorption: B-A permeability (Caco-2, pH 6.5/7.4)								
Compound	**Test Concentration**	**Permeability (10-6 cm/s, 1st replicate)**	**Permeability (10-6 cm/s, 2nd replicate)**	**Permeability (10-6 cm/s, Mean)**	**Flags**	**Percent Recovery (%, 1st replicate)**	**Percent Recovery (%, 2nd replicate)**	**Percent Recovery (%, Mean)**
O10	1.0E-05 M	0.02	0.02	<0.022	BLQ	82	72	77
C2	1.0E-05 M	0.02	0.02	<0.021	BLQ	83	83	83
Colchicine	1.0E-05 M	3.37	3.46	3.4		87	91	89
Labetalol	1.0E-05 M	27.48	24.62	26		93	92	93
Propranolol	1.0E-05 M	29.61	28.21	28.9		90	92	91
Ranitidine	1.0E-05 M	1.08	1.03	1.1		104	94	99

Intrinsic clearance (liver microsomes - human)									
Compound	**Test Concentration**	**Incubation (minutes)**	**% Compound Remaining (1st replicate)**	**% Compound Remaining (2nd replicate)**	**% Compound Remaini**	**Half-Life (minutes, 1st replicate)**	**Half-Life (minutes, 2nd**	**Half-Life (minutes, Mean)**	**Clint (µl/min/mg)**

					ng (Mean)		replicate)		
O10	1.0E-07 M	0	100.00	100.00	100.00	368.4	1251.4	>120	<57.8
O10	1.0E-07 M	15	95.20	97.55	96.38				
O10	1.0E-07 M	30	97.56	94.27	95.91				
O10	1.0E-07 M	45	95.33	95.99	95.66				
O10	1.0E-07 M	60	86.78	96.71	91.74				
C2	1.0E-07 M	0	100.00	100.00	100.00	625.1	494.0	>120	<57.8
C2	1.0E-07 M	15	103.08	106.24	104.66				
C2	1.0E-07 M	30	106.24	98.65	102.44				
C2	1.0E-07 M	45	99.93	98.47	99.20				
C2	1.0E-07 M	60	93.46	93.50	93.48				
mipramine	1.0E-07 M	180.1	184.3	>120	<57.8				
Propranolol	1.0E-07 M	217.0	394.0	>120	<57.8				
Terfenadine	1.0E-07 M	13.3	13.1	13.2					
Verapamil	1.0E-07 M	34.2	33.4	33.8					

Example 17: Comparing O10 and Setmelanotide

[0671] As shown in the examples provided herein, the non-naturally occurring melanocortin analogs of the present technology out-perform setmelanotide across numerous metrics. First, compared to setmelanotide, O10 is (1) about 408x (x, times) more potent on MC3R, (2) about 120x more potent on MC4R, and (3) has superior PK parameters as shown in at least rats, where the CSF half-life of O10 is about 2x longer, the plasma half-life is about 3x longer, the CSF AUC is about 1.5x higher, and the plasma AUC is 4.5x higher (also see Table 133 and Table 134) compared to setmelanotide.

Table 133: cAMP Signaling Assay – Agonist Mode; EC_{50} (nM)

	Setmelanotide	O10
MC3R	5.3	0.013
MC4R	0.27	0.002

Table 134: 10mg/kg SC (rat) PK Parameters

	Setmelanotide		O10	
PK Parameters	Mean CSF	Mean Plasma	Mean CSF	Mean Plasma
Cmax (ng/mL)	43.2	1164	21.3	1366
Tmax (h)	1.00	1.00	6.00	2.00
T1/2 (h)	2.79	0.938	5.62	2.78
Tlast (h)	4.00	8.00	10.0	24.0
AUC0-last (ng.h/mL)	83.1	2396	121	10731
AUC0-inf (ng.h/mL)	154	2407	226	10781

[0672] Second, as shown by at least the drug exposure over the EC_{50} analyses, O10 is present at efficacious doses in CSF for periods of time longer than setmelanotide, O10 remains present in the CSF at concentrations higher than the EC_{50}. It is predicted that O10

will be more efficacious for general obesity (e.g., obesity not caused by genetic factors related to the melanocortin system) due to higher affinity for MC3R and MC4R and PK values in plasma and CSF (as shown in the rat) compared to setmelanotide.

[0673] Third, as shown in at least the non-human primate studies, O10 reduces food intake in a single dose via 1 and 3 mg/kg SC injection in DIO cynomolgus monkeys, whereas setmelanotide did not affect food intake in 39-week toxicity study via 3 mg/kg/day SC injection in standard BMI cynomolgus monkeys. It is predicted that the 10 and 30 mg/kg oral administration doses of O10 will be efficacious considering the PK data and superior potency of O10 on MC3R and MC4R activation (Table 135).

Table 135: PL parameters O10 30 mg/kg, oral administration in monkeys

PK Parameters	**Mean**		**SD**	**CV (%)**
Cmax (ng/mL)	248	±	126	50.9
Tmax (h)	2.00	±	0.00	0.00
T1/2 (h)	2.47	±	1.53	61.9
Tlast (h)	ND	±	--	--
AUC0-last (ng.h/mL)	1006	±	456	45.4
AUC0-inf (ng.h/mL)	1041	±	437	42.0

[0674] The oral PK results suggest that O10 will also be efficacious at 10 and 30 mg/kg PO administration. As shown in the working examples, the plasma PKs of a 1 mg/kg SC injection of O10 to an oral 10 mg/kg and 30 mg/kg administration of O10 were above the EC_{50}. Food intake may thus be reduced following oral administration of O10.

[0675] As such, (1) O10 is present in efficacious levels in CSF by oral administration. This may lead to increased efficacy compared to setmelanotide (SC administration); (2) the working examples have not found a dose-limiting maximum toxic concentration for O10. This may permit dosing at higher levels and maintenance of efficacious AUCs behind the blood brain barrier; and (3) DIO nonhuman primate studies are ongoing. Based on the DIO NHP data thus far, it is predicted that O10 will be efficacious in the general obesity population.

Additional Embodiments

[0676] Various embodiments of the present technology are set forth below in paragraphs [0677] to [0828]:

[0677] 1. A non-naturally occurring melanocortin analog comprising a sequence according to Formula (IF),

$$R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}Y^1\text{-}Y^2 \text{ (IF)},$$

wherein:

R^1 is Nle;

R^2 is Asp or Glu;

R^3 is His;

R^4 is selected from dPhe, p(F)dPhe, and p(Cl)dPhe;

R^5 is Arg or His;

R^6 is Trp;

R^7 is Orn;

Y^1 is dVal;

Y^2 is dPro; and

the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between Asp or Glu at R^2 and Orn at R^7.

[0678] 2. The non-naturally occurring melanocortin analog of embodiment 1, comprising a sequence selected from the group consisting of:

Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH2 (SEQ ID NO: 43);

Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH2 (SEQ ID NO: 44);

Ac-Nle-c[Glu-His-dPhe-His-Trp-Orn]-dVal-dPro-NH2 (SEQ ID NO: 45);

Ac-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Orn]-dVal-dPro-NH2 (SEQ ID NO: 11); and

Ac-Nle-c[Glu-His-p(Cl)dPhe-Arg-Trp-Orn]-dVal-dPro-NH2 (SEQ ID NO: 12),

wherein c represents cyclization through R2 and R7 via a lactam bond.

[0679] 3. The non-naturally occurring melanocortin analog of embodiment 1 or 2, wherein the non-naturally occurring melanocortin analog is cyclized between Glu at R2 and and Orn at R7.

[0680] 4. The non-naturally occurring melanocortin analog of embodiment 3, comprising a sequence selected from the group consisting of:

Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH2 (SEQ ID NO: 43);

Ac-Nle-c[Glu-His-dPhe-His-Trp-Orn]-dVal-dPro-NH2 (SEQ ID NO: 45); and

Ac-Nle-c[Glu-His-p(Cl)dPhe-Arg-Trp-Orn]-dVal-dPro-NH2 (SEQ ID NO: 12),

wherein c represents cyclization through R2 and R7 via a lactam bond.

[0681] 5. The non-naturally occurring melanocortin analog of embodiment 1 or 2, wherein R4 is p(F)dPhe or dPhe.

[0682] 6. The non-naturally occurring melanocortin analog of embodiment 5, comprising a sequence selected from the group consisting of:

Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH2 (SEQ ID NO: 43);

Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH2 (SEQ ID NO: 44); and

Ac-Nle-c[Glu-His-dPhe-His-Trp-Orn]-dVal-dPro-NH2 (SEQ ID NO: 45),

wherein c represents cyclization through R2 and R7 via a lactam bond.

[0683] 7. The non-naturally occurring melanocortin analog of embodiment 5, comprising a sequence of:

Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH2 (SEQ ID NO: 43); or

Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH2 (SEQ ID NO: 44),

wherein c represents cyclization through R2 and R7 via a lactam bond.

[0684] 8. The non-naturally occurring melanocortin analog of embodiment 5, comprising a sequence of: Ac-Nle-c[Glu-His-dPhe-His-Trp-Orn]-dVal-dPro-NH2 (SEQ ID NO: 45), wherein c represents cyclization through R2 and R7 via a lactam bond.

[0685] 9. The non-naturally occurring melanocortin analog of embodiment 1 or 2, wherein R4 is p(F)dPhe or p(Cl)dPhe.

[0686] 10. The non-naturally occurring melanocortin analog of embodiment 9, comprising a sequence selected from the group consisting of:

Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH2 (SEQ ID NO: 43);

Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH2 (SEQ ID NO: 44);

Ac-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Orn]-dVal-dPro-NH2 (SEQ ID NO: 11); and

Ac-Nle-c[Glu-His-p(Cl)dPhe-Arg-Trp-Orn]-dVal-dPro-NH2 (SEQ ID NO: 12),

wherein c represents cyclization through R2 and R7 via a lactam bond.

[0687] 11. The non-naturally occurring melanocortin analog of embodiment 1 or 2, wherein R4 is para-fluoro-D-phenylalanine (p(F)dPhe).

[0688] 12. The non-naturally occurring melanocortin analog of any one of embodiments 1-11, comprising a sequence of: Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH2 (SEQ ID NO: 43), wherein c represents cyclization through R2 and R7 via a lactam bond.

[0689] 13. A method of reducing body weight and/or fat mass in a subject in need thereof, comprising orally administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I):

X^1-R^1-R^2-R^3-R^4-R^5-R^6-R^7-R^8-R^9-Y^1-Y^2-Y^3-Y^4 (I),

wherein:

X^1 is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

R^1 is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R^2 is selected from the group consisting of Asp, D-cysteine (dCys), Ala, D-alanine (dAla), proline (Pro), glutamic acid (Glu), and phenylalanine (Phe);

R^3 is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln);

R^4 is selected from the group consisting of D-phenylalanine (dPhe), Pro, para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

R^5 is selected from the group consisting of Arg, His, *cis*-4-guanidyl-proline (*cis*Pro(guan)), and *trans*-4-guanidyl-proline (*trans*Pro(guan));

R^6 is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2')));

R^7 is selected from the group consisting of Arg, Pro, ornithine (Orn), cysteine (Cys) and lysine (Lys);

R^8 is absent, Lys, or Trp;

R^9 is absent or Lys;

Y^1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y^2 is selected from the group consisting of dVal, dPro, and dTle;

Y^3 is absent, dVal, or dPro;

Y^4 is absent or dPro; and

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

a disulfide bond between R^2 and R^7 when R^2 is dCys, R^4 is p(Cl)dPhe, and R^7 is Cys;

a lactam bridge between R^1 or R^2 and any one of R^7-R^9 when R^1 or R^2 is Asp, R^4 is dPhe, or p(F)dPhe, and any one of R^7-R^9 is Lys; and

a lactam bridge between R^2 and R^7 when R^2 is Asp or Glu and R^7 is Orn,

provided that:

when R^3 is Pro, then X^1 and Y^3 are present and R^4 is dPhe,

when R^4 is p(Cl)dPhe, then the non-naturally occurring melanocortin analog is not cyclized through a lactam bond between Asp at R^2 and Lys at R^7,

when R^2 and/or R^3 is Phe, then R^4 is Pro and R^6 is dPhe,

when R^4 is dPhe and R^2 is Pro, then X^1 is present and R^5 is Arg, and

when R^4 is dPhe, R^2 is Ala, and R^3 is His, then R^5 is Arg.

[0690] 14. Use of a non-naturally occurring melanocortin analog for reducing body weight and/or fat mass in a subject in need thereof, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0691] 15. A method of reducing body weight and/or fat mass in an obese subject, comprising orally administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0692] 16. Use of a non-naturally occurring melanocortin analog for reducing body weight and/or fat mass in an obese subject, comprising orally administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0693] 17. The method or the use of any one of embodiments 13-16, wherein the method or the use further comprises reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in the subject.

[0694] 18. The method or the use of embodiment 17, wherein the lean mass is lean muscle mass.

[0695] 19. The method or the use of any one of embodiments 13-18, wherein the method or the use further comprises treating, preventing, or reducing glucose intolerance and/or diabetes mellitus in the subject.

[0696] 20. A method of treating, preventing, or reducing hyperplasia in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0697] 21. Use of a non-naturally occurring melanocortin analog for treating, preventing, or reducing hyperplasia in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0698] 22. A method of treating, preventing, or reducing hypothalamic obesity in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0699] 23. Use of a non-naturally occurring melanocortin analog for treating, preventing, or reducing hypothalamic obesity in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0700] 24. The method or the use of embodiment 22 or 23, wherein the hypothalamic obesity comprises congenital hypothalamic damage, damage from tumors, or damage from trauma.

[0701] 25. A method of treating, preventing, or reducing a proopiomelanocortin (POMC) deficiency in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0702] 27. A method of treating, preventing, or reducing a leptin deficiency in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0703] 29. A method of treating, preventing, or reducing a syndromic obesity in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0704] 32. A method of treating, preventing, or reducing non-alcoholic steatohepatitis (NASH) in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0705] 34. A method of treating, preventing, or reducing hyperinsulinism in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0706] 36. A method of treating, preventing, or reducing a cardiovascular disease in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0707] 39. A method of treating, preventing, or reducing osteoarthritis in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0708] 41. A method of treating, preventing, or reducing a cancer in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0709] 44. A method of treating, preventing, or reducing erectile dysfunction in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0710] 46. A method of treating, preventing, or reducing body weight gain after a weight loss in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0711] 48. A method of maintaining body weight after a weight loss in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0712] 50. A method of treating, preventing, or reducing fat mass gain after a weight loss in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0713] 52. A method of treating, preventing, or reducing glucose intolerance and/or diabetes mellitus in a subject in need thereof, comprising orally administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0714] 53. Use of a non-naturally occurring melanocortin analog for treating, preventing, or reducing glucose intolerance and/or diabetes mellitus in a subject in need thereof, comprising orally administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0715] 54. The method or the use of embodiment 52 or 53, wherein the method or the use further comprises reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in the subject.

[0716] 55. The method or the use of embodiment 54, wherein the lean mass is lean muscle mass.

[0717] 56. The method or the use of any one of embodiments 52-55, wherein the method or the use further comprises reducing body weight and/or fat mass in the subject.

[0718] 57. The method or the use of any one of embodiments 13-56, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 15 mg/kg to about 1000 mg/kg per body weight of the subject once daily.

[0719] 58. The method or the use of any one of embodiments 13-27, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 15 mg/kg to about 550 mg/kg per body weight of the subject once daily.

[0720] 59. The method or the use of any one of embodiments 13-29, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 15 mg/kg to about 100 mg/kg per body weight of the subject once daily.

[0721] 60. The method or the use of any one of embodiments 13-31, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 15 mg/kg to about 75 mg/kg per body weight of the subject once daily.

[0722] 61. The method or the use of embodiment 60, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 30 mg/kg or 60 mg/kg per body weight of the subject once daily.

[0723] 62. The method or the use of any one of embodiments 13-56, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 0.1 mg to about 100 mg once daily.

[0724] 63. The method or the use of any one of embodiments 13-56, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 10 mg or about 50 mg once daily.

[0725] 64. The method or the use of any one of embodiments 13-63, wherein the method or the use further comprises reducing obesity-related inflammation in the subject.

[0726] 65. The method or the use of any one of embodiments 13-64, wherein the method or the use further comprises preserving or improving kidney function in the subject.

[0727] 66. A method of reducing obesity-related inflammation in a subject in need thereof, comprising orally administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

[0728] 68. A method of preserving or improving kidney function in a subject in need thereof, comprising orally administering a non-naturally occurring melanocortin 4 receptor agonist to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

third dose of about 15 mg/kg administered twice a day after administration of the second dose for at least about 7 days.

[0729] 74. The method or the use of any one of embodiments 1-70, wherein the non-naturally occurring melanocortin analog is administered (i) at a first dose of about 15 mg/kg administered once a day for about 7 days; (ii) at a second dose of about 25 mg/kg administered once a day after administration of the first dose for about 7 days; (iii) at a third dose of about 20 mg/kg administered twice a day after administration of the second dose for at least about 7 days.

[0730] 75. The method or the use of any one of embodiments 13-74, wherein the non-naturally occurring melanocortin analog comprises a sequence of Formula (I), wherein:

X^1 is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

R^1 is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R^2 is selected from the group consisting of Asp, D-cysteine (dCys), Ala, D-alanine (dAla), proline (Pro), glutamic acid (Glu), and phenylalanine (Phe);

R^3 is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln);

R^4 is selected from the group consisting of D-phenylalanine (dPhe), Pro, para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

R^5 is selected from the group consisting of Arg, His, *cis*-4-guanidyl-proline (*cisPro*(guan)), and *trans*-4-guanidyl-proline (*trans*Pro(guan));

R^6 is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2'));

R^7 is selected from the group consisting of Arg, Pro, ornithine (Orn), cysteine (Cys) and lysine (Lys);

R^8 is absent, Lys, or Trp;

R^9 is absent or Lys;

Y^1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y^2 is selected from the group consisting of dVal, dPro, and dTle;

Y^3 is absent, dVal, or dPro;

Y^4 is absent or dPro;

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

a disulfide bond between R^2 and R^7 when R^2 is dCys, R^4 is p(Cl)dPhe, and R^7 is Cys;

a lactam bridge between R^1 or R^2 and any one of R^7-R^9 when R^1 or R^2 is Asp, R^4 is dPhe, or p(F)dPhe, and any one of R^7-R^9 is Lys; and

a lactam bridge between R^2 and R^7 when R^2 is Asp or Glu and R^7 is Orn;

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

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 48);

Ac-Ala-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 49);

Ac-dNle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 50);

Ac-dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 51);

His-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 52);

dHis-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 53);

Ac-Arg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 54);

Ac-dLys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 55);

Ac-Lys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 56);

Ac-His-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 57);

Ac-dHis-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 58);

Ac-Nle-c[dCys-Pro-dPhe-Arg-Trp-Cys]-dVal-dPro-NH_2 (SEQ ID NO: 59);

Ac-Nle-c[dCys-Pro-dPhe-Arg-Trp-dCys]-dVal-dPro-NH_2 (SEQ ID NO: 60);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 61);

Ac-Nle-c[Glu-Pro-dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 62);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Gly-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 63);

Ac-Nle-c[Asp-Phe-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 64);

Ac-Nle-c[Asp-His-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 65);

Ac-Nle-c[Asp-Pro-dPhe-His-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 66);

Ac-Nle-c[Asp-Pro-dPhe-Lys-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 67);

Ac-Nle-c[Asp-Pro-dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 68);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Nal(2')-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 69);

Ac-Nle-c[dCys-Pro-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro-NH_2 (SEQ ID NO: 70);

Ac-Ala-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 71);

Ac-dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 72);

Ac-Arg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 73);

Ac-Lys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 74);

Ac-dLys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 75);

Ac-His-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 76);

Ac-dHis-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 77);

Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 78);

Ac-Nle-c[Asp-Pro-p(F)dPhe-His-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 79);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 80);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH_2 (SEQ ID NO: 81);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dVal-dVal-dPro-NH_2 (SEQ ID NO: 82);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH_2 (SEQ ID NO: 83);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 84);

Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 85);

Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH_2 (SEQ ID NO: 86);

Ac-Ala-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 87);

Ac-dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 88);

Ac-Arg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 89);

Ac-Lys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 90);

Ac-dLys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 91);

Ac-His-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 92);

Ac-dHis-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 93);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 94);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dTle-NH_2 (SEQ ID NO: 95);

Ac-dHis-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 96);

Ac-Nle-c[Asp-Pro-dPhe-Arg-dTrp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 97);

Ac-Nle-c[Asp-Pro-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 98);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 99);

Ac-Nle-c[Asp-Pro-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 100);

Ac-Nle-c[Asp-Trp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 101);

Ac-Nle-c[Asp-Pro-dPhe-Pro-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 102);

Ac-Nle-c[Asp-Pro-p(Cl)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 103);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 104);

Ac-Nle-c[Glu-Pro-p(Cl)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 105);

Ac-Nle-c[Glu-Pro-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 106);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-OH (SEQ ID NO: 107);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-NH_2 (SEQ ID NO: 108);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 109);

Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 110);

Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 111);

Ac-Ala-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 112);

Ac-dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 113);

Ac-Arg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 114);

Ac-Lys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 115);

Ac-dLys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 116);

Ac-His-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 117);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dTle-dPro-NH_2 (SEQ ID NO: 118);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH_2 (SEQ ID NO: 119);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dVal-dPro-NH_2 (SEQ ID NO: 120);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH_2 (SEQ ID NO: 121);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dVal-dVal-dPro-NH_2 (SEQ ID NO: 122);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-dVal-dPro-NH_2 (SEQ ID NO: 123);

Ac-Nle-c[Asp-Pro-dPhe-transPro(guan)-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 124);

Ac-Nle-c[Asp-Pro-dPhe-cisPro(guan)-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 125);

Ac-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH_2 (SEQ ID NO: 126);

Ac-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dVal-dVal-dPro-NH_2 (SEQ ID NO: 127);

Ac-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH_2 (SEQ ID NO: 128);

Ac-Nle-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH_2 (SEQ ID NO: 129);

Ac-Ala-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 130);

Ac-dArg-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 131);

Ac-Arg-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 132);

Ac-Lys-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 133);

Ac-dLys-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 134);

Ac-His-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 135);

Ac-dHis-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 136);

Ac-Nle-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 137);

Ac-Nle-c[Asp-His-p(Cl)dPhe-His-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 138);

Ac-Nle-c[Asp-His-p(Cl)dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 139);

Ac-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 140);

Ac-Nle-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 141);

Ac-Ala-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 142);

Ac-dArg-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 143);

Ac-Arg-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 144);

Ac-dLys-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 145);

Ac-dHis-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 146);

Ac-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 147);

Ac-Nle-c[Asp-dHis-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 148);

Ac-Nle-c[Asp-Phe-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 149);

Ac-Nle-c[Asp-Gln-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 150);

Ac-Lys-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 151);

Ac-His-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 152);

Ac-Nle-c[Asp-Phe-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 153);

Ac-Nle-c[Asp-Phe-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 154);

Ac-Nle-c[Asp-Phe-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 155);

Ac-Nle-c[Asp-Phe-Phe-Pro-His-dNal(2')-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 156);

Ac-Nle-c[Asp-Phe-His-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 157);

Ac-Nle-c[Asp-Pro-His-dPhe-His-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 158);

Ac-Arg-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 159); and

Ac-dArg-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 160).

[0731] 76. The method or the use of any one of embodiments 13-75, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (IA):

$$X^1\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}R^8\text{-}Y^1\text{-}Y^2\text{-}Y^3\text{-}Y^4 \text{ (IA)},$$

wherein:

X^1 is absent or is selected from the group consisting of Nle, Arg, and dArg;

R^1 is selected from the group consisting of Nle, Arg, dArg, Asp, Ala, Lys, dLys, His, and dHis;

R^2 is selected from the group consisting of Asp, Ala, dAla, Pro, and Glu

R^3 is selected from the group consisting of His, dHis, Pro, and Gln;

R^4 is dPhe or p(F)dPhe;

R^5 is selected from the group consisting of Arg, His, *cisPro*(guan), and *trans*Pro(guan);

R^6 is Trp or dNal(2');

R^7 is selected from the group consisting of Pro, Orn, and Lys;

R^8 is absent or Lys;

Y^1 is selected from the group consisting of dVal, dPro, and dTle;

Y^2 is selected from the group consisting of dVal, dPro, and dTle;

Y^3 is absent, dVal, or dPro;

Y^4 is absent or dPro; and

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

a lactam bridge between R^1 or R^2 and R^7 or R^8 when R^1 or R^2 is Asp and R^7 or R^8 is Lys; and

a lactam bridge between R^2 and R^7 when R^2 is Asp or Glu and R^7 is Orn.

[0732] 77. The method or the use of any one of embodiments 13-76, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (IB):

$$X^1\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}Y^1\text{-}Y^2\text{-}Y^3\text{-}Y^4 \text{ (IB)},$$

wherein:

X^1 is absent or Nle;

R^1 is selected from the group consisting of Nle, Arg, dArg, Ala, Lys, dLys, His, and dHis;

R^2 is Asp or Glu;

R^3 is selected from the group consisting of His, dHis, Pro, and Gln;

R^4 is dPhe or p(F)dPhe;

R^5 is selected from the group consisting of Arg, His, *cisPro*(guan), and *trans*Pro(guan);

R^6 is Trp or dNal(2');

R^7 is Orn or Lys;

Y^1 is selected from the group consisting of dVal, dPro, and dTle;

Y^2 is selected from the group consisting of dVal, dPro, and dTle;

Y^3 is absent, dVal, or dPro;

Y^4 is absent or dPro; and

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

a lactam bridge between R^2 and R^7 when R^2 is Asp and R^7 is Lys; and

lactam bridge between Asp or Glu at R^2 and Orn or Lys at R^7.

[0733] 78. The method or the use of any one of embodiments 13-77, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (IC):

$$X^1\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}Y^1\text{-}Y^2\text{-}Y^3\text{-}Y^4 \text{ (IC)},$$

wherein:

X^1 is absent or Nle;

R^1 is selected from the group consisting of Nle, Arg, dArg, Ala, Lys, dLys, His, and dHis;

R^2 is Asp or Glu;

R^3 is His;

R^4 is p(F)dPhe;

R^5 is Arg;

R^6 is Trp;

R^7 is Orn or Lys;

Y^1 is selected from the group consisting of dVal, dPro, and dTle;

Y^2 is selected from the group consisting of dVal, dPro, and dTle;

Y^3 is absent, dVal, or dPro;

Y^4 is absent or dPro; and

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

a lactam bridge between R^2 and R^7 when R^2 is Asp and R^7 is Lys; and

lactam bridge between Asp or Glu at R^2 and Orn or Lys at R^7.

[0734] 79. The method or the use of any one of embodiments 13-77, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (ID):

$$X^1\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}R^8\text{-}Y^1\text{-}Y^2\text{-}Y^3 \text{ (ID)},$$

wherein:

X^1 is absent or norleucine (Nle);

R^1 is Nle or Asp;

R^2 is selected from the group consisting of Asp, Glu, and Pro;

R^3 is selected from the group consisting of His, dHis, Pro, and Gln;

R^4 is dPhe;

R^5 is selected from the group consisting of Arg, His, *cisPro*(guan), and *trans*Pro(guan);

R^6 is Trp;

R^7 is selected from the group consisting of Orn, Lys, and Pro;

R^8 is absent or Lys;

Y^1 is dVal or dPro;

Y^2 is dVal or dPro;

Y^3 is absent or dPro; and

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

a lactam bridge between R^1 or R^2 and R^7 or R^8 when R^1 or R^2 is Asp and R^7 or R^8 is Lys; and

a lactam bridge between R^2 and R^7 when R^2 is Asp or Glu and R^7 is Orn.

[0735] 80. The method or the use of any one of embodiments 13-76, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (IE):

$$X^1\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}Y^1\text{-}Y^2 \text{ (IE)},$$

wherein:

X^1 is absent or selected from the group consisting of Nle, Arg, and dArg;

R^1 is Asp;

R^2 is dAla or Ala;

R^3 is His;

R^4 is dPhe;

R^5 is Arg;

R^6 is Trp;

R^7 is Lys;

Y^1 is dVal;

Y^2 is dPro; and

the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between Asp at R^1 and Lys at R^7.

[0736] 81. The method or the use of any one of embodiments 13-75, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (IF):

$$R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}Y^1\text{-}Y^2 \text{ (IF)},$$

wherein:

R^1 is Nle;

R^2 is Asp or Glu;

R^3 is His;

R^4 is selected from dPhe, p(F)dPhe, and p(Cl)dPhe;

R^5 is Arg or His;

R^6 is Trp;

R^7 is Orn;

Y^1 is dVal;

Y^2 is dPro; and

the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between Asp or Glu at R^2 and Orn at R^7.

[0737] 82. The method or the use of any one of embodiments 13-81, wherein R3 is His and R4 is p(F)dPhe or dPhe.

[0738] 83. The method or the use of any one of embodiments 13-82, wherein R1 is selected from Nle, Ala, Arg, dArg, Lys, dLys, His, and dHis and R4 is p(F)dPhe.

[0739] 84. The method or the use of any one of embodiments 13-83, wherein the sequence according to any one of Formulae (I)-(IF) is selected from the group consisting of:

Ac—Ala-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 3);

Ac—dArg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 4);

Ac—Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 14);

Ac—Arg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 15);

Ac—Lys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 16);

Ac—dLys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 17);

Ac—His-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 18); and

Ac—dHis-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 19),

wherein c represents cyclization through R2 and R7 via a lactam bond.

[0740] 85. The method or the use of any one of embodiments 13-83, wherein the sequence according to any one of Formulae (I)-(IF) is selected from the group consisting of:

Ac—Ala-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro—NH2 (SEQ ID NO: 7);

Ac—dArg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro—NH2 (SEQ ID NO: 8);

Ac—Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro—NH2 (SEQ ID NO: 24);

Ac—Arg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro—NH2 (SEQ ID NO: 27);

Ac—Lys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro—NH2 (SEQ ID NO: 28);

Ac—dLys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro—NH2 (SEQ ID NO: 29);

Ac—His-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro—NH2 (SEQ ID NO: 30); and

Ac—dHis-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro—NH2 (SEQ ID NO: 31),

wherein c represents cyclization through R2 and R7 via a lactam bond.

[0741] 86. The method or the use of any one of embodiments 13-82, wherein R1 is Nle and R4 is dPhe.

[0742] 87. The method or the use of embodiment any one of embodiments 13-82 and 79, wherein the sequence according to any one of Formulae (I)-(IF) is:

Ac—Nle-c[Asp-His-dPhe-Arg-Trp-Lys]-dPro-dVal—NH2 (SEQ ID NO: 33); or

Ac—Nle-c[Asp-His-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 42),

wherein c represents cyclization through R2 and R7 via a lactam bond.

[0743] 88. The method or the use of any one of embodiments 13-82, wherein R1 is Nle and R4 is p(F)dPhe.

[0744] 89. The method or the use of embodiment any one of embodiments 13-82 and 81, wherein the sequence according to any one of Formulae (I)-(IF) is selected from the group consisting of:

Ac—Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dTle-dVal—NH2 (SEQ ID NO: 6);

Ac—Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 20);

Ac—Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dVal-dVal-dPro—NH2 (SEQ ID NO: 22);

Ac—Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro—NH2 (SEQ ID NO: 23);

Ac—Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro—NH2 (SEQ ID NO: 25); and

Ac—Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro—NH2 (SEQ ID NO: 26),

wherein c represents cyclization through R2 and R7 via a lactam bond.

[0745] 90. The method or the use of any one of embodiments 13-82, wherein R1 is Nle and R4 is dPhe or p(F)dPhe.

[0746] 91. The method or the use of embodiment any one of embodiments 13-82 and 83, wherein the sequence according to any one of Formulae (I)-(IF) is selected from the group consisting of:

Ac—Nle-c[Asp-His-p(F)dPhe-His-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 21);

Ac—Nle-c[Asp-His-dPhe-transPro(guan)-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 46); and

Ac—Nle-c[Asp-His-dPhe-cisPro(guan)-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 47),

wherein c represents cyclization through R2 and R7 via a lactam bond.

[0747] 92. The method or the use of embodiment any one of embodiments 13-82 and 83, wherein the sequence according to any one of Formulae (I)-(IF) is: Ac—Nle-c[Asp-His-p(F)dPhe-Arg-dNal(2')-Lys]-dVal-dPro—NH2 (SEQ ID NO: 5), wherein c represents cyclization through R2 and R7 via a lactam bond.

[0748] 93. The method or the use of any one of embodiments 13-78, wherein the sequence of any one of Formulae (I)-(IF) is cyclized through a lactam bond between Asp or Glu at R2 and Orn at R7.

[0749] 94. The method or the use of embodiment any one of embodiments 13-78 and 86, wherein the sequence according to any one of Formulae (I)-(IF) is selected from the group consisting of:

Ac—Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro—NH2 (SEQ ID NO: 43);

Ac—Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro—NH2 (SEQ ID NO: 44);

Ac-Nle-c[Glu-His-dPhe-His-Trp-Orn]-dVal-dPro-NH2 (SEQ ID NO: 45);

Ac—Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Orn]-dVal-dPro—NH2 (SEQ ID NO: 11); and

Ac—Nle-c[Glu-His-p(Cl)dPhe-Arg-Trp-Orn]-dVal-dPro—NH2 (SEQ ID NO: 12),

wherein c represents cyclization through R2 and R7 via a lactam bond.

[0750] 95. The method or the use of any one of embodiments 13-78, wherein the sequence of any one of Formulae (I)-(IF) is cyclized through a lactam bond between dCys at R2 and Cys at R7.

[0751] 96. The method or the use of embodiment any one of embodiments 13-78 and 88, wherein the sequence according to any one of Formulae (I)-(IF) is: Ac—Nle-c[dCys-His-p(Cl)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 5), wherein c represents cyclization through R2 and R7 via a disulfide bond.

[0752] 97. The method or the use of any one of embodiments 13-82, wherein the sequence of any one of Formulae (I)-(IF) is cyclized through a lactam bond between Asp at R2 and Lys at R8.

[0753] 98. The method or the use of embodiment any one of embodiments 13-82 and 90, wherein the sequence according to any one of Formulae (I)-(IF) is: Ac—Nle-c[Asp-His-dPhe-Arg-Trp-Pro-Lys]-dVal-dPro—NH2 (SEQ ID NO: 35), wherein c represents cyclization through R2 and R8 via a lactam bond.

[0754] 99. The method or the use of any one of embodiments 13-82, wherein the sequence of any one of Formulae (I)-(IF) is cyclized through a lactam bond between Asp at R1 and Lys at R7.

[0755] 100. The method or the use of embodiment any one of embodiments 13-82 and 92, wherein the sequence according to any one of Formulae (I)-(IF) is selected from the group consisting of:

Ac—Nle-c[Asp-dAla-His-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 38);

Ac—Arg-c[Asp-dAla-His-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 39);

Ac—dArg-c[Asp-dAla-His-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 40); and

Ac—Nle-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 41),

wherein c represents cyclization through R1 and R7 via a lactam bond.

[0756] 101. The method or the use of embodiment any one of embodiments 13-82 and 93, wherein the sequence according to any one of Formulae (I)-(IF) is: Ac-Nle-c[Asp-Pro-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 13), wherein c represents cyclization through R1 and R7 via a lactam bond.

[0757] 102. The method or the use of embodiment any one of embodiments 13-78, wherein R3 is selected from dHis, Gln and Pro and R4 is dPhe or p(F)dPhe.

[0758] 103. The method or the use of embodiment any one of embodiments 13-78 and 95, wherein the sequence according to any one of Formulae (I)-(IF) is selected from the group consisting of:

Ac—Nle-c[Asp-Gln-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 9);

Ac—Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-dPro—NH2 (SEQ ID NO: 10);

Ac—Nle-c[Asp-dHis-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 32);

Ac—Nle-c[Asp-dHis-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 36); and

Ac—Nle-c[Asp-Gln-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 37),

wherein c represents cyclization through R2 and R7 via a lactam bond.

[0759] 104. The method or the use of embodiment any one of embodiments 13-78 and 95, wherein the sequence according to any one of Formulae (I)-(IF) is: Ac-Nle-c[Asp-Phe-Phe-Pro-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 34), wherein c represents cyclization through R1 and R9 via a lactam bond.

[0760] 105. The method or the use of embodiment any one of embodiments 13-104, wherein the non-naturally occurring melanocortin analog comprises a sequence of any of one SEQ ID NOs: 2-47.

[0761] 106. The method or the use of embodiment any one of embodiments 13-105, wherein the non-naturally occurring melanocortin analog comprises a sequence of any of one SEQ ID NOs: 3-10, 13-33, and 35-47.

[0762] 107. The method or the use of embodiment any one of embodiments 13-105, wherein the non-naturally occurring melanocortin analog comprises a sequence of any of one SEQ ID NOs: 3-10, 14-33, 36, 37, and 42-47.

[0763] 108. The method or the use of embodiment any one of embodiments 13-105, wherein the non-naturally occurring melanocortin analog comprises a sequence of any of one SEQ ID NOs: 3-8, 14-31, 43, and 44.

[0764] 109. The method or the use of embodiment any one of embodiments 13-105, wherein the non-naturally occurring melanocortin analog comprises a sequence of any of one SEQ ID NOs: 10, 13, 33, 35-37, 42, and 45-47.

[0765] 110. The method or the use of embodiment any one of embodiments 13-105, wherein the non-naturally occurring melanocortin analog comprises a sequence of any of one SEQ ID NOs: 38-41.

[0766] 111. The method or the use of embodiment any one of embodiments 13-105, wherein the non-naturally occurring melanocortin analog comprises a sequence of any of one SEQ ID NOs: 11, 12, and 43-45.

[0767] 112. A method of reducing body weight and/or fat mass in a subject in need thereof, comprising orally administering about 15 mg/kg to about 100 mg/kg of a non-naturally occurring melanocortin analog to the subject,

the non-naturally occurring melanocortin analog comprising a sequence of Formula (IF).

[0768] 113. Use of a non-naturally occurring melanocortin analog for reducing body weight and/or fat mass in a subject in need thereof, comprising orally administering about 15 mg/kg to about 100 mg/kg of a non-naturally occurring melanocortin analog to the subject,

the non-naturally occurring melanocortin analog comprising a sequence of Formula (IF).

[0769] 114. A method of treating, preventing, or reducing glucose intolerance and/or diabetes mellitus in a subject in need thereof, comprising orally administering about 15 mg/kg to about 100 mg/kg of a non-naturally occurring melanocortin analog to the subject,

the non-naturally occurring melanocortin analog comprising a sequence of Formula (IF).

[0770] 115. Use of a non-naturally occurring melanocortin analog for treating, preventing, or reducing glucose intolerance and/or diabetes mellitus in a subject in need thereof, comprising orally administering about 15 mg/kg to about 100 mg/kg of a non-naturally occurring melanocortin analog to the subject,

the non-naturally occurring melanocortin analog comprising a sequence of Formula (IF).

[0771] 116. A method of reducing obesity-related inflammation in a subject in need thereof, comprising orally administering about 15 mg/kg to about 100 mg/kg of a non-naturally occurring melanocortin analog to the subject,

the non-naturally occurring melanocortin analog comprising a sequence of Formula (IF).

[0772] 117. A method of preserving or improving kidney function in a subject in need thereof, comprising orally administering about 15 mg/kg to about 100 mg/kg of a non-naturally occurring melanocortin analog to the subject,

the non-naturally occurring melanocortin analog comprising a sequence of Formula (IF).

[0773] 118. Use of a non-naturally occurring melanocortin analog for preserving or improving kidney function in a subject in need thereof, comprising orally administering about 15 mg/kg to about 100 mg/kg of a non-naturally occurring melanocortin analog to the subject,

the non-naturally occurring melanocortin analog comprising a sequence of Formula (IF).

[0774] 119. The method or use of any one of embodiments 112-118, wherein the sequence of Formula (IF) is: Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH2 (SEQ ID NO: 43), wherein c represents cyclization through R2 and R7 via a lactam bond.

[0775] 120. The method or the use of any one of embodiments 13-119, wherein, after administration of the non-naturally occurring melanocortin analog, the subject's body weight is more than 5%, more than 10%, more than 15%, more than 20%, more than 25%, more than 30%, more than 35%, or more than 40% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog.

[0776] 121. The method or the use of any one of embodiments 13-120, wherein, after administration of the non-naturally occurring melanocortin analog, the subject's fat mass is more than 5%, more than 10%, more than 15%, more than 20%, more than 25%, more than 30%, more than 35%, or more than 40% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog.

[0777] 122. A non-naturally occurring melanocortin analog comprising a sequence of: Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH2 (SEQ ID NO: 43), wherein c represents cyclization through R2 and R7 via a lactam bond.

[0778] 123. A method of reducing body weight and/or fat mass in a subject in need thereof, comprising orally administering a non-naturally occurring melanocortin analog comprising a sequence of SEQ ID NO: 43 to the subject.

[0779] 124. Use of a non-naturally occurring melanocortin analog for reducing body weight and/or fat mass in a subject in need thereof, comprising orally administering a non-naturally occurring melanocortin analog comprising a sequence of SEQ ID NO: 43 to the subject.

[0780] 125. The method or the use of embodiment 123 or 124, wherein the method or the use further comprises reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in the subject.

[0781] 126. The method or the use of embodiment 125, wherein the lean mass is lean muscle mass.

[0782] 127. The method or the use of any one of embodiments 123-126, wherein the method or the use further comprises treating, preventing, or reducing glucose intolerance and/or diabetes mellitus in the subject.

[0783] 128. A method of treating, preventing, or reducing glucose intolerance and/or diabetes mellitus in a subject in need thereof, comprising orally administering a non-naturally occurring melanocortin analog comprising a sequence of SEQ ID NO: 43 to the subject.

[0784] 129. Use of a non-naturally occurring melanocortin analog for treating, preventing, or reducing glucose intolerance and/or diabetes mellitus in a subject in need thereof, comprising orally administering a non-naturally occurring melanocortin analog comprising a sequence of SEQ ID NO: 43 to the subject.

[0785] 130. The method or the use of embodiment 128 or 129, wherein the method or the use further comprises reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in the subject.

[0786] 131. The method or the use of embodiment 130, wherein the lean mass is lean muscle mass.

[0787] 132. The method or the use of any one of embodiments 128-131, wherein the method or the use further comprises reducing body weight and/or fat mass in the subject.

[0788] 133. The method or the use of any one of embodiments 128-132, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 15 mg/kg to about 100 mg/kg per body weight of the subject once daily.

[0789] 134. The method or the use of embodiment 133, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 30 mg/kg or 60 mg/kg per body weight of the subject once daily.

[0790] 135. The method or the use of any one of embodiments 128-134, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 0.1 mg to about 100 mg once daily.

[0791] 136. The method or the use of any one of embodiments 128-135, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 10 mg or about 50 mg once daily.

[0792] 137. The method or the use of any one of embodiments 128-136, wherein the method or the use further comprises reducing obesity-related inflammation in the subject.

[0793] 138. The method or the use of any one of embodiments 128-137, wherein the method or the use further comprises preserving or improving kidney function in the subject.

[0794] 139. The method or the use of any one of embodiments 13-138, wherein the method of the use further comprises one or more of (i) reducing a lipid droplets size (e.g., an average lipid droplet size); (ii) increasing an adipose tissue mitochondrial number or adipose tissue mitochondrial concentration; (iii) increasing an adipose tissue vascularization level; (iv) increasing, maintaining, or preventing a reduction of a beige or brown adipocyte level; (v) increasing a metabolic rate; (vi) increasing a calorie burn level; or (vii) increasing, maintaining, or preventing reduction of an insulin sensitivity level, relative to a control.

[0795] 140. The method or the use of any one of embodiments 13-139, wherein the subject has a metabolic dysfunction selected from the group consisting of obesity, diabetes mellitus, metabolic syndrome, insulin resistance, non-alcoholic fatty liver disease, polycystic ovarian syndrome, metabolic acidosis, hypothyroidism, hyperlipidemia, Cushing Syndrome, and metabolic myopathies.

[0796] 141. The method or the use of any one of embodiments 13-140, wherein the non-naturally occurring melanocortin analog comprises a reduced clearance, and increased concentration, or an increased distribution during or after administration to the subject, relative to a control.

[0797] 142. The method or the use of embodiment 141, wherein the clearance is a liver or a liver microsome clearance.

[0798] 143. The method or the use of embodiment 141, wherein the concentration is an aqueous concentration.

[0799] 144. The method or the use of embodiment 143, wherein the aqueous concentration comprises an intestinal fluid concentration or a gastric fluid concentration.

[0800] 145. The method or the use of any one of embodiments 13-144, wherein the concentration of the non-naturally occurring melanocortin analog in the plasma or a tissue of the subject is at least about 5 ng/mL to at least about 2000 ng/mL about 24 hours after administration of the non-naturally occurring melanocortin analog.

[0801] 146. The method or the use of any one of embodiments 13-144, wherein the non-naturally occurring melanocortin analog is administered to the subject until the concentration of the non-naturally occurring melanocortin analog in the plasma or a tissue of the subject is at least about 5 ng/mL to at least about 2000 ng/mL after administration of the non-naturally occurring melanocortin analog.

[0802] 147. The method or the use of embodiment 145 or 146, wherein concentration is at least about 5 ng/mL after administration of the non-naturally occurring melanocortin analog.

[0803] 148. The method or the use of embodiment 145 or 146, wherein concentration is at least about 10 ng/mL after administration of the non-naturally occurring melanocortin analog.

[0804] 149. The method or the use of embodiment 145 or 146, wherein concentration is at least about 50 ng/mL after administration of the non-naturally occurring melanocortin analog.

[0805] 150. The method or the use of embodiment 145 or 146, wherein concentration is at least about 100 ng/mL after administration of the non-naturally occurring melanocortin analog.

[0806] 151. The method or the use of embodiment 145 or 146, wherein concentration is at least about 200 ng/mL after administration of the non-naturally occurring melanocortin analog.

[0807] 152. The method or the use of embodiment 145 or 146, wherein concentration is at least about 300 ng/mL after administration of the non-naturally occurring melanocortin analog.

[0808] 153. The method or the use of embodiment 145 or 146, wherein concentration is at least about 400 ng/mL after administration of the non-naturally occurring melanocortin analog.

[0809] 154. The method or the use of embodiment 145 or 146, wherein concentration is at least about 500 ng/mL after administration of the non-naturally occurring melanocortin analog.

[0810] 155. The method or the use of embodiment 145 or 146, wherein concentration is at least about 750 ng/mL after administration of the non-naturally occurring melanocortin analog.

[0811] 156. The method or the use of embodiment 145 or 146, wherein concentration is at least about 1000 ng/mL after administration of the non-naturally occurring melanocortin analog.

[0812] 157. The method or the use of embodiment 145 or 146, wherein concentration is at least about 1500 ng/mL after administration of the non-naturally occurring melanocortin analog.

[0813] 158. The method or the use of embodiment 145 or 146, wherein concentration is at least about 2000 ng/mL after administration of the non-naturally occurring melanocortin analog.

[0814] 159. The method or the use of any one of embodiments 145-158, wherein the concentration is a maximum concentration (Cmax).

[0815] 160. The method or the use of any one of embodiments 18-159, wherein the non-naturally occurring melanocortin analog is administered as a single dosage unit.

[0816] 161. The method or the use of any one of embodiments 13-159, wherein the non-naturally occurring melanocortin analog dose is administered as multiple dosage units.

[0817] 162. The method or the use of embodiment 161, wherein the multiple dosage units individually comprise about 2.5 mg/mL to about 100 mg/mL of the non-naturally occurring melanocortin analog.

[0818] 163. The method or the use of embodiment 162, wherein the multiple dosage units individually comprise about 2.5 mg/mL to about 10 mg/mL of the non-naturally occurring melanocortin analog.

[0819] 164. The method or the use of embodiment 161, wherein the multiple dosage units individually comprise about 6 mg/mL of the non-naturally occurring melanocortin analog.

[0820] 165. The method or the use of embodiment 161, wherein the non-naturally occurring melanocortin analog is administered as about 5 dosage units to about 10 dosage units.

[0821] 166. The method or the use of embodiment 161, wherein the non-naturally occurring melanocortin analog is administered as 5 dosage units.

[0822] 167. The method or the use of embodiment 161, wherein the non-naturally occurring melanocortin analog is administered as 10 dosage units.

[0823] 168. The method or the use of any one of embodiments 13-167, wherein the dosage unit is a capsule.

[0824] 169. The method or the use of embodiment 168, wherein the capsule comprises the non-naturally occurring melanocortin analog suspended in a saline solution.

[0825] 170. The method or the use of embodiment 169, wherein the saline solution is about 100% saline.

[0826] 171. The method or the use of embodiment 169, wherein the saline solution is about 95% saline.

[0827] 172. The method or the use of embodiment 169, wherein the saline solution is about 90% saline.

[0828] 173. The method or the use of embodiment 171 or 172, wherein the saline solution comprises dimethyl sulfoxide (DMSO).

[0829] From the foregoing, it will be appreciated that specific embodiments of the present technology have been described herein for purposes of illustration, but that various modifications may be made without deviating from the scope of the present technology. Accordingly, the present technology is not limited except as by the appended claims.

CLAIMS

I/We claim:

1. A non-naturally occurring melanocortin analog comprising a sequence according to Formula (IF),

R^1-R^2-R^3-R^4-R^5-R^6-R^7-Y^1-Y^2 (IF),

wherein:

R^1 is Nle;

R^2 is Asp or Glu;

R^3 is His;

R^4 is selected from dPhe, p(F)dPhe, and p(Cl)dPhe;

R^5 is Arg or His;

R^6 is Trp;

R^7 is Orn;

Y^1 is dVal;

Y^2 is dPro; and

the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between Asp or Glu at R^2 and Orn at R^7.

2. The non-naturally occurring melanocortin analog of claim 1, comprising a sequence selected from the group consisting of:

Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 43);

Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 44);

Ac-Nle-c[Glu-His-dPhe-His-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 45);

Ac-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 11); and

Ac-Nle-c[Glu-His-p(Cl)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 12),

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

3. The non-naturally occurring melanocortin analog of claim 1 or 2, wherein the non-naturally occurring melanocortin analog is cyclized between Glu at R^2 and and Orn at R^7.

4. The non-naturally occurring melanocortin analog of claim 3, comprising a sequence selected from the group consisting of:

Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 43);

Ac-Nle-c[Glu-His-dPhe-His-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 45); and

Ac-Nle-c[Glu-His-p(Cl)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 12),

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

5. The non-naturally occurring melanocortin analog of claim 1 or 2, wherein R^4 is p(F)dPhe or dPhe.

6. The non-naturally occurring melanocortin analog of claim 5, comprising a sequence selected from the group consisting of:

Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 43);

Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 44); and

Ac-Nle-c[Glu-His-dPhe-His-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 45),

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

7. The non-naturally occurring melanocortin analog of claim 5, comprising a sequence of:

Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 43); or

Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 44),

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

8. The non-naturally occurring melanocortin analog of claim 5, comprising a sequence of: Ac-Nle-c[Glu-His-dPhe-His-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 45), wherein c represents cyclization through R^2 and R^7 via a lactam bond.

9. The non-naturally occurring melanocortin analog of claim 1 or 2, wherein R^4 is p(F)dPhe or p(Cl)dPhe.

10. The non-naturally occurring melanocortin analog of claim 9, comprising a sequence selected from the group consisting of:

Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 43);

Ac-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 44);

Ac-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 11); and

Ac-Nle-c[Glu-His-p(Cl)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 12),

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

11. The non-naturally occurring melanocortin analog of claim 1 or 2, wherein R^4 is para-fluoro-D-phenylalanine (p(F)dPhe).

12. The non-naturally occurring melanocortin analog of any one of claims 1-11, comprising a sequence of: Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 43), wherein c represents cyclization through R^2 and R^7 via a lactam bond.

13. A method of reducing body weight and/or fat mass in a subject in need thereof, comprising orally administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I):

$$X^1\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}R^8\text{-}R^9\text{-}Y^1\text{-}Y^2\text{-}Y^3\text{-}Y^4 \quad (I),$$

wherein:

X^1 is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

R^1 is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R^2 is selected from the group consisting of Asp, D-cysteine (dCys), Ala, D-alanine (dAla), proline (Pro), glutamic acid (Glu), and phenylalanine (Phe);

R^3 is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln);

R^4 is selected from the group consisting of D-phenylalanine (dPhe), Pro, para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

R^5 is selected from the group consisting of Arg, His, *cis*-4-guanidyl-proline (*cis*Pro(guan)), and *trans*-4-guanidyl-proline (*trans*Pro(guan));

R^6 is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2')));

R^7 is selected from the group consisting of Arg, Pro, ornithine (Orn), cysteine (Cys) and lysine (Lys);

R^8 is absent, Lys, or Trp;

R^9 is absent or Lys;

Y^1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y^2 is selected from the group consisting of dVal, dPro, and dTle;

Y^3 is absent, dVal, or dPro;

Y^4 is absent or dPro; and

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

a disulfide bond between R^2 and R^7 when R^2 is dCys, R^4 is p(Cl)dPhe, and R^7 is Cys;

a lactam bridge between R^1 or R^2 and any one of R^7-R^9 when R^1 or R^2 is Asp, R^4 is dPhe, or p(F)dPhe, and any one of R^7-R^9 is Lys; and

a lactam bridge between R^2 and R^7 when R^2 is Asp or Glu and R^7 is Orn,

provided that:

when R^3 is Pro, then X^1 and Y^3 are present and R^4 is dPhe,

when R^4 is p(Cl)dPhe, then the non-naturally occurring melanocortin analog is not cyclized through a lactam bond between Asp at R^2 and Lys at R^7,

when R^2 and/or R^3 is Phe, then R^4 is Pro and R^6 is dPhe,

when R^4 is dPhe and R^2 is Pro, then X^1 is present and R^5 is Arg, and

when R^4 is dPhe, R^2 is Ala, and R^3 is His, then R^5 is Arg.

14. Use of a non-naturally occurring melanocortin analog for reducing body weight and/or fat mass in a subject in need thereof, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

15. A method of reducing body weight and/or fat mass in an obese subject, comprising orally administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

16. Use of a non-naturally occurring melanocortin analog for reducing body weight and/or fat mass in an obese subject, comprising orally administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

17. The method or the use of any one of claims 13-16, wherein the method or the use further comprises reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in the subject.

18. The method or the use of claim 17, wherein the lean mass is lean muscle mass.

19. The method or the use of any one of claims 13-18, wherein the method or the use further comprises treating, preventing, or reducing glucose intolerance and/or diabetes mellitus in the subject.

20. A method of treating, preventing, or reducing hyperplasia in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

21. Use of a non-naturally occurring melanocortin analog for treating, preventing, or reducing hyperplasia in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

22. A method of treating, preventing, or reducing hypothalamic obesity in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

23. Use of a non-naturally occurring melanocortin analog for treating, preventing, or reducing hypothalamic obesity in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

24. The method or the use of claim 22 or 23, wherein the hypothalamic obesity comprises congenital hypothalamic damage, damage from tumors, or damage from trauma.

25. A method of treating, preventing, or reducing a proopiomelanocortin (POMC) deficiency in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

26. Use of a non-naturally occurring melanocortin analog for treating, preventing, or reducing a POMC deficiency in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

27. A method of treating, preventing, or reducing a leptin deficiency in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

28. Use of a non-naturally occurring melanocortin analog for treating, preventing, or reducing a leptin deficiency in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

29. A method of treating, preventing, or reducing a syndromic obesity in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

30. Use of a non-naturally occurring melanocortin analog for treating, preventing, or reducing a syndromic obesity in a subject in need thereof, comprising administering a

non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

31. The method or the use of claim 29 or 30, wherein the syndromic obesity is selected from the group consisting of Prader–Willi syndrome, Wilms tumor, Aniridia, Genitourinary, Range of Developmental Delays (WAGR) syndrome, Bardet-Biedl syndrome, Fragile X syndrome, Cohen syndrome, Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1) deficiency, Alstrom syndrome, MC4 haploinsufficiency, 17p11.2 deletion syndrome, and 2q37 deletion syndrome.

32. A method of treating, preventing, or reducing non-alcoholic steatohepatitis (NASH) in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

33. Use of a non-naturally occurring melanocortin analog for treating, preventing, or reducing NASH in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

34. A method of treating, preventing, or reducing hyperinsulinism in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

35. Use of a non-naturally occurring melanocortin analog for treating, preventing, or reducing hyperinsulinism in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

36. A method of treating, preventing, or reducing a cardiovascular disease in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

37. Use of a non-naturally occurring melanocortin analog for treating, preventing, or reducing a cardiovascular disease in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

38. The method or the use of claim 36 of 451, wherein the cardiovascular disease comprises a stroke or a heart attack.

39. A method of treating, preventing, or reducing osteoarthritis in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

40. Use of a non-naturally occurring melanocortin analog for treating, preventing, or reducing osteoarthritis in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

41. A method of treating, preventing, or reducing a cancer in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

42. Use of non-naturally occurring melanocortin analog for treating, preventing, or reducing a cancer in a subject in need thereof, comprising administering a non-naturally

occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

43. The method or the use of claim 41 or 42, wherein the method or the use further comprises reducing a risk of the cancer.

44. A method of treating, preventing, or reducing erectile dysfunction in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

45. Use of a non-naturally occurring melanocortin analog for treating, preventing, or reducing erectile dysfunction in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

46. A method of treating, preventing, or reducing body weight gain after a weight loss in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

47. Use of a non-naturally occurring melanocortin analog for treating, preventing, or reducing body weight gain after a weight loss in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

48. A method of maintaining body weight after a weight loss in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

49. Use of a non-naturally occurring melanocortin analog for maintaining body weight after a weight loss in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

50. A method of treating, preventing, or reducing fat mass gain after a weight loss in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

51. Use of a non-naturally occurring melanocortin analog for treating, preventing, or reducing fat mass gain after a weight loss in a subject in need thereof, comprising administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

52. A method of treating, preventing, or reducing glucose intolerance and/or diabetes mellitus in a subject in need thereof, comprising orally administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

53. Use of a non-naturally occurring melanocortin analog for treating, preventing, or reducing glucose intolerance and/or diabetes mellitus in a subject in need thereof, comprising orally administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

54. The method or the use of claim 52 or 53, wherein the method or the use further comprises reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in the subject.

55. The method or the use of claim 54, wherein the lean mass is lean muscle mass.

56. The method or the use of any one of claims 52-55, wherein the method or the use further comprises reducing body weight and/or fat mass in the subject.

57. The method or the use of any one of claims 13-56, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 15 mg/kg to about 1000 mg/kg per body weight of the subject once daily.

58. The method or the use of any one of claims 13-27, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 15 mg/kg to about 550 mg/kg per body weight of the subject once daily.

59. The method or the use of any one of claims 13-29, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 15 mg/kg to about 100 mg/kg per body weight of the subject once daily.

60. The method or the use of any one of claims 13-31, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 15 mg/kg to about 75 mg/kg per body weight of the subject once daily.

61. The method or the use of claim 60, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 30 mg/kg or 60 mg/kg per body weight of the subject once daily.

62. The method or the use of any one of claims 13-56, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 0.1 mg to about 100 mg once daily.

63. The method or the use of any one of claims 13-56, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 10 mg or about 50 mg once daily.

64. The method or the use of any one of claims 13-63, wherein the method or the use further comprises reducing obesity-related inflammation in the subject.

65. The method or the use of any one of claims 13-64, wherein the method or the use further comprises preserving or improving kidney function in the subject.

66. A method of reducing obesity-related inflammation in a subject in need thereof, comprising orally administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

67. Use of a non-naturally occurring melanocortin analog for reducing obesity-related inflammation in a subject in need thereof, comprising orally administering a non-naturally occurring melanocortin analog to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

68. A method of preserving or improving kidney function in a subject in need thereof, comprising orally administering a non-naturally occurring melanocortin 4 receptor agonist to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

69. Use of a non-naturally occurring melanocortin analog for preserving or improving kidney function in a subject in need thereof, comprising orally administering a non-naturally occurring melanocortin 4 receptor agonist to the subject, the non-naturally occurring melanocortin analog comprising a sequence of Formula (I).

70. The method or the use of any one of claims 13-68, wherein the subject has a metabolic dysfunction selected from the group consisting of obesity, diabetes mellitus, metabolic syndrome, insulin resistance, non-alcoholic fatty liver disease, polycystic ovarian syndrome, metabolic acidosis, hypothyroidism, hyperlipidemia, Cushing Syndrome, and metabolic myopathies.

71. The method or the use of any one of claims 1-70, wherein the non-naturally occurring melanocortin analog is administered (i) at a first dose of about 5 mg/kg to about 20 mg/kg administered once a day for about 5 days to about 10 days; (ii) at a second dose of about 10 mg/kg to about 40 mg/kg administered once a day after administration of the first dose for about 5 days to about 10 days; (iii) at a third dose of about 5 mg/kg to about 30 mg/kg administered twice a day after administration of the second dose for at least about 5 days to about 10 days.

72. The method or the use of any one of claims 1-70, wherein the non-naturally occurring melanocortin analog is administered (i) at a first dose of about 5 mg/kg administered once a day for about 7 days; (ii) at a second dose of about 15 mg/kg administered once a day after administration of the first dose for about 7 days; (iii) at a third dose of about 10 mg/kg administered twice a day after administration of the second dose for at least about 7 days.

73. The method or the use of any one of claims 1-70, wherein the non-naturally occurring melanocortin analog is administered (i) at a first dose of about 10 mg/kg administered once a day for about 7 days; (ii) at a second dose of about 20 mg/kg administered once a day after administration of the first dose for about 7 days; (iii) at a third dose of about 15 mg/kg administered twice a day after administration of the second dose for at least about 7 days.

74. The method or the use of any one of claims 1-70, wherein the non-naturally occurring melanocortin analog is administered (i) at a first dose of about 15 mg/kg administered once a day for about 7 days; (ii) at a second dose of about 25 mg/kg administered once a day after administration of the first dose for about 7 days; (iii) at a third dose of about 20 mg/kg administered twice a day after administration of the second dose for at least about 7 days.

75. The method or the use of any one of claims 13-74, wherein the non-naturally occurring melanocortin analog comprises a sequence of Formula (I), wherein:

X^1 is absent or is selected from the group consisting of norleucine (Nle), arginine (Arg), and D-arginine (dArg);

R^1 is selected from the group consisting of Nle, Arg, dArg, aspartic acid (Asp), alanine (Ala), lysine (Lys), D-lysine (dLys), histidine (His), and D-histidine (dHis);

R^2 is selected from the group consisting of Asp, D-cysteine (dCys), Ala, D-alanine (dAla), proline (Pro), glutamic acid (Glu), and phenylalanine (Phe);

R^3 is selected from the group consisting of His, dHis, Pro, Phe, and glutamine (Gln);

R^4 is selected from the group consisting of D-phenylalanine (dPhe), Pro, para-fluoro-D-phenylalanine (p(F)dPhe), and para-chloro-D-phenylalanine (p(Cl)dPhe);

R^5 is selected from the group consisting of Arg, His, *cis*-4-guanidyl-proline (*cisPro*(guan)), and *trans*-4-guanidyl-proline (*trans*Pro(guan));

R^6 is selected from the group consisting of dPhe, tryptophan (Trp), and 2'-D-naphthylalanine (dNal(2')));

R^7 is selected from the group consisting of Arg, Pro, ornithine (Orn), cysteine (Cys) and lysine (Lys);

R^8 is absent, Lys, or Trp;

R^9 is absent or Lys;

Y^1 is selected from the group consisting of D-valine (dVal), D-proline (dPro), and D-tert-leucine (dTle);

Y^2 is selected from the group consisting of dVal, dPro, and dTle;

Y^3 is absent, dVal, or dPro;

Y^4 is absent or dPro;

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

a disulfide bond between R^2 and R^7 when R^2 is dCys, R^4 is p(Cl)dPhe, and R^7 is Cys;

a lactam bridge between R^1 or R^2 and any one of R^7-R^9 when R^1 or R^2 is Asp, R^4 is dPhe, or p(F)dPhe, and any one of R^7-R^9 is Lys; and

a lactam bridge between R^2 and R^7 when R^2 is Asp or Glu and R^7 is Orn;

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

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 48);

Ac-Ala-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 49);

Ac-dNle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 50);

Ac-dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 51);

His-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 52);

dHis-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 53);

Ac-Arg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 54);

Ac-dLys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 55);

Ac-Lys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 56);

Ac-His-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 57);

Ac-dHis-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 58);

Ac-Nle-c[dCys-Pro-dPhe-Arg-Trp-Cys]-dVal-dPro-NH_2 (SEQ ID NO: 59);

Ac-Nle-c[dCys-Pro-dPhe-Arg-Trp-dCys]-dVal-dPro-NH_2 (SEQ ID NO: 60);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 61);

Ac-Nle-c[Glu-Pro-dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 62);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Gly-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 63);

Ac-Nle-c[Asp-Phe-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 64);

Ac-Nle-c[Asp-His-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 65);

Ac-Nle-c[Asp-Pro-dPhe-His-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 66);

Ac-Nle-c[Asp-Pro-dPhe-Lys-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 67);

Ac-Nle-c[Asp-Pro-dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 68);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Nal(2')-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 69);

Ac-Nle-c[dCys-Pro-p(F)dPhe-Arg-Trp-Cys]-dVal-dPro-NH_2 (SEQ ID NO: 70);

Ac-Ala-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 71);

Ac-dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 72);

Ac-Arg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 73);

Ac-Lys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 74);

Ac-dLys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 75);

Ac-His-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 76);

Ac-dHis-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 77);

Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 78);

Ac-Nle-c[Asp-Pro-p(F)dPhe-His-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 79);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 80);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH_2 (SEQ ID NO: 81);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dVal-dVal-dPro-NH_2 (SEQ ID NO: 82);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH_2 (SEQ ID NO: 83);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 84);

Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 85);

Ac-Nle-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH_2 (SEQ ID NO: 86);

Ac-Ala-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 87);

Ac-dArg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 88);

Ac-Arg-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 89);

Ac-Lys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 90);

Ac-dLys-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 91);

Ac-His-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 92);

Ac-dHis-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 93);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 94);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dTle-NH_2 (SEQ ID NO: 95);

Ac-dHis-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 96);

Ac-Nle-c[Asp-Pro-dPhe-Arg-dTrp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 97);

Ac-Nle-c[Asp-Pro-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 98);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 99);

Ac-Nle-c[Asp-Pro-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 100);

Ac-Nle-c[Asp-Trp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 101);

Ac-Nle-c[Asp-Pro-dPhe-Pro-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 102);

Ac-Nle-c[Asp-Pro-p(Cl)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 103);

Ac-Nle-c[Asp-Pro-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 104);

Ac-Nle-c[Glu-Pro-p(Cl)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 105);

Ac-Nle-c[Glu-Pro-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 106);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-OH (SEQ ID NO: 107);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-NH_2 (SEQ ID NO: 108);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-OH (SEQ ID NO: 109);

Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 110);

Ac-Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 111);

Ac-Ala-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 112);

Ac-dArg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 113);

Ac-Arg-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 114);

Ac-Lys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 115);

Ac-dLys-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 116);

Ac-His-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 117);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dTle-dPro-NH_2 (SEQ ID NO: 118);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH_2 (SEQ ID NO: 119);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dVal-dPro-NH_2 (SEQ ID NO: 120);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH_2 (SEQ ID NO: 121);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dVal-dVal-dPro-NH_2 (SEQ ID NO: 122);

Ac-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dVal-dPro-dVal-dPro-NH_2 (SEQ ID NO: 123);

Ac-Nle-c[Asp-Pro-dPhe-transPro(guan)-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 124);

Ac-Nle-c[Asp-Pro-dPhe-cisPro(guan)-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 125);

Ac-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dTle-dTle-dVal-NH_2 (SEQ ID NO: 126);

Ac-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dVal-dVal-dPro-NH_2 (SEQ ID NO: 127);

Ac-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH_2 (SEQ ID NO: 128);

Ac-Nle-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro-NH_2 (SEQ ID NO: 129);

Ac-Ala-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 130);

Ac-dArg-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 131);

Ac-Arg-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 132);

Ac-Lys-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 133);

Ac-dLys-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 134);

Ac-His-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 135);

Ac-dHis-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 136);

Ac-Nle-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 137);

Ac-Nle-c[Asp-His-p(Cl)dPhe-His-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 138);

Ac-Nle-c[Asp-His-p(Cl)dPhe-Arg-dNal(2')-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 139);

Ac-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 140);

Ac-Nle-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 141);

Ac-Ala-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 142);

Ac-dArg-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 143);

Ac-Arg-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 144);

Ac-dLys-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 145);

Ac-dHis-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 146);

Ac-Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 147);

Ac-Nle-c[Asp-dHis-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 148);

Ac-Nle-c[Asp-Phe-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 149);

Ac-Nle-c[Asp-Gln-p(Cl)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 150);

Ac-Lys-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 151);

Ac-His-c[Asp-His-p(Cl)dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 152);

Ac-Nle-c[Asp-Phe-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 153);

Ac-Nle-c[Asp-Phe-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 154);

Ac-Nle-c[Asp-Phe-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 155);

Ac-Nle-c[Asp-Phe-Phe-Pro-His-dNal(2')-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 156);

Ac-Nle-c[Asp-Phe-His-dPhe-Arg-Trp-Lys]-dTle-dPro-NH_2 (SEQ ID NO: 157);

Ac-Nle-c[Asp-Pro-His-dPhe-His-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 158);

Ac-Arg-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 159); and

Ac-dArg-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH_2 (SEQ ID NO: 160).

76. The method or the use of any one of claims 13-75, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (IA):

$$X^1\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}R^8\text{-}Y^1\text{-}Y^2\text{-}Y^3\text{-}Y^4 \quad (IA),$$

wherein:

X^1 is absent or is selected from the group consisting of Nle, Arg, and dArg;

R^1 is selected from the group consisting of Nle, Arg, dArg, Asp, Ala, Lys, dLys, His, and dHis;

R^2 is selected from the group consisting of Asp, Ala, dAla, Pro, and Glu

R^3 is selected from the group consisting of His, dHis, Pro, and Gln;

R^4 is dPhe or p(F)dPhe;

R^5 is selected from the group consisting of Arg, His, *cisPro*(guan), and *trans*Pro(guan);

R^6 is Trp or dNal(2');

R^7 is selected from the group consisting of Pro, Orn, and Lys;

R^8 is absent or Lys;

Y^1 is selected from the group consisting of dVal, dPro, and dTle;

Y^2 is selected from the group consisting of dVal, dPro, and dTle;

Y^3 is absent, dVal, or dPro;

Y^4 is absent or dPro; and

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

a lactam bridge between R^1 or R^2 and R^7 or R^8 when R^1 or R^2 is Asp and R^7 or R^8 is Lys; and

a lactam bridge between R^2 and R^7 when R^2 is Asp or Glu and R^7 is Orn.

77. The method or the use of any one of claims 13-76, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (IB):

$$X^1\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}Y^1\text{-}Y^2\text{-}Y^3\text{-}Y^4 \text{ (IB)},$$

wherein:

X^1 is absent or Nle;

R^1 is selected from the group consisting of Nle, Arg, dArg, Ala, Lys, dLys, His, and dHis;

R^2 is Asp or Glu;

R^3 is selected from the group consisting of His, dHis, Pro, and Gln;

R^4 is dPhe or p(F)dPhe;

R^5 is selected from the group consisting of Arg, His, *cisPro*(guan), and *trans*Pro(guan);

R^6 is Trp or dNal(2');

R^7 is Orn or Lys;

Y^1 is selected from the group consisting of dVal, dPro, and dTle;

Y^2 is selected from the group consisting of dVal, dPro, and dTle;

Y^3 is absent, dVal, or dPro;

Y^4 is absent or dPro; and

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

a lactam bridge between R^2 and R^7 when R^2 is Asp and R^7 is Lys; and

lactam bridge between Asp or Glu at R^2 and Orn or Lys at R^7.

78. The method or the use of any one of claims 13-77, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (IC):

$$X^1\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}Y^1\text{-}Y^2\text{-}Y^3\text{-}Y^4 \text{ (IC)},$$

wherein:

X^1 is absent or Nle;

R^1 is selected from the group consisting of Nle, Arg, dArg, Ala, Lys, dLys, His, and dHis;

R^2 is Asp or Glu;

R^3 is His;

R^4 is p(F)dPhe;

R^5 is Arg;

R^6 is Trp;

R^7 is Orn or Lys;

Y^1 is selected from the group consisting of dVal, dPro, and dTle;

Y^2 is selected from the group consisting of dVal, dPro, and dTle;

Y^3 is absent, dVal, or dPro;

Y^4 is absent or dPro; and

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

a lactam bridge between R^2 and R^7 when R^2 is Asp and R^7 is Lys; and

lactam bridge between Asp or Glu at R^2 and Orn or Lys at R^7.

79. The method or the use of any one of claims 13-77, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (ID):

$$X^1\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}R^8\text{-}Y^1\text{-}Y^2\text{-}Y^3 \text{ (ID)},$$

wherein:

X^1 is absent or norleucine (Nle);

R^1 is Nle or Asp;

R^2 is selected from the group consisting of Asp, Glu, and Pro;

R^3 is selected from the group consisting of His, dHis, Pro, and Gln;

R^4 is dPhe;

R^5 is selected from the group consisting of Arg, His, *cisPro*(guan), and *trans*Pro(guan);

R^6 is Trp;

R^7 is selected from the group consisting of Orn, Lys, and Pro;

R^8 is absent or Lys;

Y^1 is dVal or dPro;

Y^2 is dVal or dPro;

Y^3 is absent or dPro; and

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

a lactam bridge between R^1 or R^2 and R^7 or R^8 when R^1 or R^2 is Asp and R^7 or R^8 is Lys; and

a lactam bridge between R^2 and R^7 when R^2 is Asp or Glu and R^7 is Orn.

80. The method or the use of any one of claims 13-76, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (IE):

$$X^1\text{-}R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}Y^1\text{-}Y^2 \text{ (IE)},$$

wherein:

X^1 is absent or selected from the group consisting of Nle, Arg, and dArg;

R^1 is Asp;

R^2 is dAla or Ala;

R^3 is His;

R^4 is dPhe;

R^5 is Arg;

R^6 is Trp;

R^7 is Lys;

Y^1 is dVal;

Y^2 is dPro; and

the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between Asp at R^1 and Lys at R^7.

81. The method or the use of any one of claims 13-75, wherein the non-naturally occurring melanocortin analog comprises a sequence according to Formula (IF):

$$R^1\text{-}R^2\text{-}R^3\text{-}R^4\text{-}R^5\text{-}R^6\text{-}R^7\text{-}Y^1\text{-}Y^2 \text{ (IF)},$$

wherein:

R^1 is Nle;

R^2 is Asp or Glu;

R^3 is His;

R^4 is selected from dPhe, p(F)dPhe, and p(Cl)dPhe;

R^5 is Arg or His;

R^6 is Trp;

R^7 is Orn;

Y^1 is dVal;

Y^2 is dPro; and

the non-naturally occurring melanocortin analog is cyclized through a lactam bridge between Asp or Glu at R^2 and Orn at R^7.

82. The method or the use of any one of claims 13-81, wherein R^3 is His and R^4 is p(F)dPhe or dPhe.

83. The method or the use of any one of claims 13-82, wherein R^1 is selected from Nle, Ala, Arg, dArg, Lys, dLys, His, and dHis and R^4 is p(F)dPhe.

84. The method or the use of any one of claims 13-83, wherein the sequence according to any one of Formulae (I)-(IF) is selected from the group consisting of:

Ac—Ala-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 3);

Ac—dArg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 4);

Ac—Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 14);

Ac—Arg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 15);

Ac—Lys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 16);

Ac—dLys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 17);

Ac—His-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 18); and

Ac—dHis-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 19),

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

85. The method or the use of any one of claims 13-83, wherein the sequence according to any one of Formulae (I)-(IF) is selected from the group consisting of:

Ac—Ala-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro—NH2 (SEQ ID NO: 7);

Ac—dArg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro—NH2 (SEQ ID NO: 8);

Ac—Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro—NH2 (SEQ ID NO: 24);

Ac—Arg-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro—NH2 (SEQ ID NO: 27);

Ac—Lys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro—NH2 (SEQ ID NO: 28);

Ac—dLys-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro—NH2 (SEQ ID NO: 29);

Ac—His-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro—NH2 (SEQ ID NO: 30); and

Ac—dHis-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro—NH2 (SEQ ID NO: 31),

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

86. The method or the use of any one of claims 13-82, wherein R^1 is Nle and R^4 is dPhe.

87. The method or the use of claim any one of claims 13-82 and 79, wherein the sequence according to any one of Formulae (I)-(IF) is:

Ac—Nle-c[Asp-His-dPhe-Arg-Trp-Lys]-dPro-dVal—NH2 (SEQ ID NO: 33); or

Ac—Nle-c[Asp-His-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 42),

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

88. The method or the use of any one of claims 13-82, wherein R^1 is Nle and R^4 is p(F)dPhe.

89. The method or the use of claim any one of claims 13-82 and 81, wherein the sequence according to any one of Formulae (I)-(IF) is selected from the group consisting of:

Ac—Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dTle-dVal—NH2 (SEQ ID NO: 6);

Ac—Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 20);

Ac—Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dVal-dVal-dVal-dPro—NH2 (SEQ ID NO: 22);

Ac—Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro—NH2 (SEQ ID NO: 23);

Ac—Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dTle-dPro—NH2 (SEQ ID NO: 25); and

Ac—Nle-Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Lys]-dPro-dVal-dPro—NH2 (SEQ ID NO: 26),

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

90. The method or the use of any one of claims 13-82, wherein R^1 is Nle and R^4 is dPhe or p(F)dPhe.

91. The method or the use of claim any one of claims 13-82 and 83, wherein the sequence according to any one of Formulae (I)-(IF) is selected from the group consisting of:

Ac—Nle-c[Asp-His-p(F)dPhe-His-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 21);

Ac—Nle-c[Asp-His-dPhe-transPro(guan)-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 46); and

Ac—Nle-c[Asp-His-dPhe-cisPro(guan)-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 47),

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

92. The method or the use of claim any one of claims 13-82 and 83, wherein the sequence according to any one of Formulae (I)-(IF) is: Ac—Nle-c[Asp-His-p(F)dPhe-Arg-dNal(2')-Lys]-dVal-dPro—NH2 (SEQ ID NO: 5), wherein c represents cyclization through R^2 and R^7 via a lactam bond.

93. The method or the use of any one of claims 13-78, wherein the sequence of any one of Formulae (I)-(IF) is cyclized through a lactam bond between Asp or Glu at R^2 and Orn at R^7.

94. The method or the use of claim any one of claims 13-78 and 86, wherein the sequence according to any one of Formulae (I)-(IF) is selected from the group consisting of:

Ac—Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro—NH2 (SEQ ID NO: 43);

Ac—Nle-c[Asp-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro—NH2 (SEQ ID NO: 44);

Ac-Nle-c[Glu-His-dPhe-His-Trp-Orn]-dVal-dPro-NH2 (SEQ ID NO: 45);

Ac—Nle-c[Asp-His-p(Cl)dPhe-Arg-Trp-Orn]-dVal-dPro—NH2 (SEQ ID NO: 11); and

Ac—Nle-c[Glu-His-p(Cl)dPhe-Arg-Trp-Orn]-dVal-dPro—NH2 (SEQ ID NO: 12),

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

95. The method or the use of any one of claims 13-78, wherein the sequence of any one of Formulae (I)-(IF) is cyclized through a lactam bond between dCys at R^2 and Cys at R^7.

96. The method or the use of claim any one of claims 13-78 and 88, wherein the sequence according to any one of Formulae (I)-(IF) is: Ac—Nle-c[dCys-His-p(Cl)dPhe-Arg-Trp-Cys]-dVal-dPro—NH2 (SEQ ID NO: 5), wherein c represents cyclization through R^2 and R^7 via a disulfide bond.

97. The method or the use of any one of claims 13-82, wherein the sequence of any one of Formulae (I)-(IF) is cyclized through a lactam bond between Asp at R^2 and Lys at R^8.

98. The method or the use of claim any one of claims 13-82 and 90, wherein the sequence according to any one of Formulae (I)-(IF) is: Ac—Nle-c[Asp-His-dPhe-Arg-Trp-Pro-Lys]-dVal-dPro—NH2 (SEQ ID NO: 35), wherein c represents cyclization through R^2 and R^8 via a lactam bond.

99. The method or the use of any one of claims 13-82, wherein the sequence of any one of Formulae (I)-(IF) is cyclized through a lactam bond between Asp at R^1 and Lys at R^7.

100. The method or the use of claim any one of claims 13-82 and 92, wherein the sequence according to any one of Formulae (I)-(IF) is selected from the group consisting of:

Ac—Nle-c[Asp-dAla-His-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 38);

Ac—Arg-c[Asp-dAla-His-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 39);

Ac—dArg-c[Asp-dAla-His-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 40); and

Ac—Nle-c[Asp-Ala-His-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 41),

wherein c represents cyclization through R^1 and R^7 via a lactam bond.

101. The method or the use of claim any one of claims 13-82 and 93, wherein the sequence according to any one of Formulae (I)-(IF) is: Ac-Nle-c[Asp-Pro-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 13), wherein c represents cyclization through R^1 and R^7 via a lactam bond.

102. The method or the use of claim any one of claims 13-78, wherein R^3 is selected from dHis, Gln and Pro and R^4 is dPhe or p(F)dPhe.

103. The method or the use of claim any one of claims 13-78 and 95, wherein the sequence according to any one of Formulae (I)-(IF) is selected from the group consisting of:

Ac—Nle-c[Asp-Gln-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 9);

Ac—Nle-Nle-c[Asp-Pro-dPhe-Arg-Trp-Lys]-dPro-dVal-dPro—NH2 (SEQ ID NO: 10);

Ac—Nle-c[Asp-dHis-p(F)dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 32);

Ac—Nle-c[Asp-dHis-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 36); and

Ac—Nle-c[Asp-Gln-dPhe-Arg-Trp-Lys]-dVal-dPro—NH2 (SEQ ID NO: 37),

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

104. The method or the use of claim any one of claims 13-78 and 95, wherein the sequence according to any one of Formulae (I)-(IF) is: Ac-Nle-c[Asp-Phe-Phe-Pro-His-dPhe-Arg-Trp-Lys]-dVal-dPro-NH2 (SEQ ID NO: 34), wherein c represents cyclization through R^1 and R^9 via a lactam bond.

105. The method or the use of claim any one of claims 13-104, wherein the non-naturally occurring melanocortin analog comprises a sequence of any of one SEQ ID NOs: 2-47.

106. The method or the use of claim any one of claims 13-105, wherein the non-naturally occurring melanocortin analog comprises a sequence of any of one SEQ ID NOs: 3-10, 13-33, and 35-47.

107. The method or the use of claim any one of claims 13-105, wherein the non-naturally occurring melanocortin analog comprises a sequence of any of one SEQ ID NOs: 3-10, 14-33, 36, 37, and 42-47.

108. The method or the use of claim any one of claims 13-105, wherein the non-naturally occurring melanocortin analog comprises a sequence of any of one SEQ ID NOs: 3-8, 14-31, 43, and 44.

109. The method or the use of claim any one of claims 13-105, wherein the non-naturally occurring melanocortin analog comprises a sequence of any of one SEQ ID NOs: 10, 13, 33, 35-37, 42, and 45-47.

110. The method or the use of claim any one of claims 13-105, wherein the non-naturally occurring melanocortin analog comprises a sequence of any of one SEQ ID NOs: 38-41.

111. The method or the use of claim any one of claims 13-105, wherein the non-naturally occurring melanocortin analog comprises a sequence of any of one SEQ ID NOs: 11, 12, and 43-45.

112. A method of reducing body weight and/or fat mass in a subject in need thereof, comprising orally administering about 15 mg/kg to about 100 mg/kg of a non-naturally occurring melanocortin analog to the subject,

the non-naturally occurring melanocortin analog comprising a sequence of Formula (IF).

113. Use of a non-naturally occurring melanocortin analog for reducing body weight and/or fat mass in a subject in need thereof, comprising orally administering about 15 mg/kg to about 100 mg/kg of a non-naturally occurring melanocortin analog to the subject,

the non-naturally occurring melanocortin analog comprising a sequence of Formula (IF).

114. A method of treating, preventing, or reducing glucose intolerance and/or diabetes mellitus in a subject in need thereof, comprising orally administering about 15 mg/kg to about 100 mg/kg of a non-naturally occurring melanocortin analog to the subject,

the non-naturally occurring melanocortin analog comprising a sequence of Formula (IF).

115. Use of a non-naturally occurring melanocortin analog for treating, preventing, or reducing glucose intolerance and/or diabetes mellitus in a subject in need thereof, comprising orally administering about 15 mg/kg to about 100 mg/kg of a non-naturally occurring melanocortin analog to the subject,

the non-naturally occurring melanocortin analog comprising a sequence of Formula (IF).

116. A method of reducing obesity-related inflammation in a subject in need thereof, comprising orally administering about 15 mg/kg to about 100 mg/kg of a non-naturally occurring melanocortin analog to the subject,

the non-naturally occurring melanocortin analog comprising a sequence of Formula (IF).

117. A method of preserving or improving kidney function in a subject in need thereof, comprising orally administering about 15 mg/kg to about 100 mg/kg of a non-naturally occurring melanocortin analog to the subject,

the non-naturally occurring melanocortin analog comprising a sequence of Formula (IF).

118. Use of a non-naturally occurring melanocortin analog for preserving or improving kidney function in a subject in need thereof, comprising orally administering about 15 mg/kg to about 100 mg/kg of a non-naturally occurring melanocortin analog to the subject,

the non-naturally occurring melanocortin analog comprising a sequence of Formula (IF).

119. The method or use of any one of claims 112-118, wherein the sequence of

Formula (IF) is: Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 43), wherein c represents cyclization through R^2 and R^7 via a lactam bond.

120. The method or the use of any one of claims 13-119, wherein, after administration of the non-naturally occurring melanocortin analog, the subject's body weight is more than 5%, more than 10%, more than 15%, more than 20%, more than 25%, more than 30%, more than 35%, or more than 40% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog.

121. The method or the use of any one of claims 13-120, wherein, after administration of the non-naturally occurring melanocortin analog, the subject's fat mass is more than 5%, more than 10%, more than 15%, more than 20%, more than 25%, more than 30%, more than 35%, or more than 40% reduced from baseline prior to administration of the non-naturally occurring melanocortin analog.

122. A non-naturally occurring melanocortin analog comprising a sequence of: Ac-Nle-c[Glu-His-p(F)dPhe-Arg-Trp-Orn]-dVal-dPro-NH_2 (SEQ ID NO: 43), wherein c represents cyclization through R^2 and R^7 via a lactam bond.

123. A method of reducing body weight and/or fat mass in a subject in need thereof, comprising orally administering a non-naturally occurring melanocortin analog comprising a sequence of SEQ ID NO: 43 to the subject.

124. Use of a non-naturally occurring melanocortin analog for reducing body weight and/or fat mass in a subject in need thereof, comprising orally administering a non-naturally occurring melanocortin analog comprising a sequence of SEQ ID NO: 43 to the subject.

125. The method or the use of claim 123 or 124, wherein the method or the use further comprises reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in the subject.

126. The method or the use of claim 125, wherein the lean mass is lean muscle mass.

127. The method or the use of any one of claims 123-126, wherein the method or the use further comprises treating, preventing, or reducing glucose intolerance and/or diabetes mellitus in the subject.

128. A method of treating, preventing, or reducing glucose intolerance and/or diabetes mellitus in a subject in need thereof, comprising orally administering a non-naturally occurring melanocortin analog comprising a sequence of SEQ ID NO: 43 to the subject.

129. Use of a non-naturally occurring melanocortin analog for treating, preventing, or reducing glucose intolerance and/or diabetes mellitus in a subject in need thereof, comprising orally administering a non-naturally occurring melanocortin analog comprising a sequence of SEQ ID NO: 43 to the subject.

130. The method or the use of claim 128 or 129, wherein the method or the use further comprises reducing lean mass loss, maintaining lean mass, or promoting lean mass gain in the subject.

131. The method or the use of claim 130, wherein the lean mass is lean muscle mass.

132. The method or the use of any one of claims 128-131, wherein the method or the use further comprises reducing body weight and/or fat mass in the subject.

133. The method or the use of any one of claims 128-132, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 15 mg/kg to about 100 mg/kg per body weight of the subject once daily.

134. The method or the use of claim 133, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 30 mg/kg or 60 mg/kg per body weight of the subject once daily.

135. The method or the use of any one of claims 128-134, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 0.1 mg to about 100 mg once daily.

136. The method or the use of any one of claims 128-135, wherein the non-naturally occurring melanocortin analog is administered at a dose of about 10 mg or about 50 mg once daily.

137. The method or the use of any one of claims 128-136, wherein the method or the use further comprises reducing obesity-related inflammation in the subject.

138. The method or the use of any one of claims 128-137, wherein the method or the use further comprises preserving or improving kidney function in the subject.

139. The method or the use of any one of claims 13-138, wherein the method of the use further comprises one or more of (i) reducing a lipid droplets size (e.g., an average lipid droplet size); (ii) increasing an adipose tissue mitochondrial number or adipose tissue mitochondrial concentration; (iii) increasing an adipose tissue vascularization level; (iv) increasing, maintaining, or preventing a reduction of a beige or brown adipocyte level; (v) increasing a metabolic rate; (vi) increasing a calorie burn level; or (vii) increasing, maintaining, or preventing reduction of an insulin sensitivity level, relative to a control.

140. The method or the use of any one of claims 13-139, wherein the subject has a metabolic dysfunction selected from the group consisting of obesity, diabetes mellitus, metabolic syndrome, insulin resistance, non-alcoholic fatty liver disease, polycystic ovarian syndrome, metabolic acidosis, hypothyroidism, hyperlipidemia, Cushing Syndrome, and metabolic myopathies.

141. The method or the use of any one of claims 13-140, wherein the non-naturally occurring melanocortin analog comprises a reduced clearance, and increased concentration, or an increased distribution during or after administration to the subject, relative to a control.

142. The method or the use of claim 141, wherein the clearance is a liver or a liver microsome clearance.

143. The method or the use of claim 141, wherein the concentration is an aqueous concentration.

144. The method or the use of claim 143, wherein the aqueous concentration comprises an intestinal fluid concentration or a gastric fluid concentration.

145. The method or the use of any one of claims 13-144, wherein the concentration of the non-naturally occurring melanocortin analog in the plasma or a tissue of the subject is at least about 5 ng/mL to at least about 2000 ng/mL about 24 hours after administration of the non-naturally occurring melanocortin analog.

146. The method or the use of any one of claims 13-144, wherein the non-naturally occurring melanocortin analog is administered to the subject until the concentration of the non-naturally occurring melanocortin analog in the plasma or a tissue of the subject is at least about 5 ng/mL to at least about 2000 ng/mL after administration of the non-naturally occurring melanocortin analog.

147. The method or the use of claim 145 or 146, wherein concentration is at least about 5 ng/mL after administration of the non-naturally occurring melanocortin analog.

148. The method or the use of claim 145 or 146, wherein concentration is at least about 10 ng/mL after administration of the non-naturally occurring melanocortin analog.

149. The method or the use of claim 145 or 146, wherein concentration is at least about 50 ng/mL after administration of the non-naturally occurring melanocortin analog.

150. The method or the use of claim 145 or 146, wherein concentration is at least about 100 ng/mL after administration of the non-naturally occurring melanocortin analog.

151. The method or the use of claim 145 or 146, wherein concentration is at least about 200 ng/mL after administration of the non-naturally occurring melanocortin analog.

152. The method or the use of claim 145 or 146, wherein concentration is at least about 300 ng/mL after administration of the non-naturally occurring melanocortin analog.

153. The method or the use of claim 145 or 146, wherein concentration is at least about 400 ng/mL after administration of the non-naturally occurring melanocortin analog.

154. The method or the use of claim 145 or 146, wherein concentration is at least about 500 ng/mL after administration of the non-naturally occurring melanocortin analog.

155. The method or the use of claim 145 or 146, wherein concentration is at least about 750 ng/mL after administration of the non-naturally occurring melanocortin analog.

156. The method or the use of claim 145 or 146, wherein concentration is at least about 1000 ng/mL after administration of the non-naturally occurring melanocortin analog.

157. The method or the use of claim 145 or 146, wherein concentration is at least about 1500 ng/mL after administration of the non-naturally occurring melanocortin analog.

158. The method or the use of claim 145 or 146, wherein concentration is at least about 2000 ng/mL after administration of the non-naturally occurring melanocortin analog.

159. The method or the use of any one of claims 145-158, wherein the concentration is a maximum concentration (C_{max}).

160. The method or the use of any one of claims 18-159, wherein the non-naturally occurring melanocortin analog is administered as a single dosage unit.

161. The method or the use of any one of claims 13-159, wherein the non-naturally occurring melanocortin analog dose is administered as multiple dosage units.

162. The method or the use of claim 161, wherein the multiple dosage units individually comprise about 2.5 mg/mL to about 100 mg/mL of the non-naturally occurring melanocortin analog.

163. The method or the use of claim 162, wherein the multiple dosage units individually comprise about 2.5 mg/mL to about 10 mg/mL of the non-naturally occurring melanocortin analog.

164. The method or the use of claim 161, wherein the multiple dosage units individually comprise about 6 mg/mL of the non-naturally occurring melanocortin analog.

165. The method or the use of claim 161, wherein the non-naturally occurring melanocortin analog is administered as about 5 dosage units to about 10 dosage units.

166. The method or the use of claim 161, wherein the non-naturally occurring melanocortin analog is administered as 5 dosage units.

167. The method or the use of claim 161, wherein the non-naturally occurring melanocortin analog is administered as 10 dosage units.

168. The method or the use of any one of claims 13-167, wherein the dosage unit is a capsule.

169. The method or the use of claim 168, wherein the capsule comprises the non-naturally occurring melanocortin analog suspended in a saline solution.

170. The method or the use of claim 169, wherein the saline solution is about 100% saline.

171. The method or the use of claim 169, wherein the saline solution is about 95% saline.

172. The method or the use of claim 169, wherein the saline solution is about 90% saline.

173. The method or the use of claim 171 or 172, wherein the saline solution comprises dimethyl sulfoxide (DMSO).