

CLAIMS

1. An antibody, or antigen binding fragment thereof, that specifically binds to human growth differentiation factor 15 (GDF15), comprising at least one of the following:
 - a) a light chain complementarity determining region 1 (LCDR-1) comprising the amino acid sequence of SEQ ID NO:95, a LCDR-2 comprising the amino acid sequence of SEQ ID NO:28, a LCDR-3 comprising the amino acid sequence of SEQ ID NO:9, a heavy chain complementarity determining region 1 (HCDR-1) comprising the amino acid sequence of SEQ ID NO:32, a HCDR-2 comprising the amino acid sequence of SEQ ID NO:165, and a HCDR-3 comprising the amino acid sequence of SEQ ID NO:52;
 - ~~b) LCDR-1 amino acid sequence selected from the group consisting of the sequence of SEQ ID NO:7, 27, 36, 46, 55, 62, 82, 88, 95, 101, 129, 138, 150, 157, 174, and 184;~~
 - ~~c) a LCDR-2 amino acid sequence selected from the group consisting of the sequence of SEQ ID NO:8, 28, 37, 47, 70, 108, 114, 122, 130, 175, and 185;~~
 - ~~d) a LCDR-3 amino acid sequence selected from the group consisting of the sequence of SEQ ID NO:9, 29, 38, 48, 63, 76, 89, 102, 176, and 186;~~
 - ~~e) a HCDR-1 amino acid sequence selected from the group consisting of the sequence of SEQ ID NO:17, 32, 41, 58, 66, 117, 125, 133, 153, 171, and 179;~~
 - ~~f) a HCDR-2 amino acid sequence selected from the group consisting of the sequence of SEQ ID NO:18, 33, 42, 51, 59, 67, 85, 92, 98, 105, 118, 126, 134, 141, 146, 165, 172, and 180;~~
 - ~~g) a HCDR-3 amino acid sequence selected from the group consisting of the sequence of SEQ ID NO:1, 19, 43, 52, 79, 111, 119, 135, 147, 154, 160, 173, and 181;~~
 - ~~h)b) the HCDR-1, HCDR-2, and HCDR-3 amino acid sequences as set forth in the amino acid sequence of SEQ ID NO:166, and the LCDR-1, LCDR-2, and LCDR-3 amino acid sequences as set forth in the amino acid sequence of SEQ ID NO:163;~~
 - ~~i)c) the amino acid sequence encoded by the insert of the plasmid deposited at the ATCC and having ATCC Accession No. PTA-125038, and the amino acid sequence encoded by the insert of the plasmid deposited at the ATCC and having ATCC Accession No. PTA-125039;~~
 - ~~j) a heavy chain variable domain (VH) comprising an amino acid sequence at least 90% identical to the sequence of SEQ ID NO:166, and a light chain variable domain (VL) comprising an amino acid sequence at least 90% identical to the sequence of SEQ ID NO:163;~~

~~k)d)~~ a VH comprising the amino acid sequence of SEQ ID NO:166 and a VL comprising the amino acid sequence of SEQ ID NO:163; and
l) ~~an antibody that competes for binding to GDF15 with at least one antibody from (a)-~~
~~(k) above~~
e) a HC comprising the amino acid sequence of SEQ ID NO:164, and a LC comprising the amino acid sequence of SEQ ID NO:162.

2. The antibody, or antigen binding fragment thereof, of claim 1, comprising a human Fc domain selected from the group consisting of an Fc domain of IgA₁ IgA₂, IgD, IgE, IgM, IgG₁, IgG₂, IgG₃, or IgG₄.

3. The antibody, or antigen binding fragment thereof, of any one of claims 1 –2, comprising:

~~a) a heavy chain (HC) comprising an amino acid sequence at least 90% identical to the sequence of SEQ ID NO:164, and a light chain (LC) comprising an amino acid sequence at least 90% identical to the sequence of SEQ ID NO:162;~~

b) a HC comprising the amino acid sequence of SEQ ID NO:164, and a LC comprising the amino acid sequence of SEQ ID NO:162.

4. The antibody, or antigen binding fragment thereof, of any one of claims 1 –3, wherein the antibody, or antigen binding fragment thereof, binds human or cynomolgus monkey GDF15 with a K_D about or less than a value selected from the group consisting of about 10nM, 5nM, 2nM, 1nM, 900pM, 800pM, 700pM, 600pM, 500pM, 400pM, 300pM, 250pM, 200pM, 150pM, 100pM, 50pM, 40pM, 30pM, 25pM, 20pM, 15pM, and 10pM.

5. An isolated nucleic acid encoding the antibody, or antigen-binding portion thereof, of any one of claims 1 –4.

6. An isolated nucleic acid comprising:

a) the nucleic acid sequence of SEQ ID NO:167, the nucleic acid sequence of SEQ ID NO:168, or both,

b) the nucleic acid sequence of SEQ ID NO:169, the nucleic acid sequence of SEQ ID NO:170, or both, and

c) the nucleic acid sequence of the insert of the plasmid deposited with the ATCC and having the Accession Number PTA-125038, the nucleic acid sequence of the insert

of the plasmid deposited with the ATCC and having the Accession Number PTA-125039, or both.

7. A vector comprising the nucleic acid of claim 5 ~~or 6~~.

8. A host cell comprising the vector of claim 7.

9. The host cell of claim 8, wherein said host cell is a mammalian cell selected from the group consisting of a CHO cell, a COS cell, a HEK-293 cell, an NS0 cell, a PER.C6[®] cell, or an Sp2.0 cell.

10. A method of making an antibody, or antigen binding fragment thereof, comprising culturing the host cell of claim 8 under a condition wherein said antibody, or antigen binding fragment thereof, is expressed by said host cell.

11. A pharmaceutical composition comprising an antibody, or antigen binding fragment thereof, of any one of claims 1 –4, and a pharmaceutically acceptable carrier or excipient.

~~12. A method of treating a medical condition, disease or disorder mediated by or associated with expression of GDF15, in a subject in need thereof, said method comprising administering a therapeutically effective amount of the antibody, or antigen binding fragment thereof, of any one of claims 1 – 4, or the pharmaceutical composition of claim 11.~~

~~13. The method of claim 12, wherein the condition is cachexia associated with cancer, chemotherapy, chemotherapy in combination with an immuno-oncology therapy, chronic obstructive pulmonary disease, chronic kidney disease, chronic heart failure, congestive heart failure, or sarcopenia.~~

~~14. A method of decreasing the level of free GDF15 in a subject in need thereof, said method comprising administering a therapeutically effective amount of the antibody, or antigen binding fragment thereof, of any one of claims 1 –4, or the pharmaceutical composition of claim 11, whereby the level of free GDF15 is reduced.~~

15. — A method for reducing the activity of GDF15 in a subject in need thereof, the method comprising administering a therapeutically effective amount of the antibody, or antigen binding fragment thereof, of any one of claims 1—4, or the pharmaceutical composition of claim 11.

16. — The method of claim 15, wherein the activity of GDF15 is at least one activity selected from the group consisting of: (a) decreasing food intake; (b) decreasing appetite; (c) decreasing body weight; (d) increasing weight loss; (e) decreasing fat mass; (f) decreasing lean mass; (g) increasing loss of fat mass; (h) increasing loss of lean muscle mass; (i) binding to GFRAL; (j) increasing downstream signaling mediated by RET; (k) increasing phosphorylation of ERK; (l) increasing phosphorylation of ribosomal protein S6; (m) increasing RET-mediated activation of the MAPK signaling pathway; (n) increasing RET activation of the AKT signaling pathway; and (o) increasing activation of the PLC- β 1 signaling pathway.

17. — A method for treating cancer in a patient in need thereof, comprising administering to the patient a combination therapy providing a synergistic therapeutic effect, the method comprising administering a synergistic therapeutically effective amount of the antibody, or antigen binding fragment thereof, of any one of claims 1—4, or the pharmaceutical composition of claim 11, and
a) — a synergistic therapeutically effective amount of an anti-CD40 antagonist antibody; or
b) — a synergistic therapeutically effective amount of a PD-1 axis binding antagonist, wherein the PD-1 axis binding antagonist is not avelumab.

18. — The method of claim 17(b), wherein the PD-1 axis binding antagonist is an anti-PD-1 antibody selected from the group consisting of nivolumab, pembrolizumab, spartalizumab, pidilizumab, tislelizumab, AMP-224, AMP-514, cemiplimab, and sasanlimab (PF-06801591).

19. — The method of claim 17(b), wherein the PD-1 axis binding antagonist is an anti-PD-L1 antibody selected from the group consisting of atezolizumab, durvalumab, BMS-936559, MEDI4736, and MPDL3280A, and wherein the anti-PD-L1 antibody is not avelumab.

20. — The method of any one of claims 18-19, wherein the cancer is selected from the group consisting of melanoma, non-small cell lung cancer, renal cell carcinoma, Merkel cell carcinoma, ovarian cancer, breast cancer, pancreatic cancer, urothelial cancer and castration-resistant prostate cancer.

21. — The method of claim 17(a), wherein the cancer is selected from the group consisting of gastric cancer, sarcoma, lymphoma, Hodgkin's lymphoma, leukemia, head and neck cancer, squamous cell head and neck cancer, thymic cancer, epithelial cancer, salivary cancer, liver cancer, stomach cancer, thyroid cancer, lung cancer, ovarian cancer, breast cancer, prostate cancer, esophageal cancer, pancreatic cancer, glioma, leukemia, multiple myeloma, renal cell carcinoma, bladder cancer, cervical cancer, choriocarcinoma, colon cancer, oral cancer, skin cancer, and melanoma.

22. — A kit for the treatment of cancer, comprising a synergistic therapeutically effective amount of an anti-GDF15 antibody, and a synergistic therapeutically effective amount of an anti-PD-1 antibody.

23. — A kit for the treatment of cancer, comprising a therapeutically effective amount of an anti-GDF15 antibody, and a therapeutically effective amount of an anti-CD40 antibody.

24. — A method for enhancing the therapeutic effect of an immune modulator administered to a subject for the treatment of cancer, the method comprising administering to the subject receiving the immune modulator an effective amount of the anti-GDF15 antibody, or antigen binding fragment thereof, of any one claims 1–4, or the pharmaceutical composition of claim 11.

25. — The method of claim 24, wherein the cancer is selected from the group consisting of breast cancer, gastric cancer, liver cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, glioma, glioblastoma, renal cancer, endometrial cancer, and colorectal cancer.

26. — A method of decreasing or inhibiting toxicity in a subject experiencing cytokine release syndrome (CRS) or cytokine storm or vulnerable to CRS or cytokine storm, the method comprising administering to the subject an effective amount of the anti-GDF15 antibody, or antigen binding fragment thereof, of any one claims 1–4, or the pharmaceutical composition of claim 11.

27. — The method of claim 26, wherein the subject is undergoing cancer therapy and said method does not reduce the efficacy of the cancer therapy.

28. — The method of claim 27, wherein the cancer therapy comprises an immune modulator such as an anti-CD40 antibody, an anti-CD47 antibody, an anti-CTLA4 antibody, an anti-4-1BB antibody, IL-12, or IL-15.

29. — The method of any one of claims 26–28, wherein the cause of the CRS or cytokine storm comprises an infectious stimuli, condition, or syndrome, or wherein the cause of said cytokine release syndrome or cytokine storm comprises a non-infectious stimuli, condition, or syndrome, or any combination thereof.

30. — The method of claim 29, wherein the infectious stimuli, condition, or syndrome comprises influenza, bird flu, severe acute respiratory syndrome (SARS), Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis (HLH), sepsis, gram-negative sepsis, malaria, an Ebola virus, a variola virus, a systemic Gram-negative bacterial infection, or Jarisch-Herxheimer syndrome, or wherein said non-infectious stimuli, condition, or syndrome comprises is hemophagocytic lymphohistiocytosis (HLH), sporadic HLH, macrophage activation syndrome (MAS), chronic arthritis, systemic Juvenile idiopathic Arthritis (sJIA), Still's Disease, a Cryopyrin-associated Periodic Syndrome (CAPS), Familial Cold Auto-inflammatory Syndrome (FCAS), Familial Cold Urticaria (FCU), Muckle-Well Syndrome (MWS), Chronic Infantile Neurological Cutaneous and, Articular (CINCA) Syndrome, a cryopyrinopathy comprising inherited or de novo gain of function mutations in the NLRP3 gene, a hereditary auto-inflammatory disorder, acute pancreatitis, a severe burns, a trauma, an acute respiratory distress syndrome, an immunotherapy, a monoclonal antibody therapy, secondary to drug use, is secondary to inhalation of toxins, a lipopolysaccharide (LPS), a Gram-positive toxins, fungal toxins, glycosylphosphatidylinositol (GPI), or modulation of RIG-1 gene expression.

~~31~~12. A therapeutically effective amount of the antibody, or antigen binding fragment thereof, of any one of claims 1 - 4, or the pharmaceutical composition of claim 11, for use in ~~a method of the treatment of~~ treating a medical condition, disease or disorder mediated by or associated with expression of GDF15, in a subject in need thereof.

~~32~~13. A therapeutically effective amount of the antibody, or antigen binding fragment thereof, of any one of claims 1 - 4, or the pharmaceutical composition of claim 11, for use in ~~a method~~the treatment of decreasing the level of free GDF15 in a subject in need thereof.

~~33~~14. A therapeutically effective amount of the antibody, or antigen binding fragment thereof, of any one of claims 1 - 4, or the pharmaceutical composition of claim 11, for use in a ~~method~~method for treating the treatment of for reducing the activity of GDF15 in a subject in need thereof.

~~34~~15. A therapeutically effective amount of the antibody, or antigen binding fragment thereof, of any one of claims 1 - 4, or the pharmaceutical composition of claim 11, for use in a ~~method for treating the treatment of~~method for treating the treatment of cancer in a patient in need thereof, wherein the antibody, or antigen binding fragment thereof, or pharmaceutical composition, is to be administered in combination with:

- a) a synergistic therapeutically effective amount of an anti-CD40 antagonist antibody; or
- b) a synergistic therapeutically effective amount of a PD-1 axis binding antagonist, wherein the PD-1 axis binding antagonist is not avelumab.

~~35~~16. An effective amount of the antibody, or antigen binding fragment thereof, of any one of claims 1 - 4, or the pharmaceutical composition of claim 11, for use in a method for enhancing the therapeutic effect of an immune modulator to be administered to a subject for the treatment of cancer.

~~36~~17. An effective amount of the antibody, or antigen binding fragment thereof, of any one of claims 1 - 4, or the pharmaceutical composition of claim 11, for use in a method of decreasing or inhibiting toxicity in a subject experiencing cytokine release syndrome (CRS) or cytokine storm or vulnerable to CRS or cytokine storm.