

Claims

~~What is claimed is:~~

1. An antibody that binds human GFRAL, comprising an antibody heavy chain variable (VH) domain and an antibody light chain variable (VL) domain, wherein:

(i) the VH domain comprises~~esing~~ the QUEL-0201 set of heavy chain complementarity determining regions (HCDRs) HCDR1 SEQ ID NO: 13, HCDR2 SEQ ID NO: 14 and HCDR3 SEQ ID NO: 15, and

the VL domain ~~comprises~~esing the QUEL-0201 set of light chain complementarity determining regions (LCDRs) LCDR1 SEQ ID NO: 18, LCDR2 SEQ ID NO: 19 and LCDR3 SEQ ID NO: 20,

(ii) the VH domain comprises the QUEL-0301 set of heavy chain complementarity determining regions (HCDRs) HCDR1 SEQ ID NO: 23, HCDR2 SEQ ID NO: 24 and HCDR3 SEQ ID NO: 25, and

the VL domain comprises the QUEL-0301 set of light chain complementarity determining regions (LCDRs) LCDR1 SEQ ID NO: 28, LCDR2 SEQ ID NO: 29 and LCDR3 SEQ ID NO: 30,
or

(iii) the VH domain comprises the QUEL-0101 set of heavy chain complementarity determining regions (HCDRs) HCDR1 SEQ ID NO: 3, HCDR2 SEQ ID NO: 4 and HCDR3 SEQ ID NO: 5, and

the VL domain comprises the QUEL-0101 set of light chain complementarity determining regions (LCDRs) LCDR1 SEQ ID NO: 8, LCDR2 SEQ ID NO: 9 and LCDR3 SEQ ID NO: 10.

2. An antibody that binds human GFRAL, comprising

(i) a VH domain having at least 90 % amino acid sequence identity to the QUEL-0201 VH domain SEQ ID NO: 12 and

a VL domain having at least 90 % amino acid sequence identity to the QUEL-0201 VL domain SEQ ID NO: 17,

(ii) a VH domain having at least 90 % amino acid sequence identity to the QUEL-0301 VH domain SEQ ID NO: 22 and

a VL domain having at least 90 % amino acid sequence identity to the QUEL-0301 VL domain SEQ ID NO: 27, or

(iii) a VH domain having at least 90 % amino acid sequence identity to the QUEL-0101 VH domain SEQ ID NO: 2 and

a VL domain having at least 90 % amino acid sequence identity to the QUEL-0101 VL domain SEQ ID NO: 7.

~~3. — An antibody that binds human GFRAL comprising a VH domain encoded by a nucleotide sequence produced by recombination of gene segmentsIGHV1-3 (e.g., IGHV1-3*01) and IGHJ6 (e.g., IGHJ6*02), and a VL domain encoded by a nucleotide sequence produced by recombination of gene segments IGLV1-40 (e.g., IGLV1-40*01) and IGLJ3 (e.g., IGLJ3*02).~~

~~4. — An antibody according to claim 3, wherein the VH domain is encoded by a nucleotide sequence produced by recombination of gene segments IGHV1-3 (e.g., IGHV1-3*01), IGHD5-18 (e.g., IGHD5-18*01) and IGHJ6 (e.g., IGHJ6*02).~~

~~5. — An antibody that competes for binding human GFRAL with a QUEL-0201 IgG comprising QUEL-0201 VH domain SEQ ID NO: 12 and QUEL-0201 VL domain SEQ ID NO: 17.~~

63. An antibody according to any of claims 1 to or 52, which

(i) binds human GFRAL with an affinity of 1 nM or stronger as determined by surface plasmon resonance,

(ii) cross-reacts with mouse GFRAL, having an affinity for mouse GFRAL within 10-fold of its affinity for human GFRAL, and/or

(iii) inhibits GFRAL with a potency of 15 nM or stronger, preferably with a potency of 10 nM or stronger, wherein the potency is determined as IC50 in an in vitro assay of ERK phosphorylation in response to GDF15.

74. An antibody according to claim 63, which wherein:

- the VH domain comprises the QUEL-0201 set of heavy chain complementarity determining regions (HCDRs) HCDR1 SEQ ID NO: 13, HCDR2 SEQ ID NO: 14 and HCDR3 SEQ ID NO: 15 and the VL domain comprises the QUEL-0201 set of light chain complementarity determining regions (LCDRs) LCDR1 SEQ ID NO: 18, LCDR2 SEQ ID NO: 19 and LCDR3 SEQ ID NO: 20, and
- the antibody binds human GFRAL with an affinity of 100 pM or stronger or with an affinity in the range of 50 pM-200 pM, as determined by surface plasmon resonance.

5. An antibody according to claim 3, wherein:

- the VH domain comprises the QUEL-0301 set of heavy chain complementarity determining regions (HCDRs) HCDR1 SEQ ID NO: 23, HCDR2 SEQ ID NO: 24 and HCDR3 SEQ ID NO: 25 and the VL domain comprises the QUEL-0301 set of light chain complementarity determining regions (LCDRs) LCDR1 SEQ ID NO: 28, LCDR2 SEQ ID NO: 29 and LCDR3 SEQ ID NO: 30, and

- the antibody binds human GFRAL with an affinity of 1 pM or stronger or with an affinity in the range of 0.5 pM - 2 pM as determined by surface plasmon resonance and/or cross-reacts with mouse GFRAL, having an affinity for mouse GFRAL of 10 nM or stronger as determined by surface plasmon resonance.

6. An antibody according to claim 3, wherein:

- the VH domain comprises the QUEL-0101 set of heavy chain complementarity determining regions (HCDRs) HCDR1 SEQ ID NO: 3, HCDR2 SEQ ID NO: 4 and HCDR3 SEQ ID NO: 5 and the VL domain comprises the QUEL-0101 set of light chain complementarity determining regions (LCDRs) LCDR1 SEQ ID NO: 8, LCDR2 SEQ ID NO: 9 and LCDR3 SEQ ID NO: 10, and
- the antibody binds human GFRAL with an affinity of 200 pM or stronger or with an affinity in the range of 100 pM-400 pM as determined by surface plasmon resonance and/or inhibits GFRAL with a potency of 5 nM or stronger.

~~8. An antibody according to claim 6 which binds human GFRAL with an affinity in the range 50 pM—200 pM.~~

~~9. An antibody according to any of claims 1 to 8 which cross-reacts with mouse GFRAL, having an affinity for mouse GFRAL within 10-fold of its affinity for human GFRAL.~~

~~10. An antibody according to any of claims 1 to 9 which inhibits GFRAL with a potency of 15 nM or stronger, wherein the potency is determined as IC50 in an in vitro assay of ERK phosphorylation in response to GDF15.~~

~~11. An antibody according to claim 10, wherein the potency is 10 nM or stronger.~~

~~127.~~ An antibody according to any of claims 1 to ~~116~~, comprising

(i) a VH domain having at least 95 % amino acid sequence identity to the QUEL-0201 VH domain SEQ ID NO: 12 and

a VL domain having at least 95 % amino acid sequence identity to the QUEL-0201 VL domain SEQ ID NO: 17,

(ii) a VH domain having at least 95 % amino acid sequence identity to the QUEL-0301 VH domain SEQ ID NO: 22 and

a VL domain having at least 95 % amino acid sequence identity to the QUEL-0301 VL domain SEQ ID NO: 27, or

(iii) a VH domain having at least 95 % amino acid sequence identity to the QUEL-0101 VH domain SEQ ID NO: 2 and

a VL domain having at least 95 % amino acid sequence identity to the QUEL-0101 VL domain SEQ ID NO: 7.

~~138.~~ An antibody according to any preceding claim, comprising

(i) a VH domain having at least 98 % amino acid sequence identity to the QUEL-0201 VH domain SEQ ID NO: 12 and

a VL domain having at least 98 % amino acid sequence identity to the QUEL-0201 VL domain SEQ ID NO: 17

(ii) a VH domain having at least 98 % amino acid sequence identity to the QUEL-0301 VH domain SEQ ID NO: 22 and

a VL domain having at least 98 % amino acid sequence identity to the QUEL-0301 VL domain SEQ ID NO: 27, or

(iii) a VH domain having at least 98 % amino acid sequence identity to the QUEL-0101 VH domain SEQ ID NO: 2 and

a VL domain having at least 98 % amino acid sequence identity to the QUEL-0101 VL domain SEQ ID NO: 7.

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~~149.~~ An antibody according to claim ~~138~~, comprising

(i) the QUEL-0201 VH domain SEQ ID NO: 12, optionally with one or two amino acid alterations and

the QUEL-0201 VL domain SEQ ID NO: 17, optionally with one or two amino acid alterations,

(ii) the QUEL-0301 VH domain SEQ ID NO: 22, optionally with one or two amino acid alterations and

the QUEL-0301 VL domain SEQ ID NO: 27, optionally with one or two amino acid alterations, or

(iii) the QUEL-0101 VH domain SEQ ID NO: 2, optionally with one or two amino acid alterations and

the QUEL-0101 VL domain SEQ ID NO: 7, optionally with one or two amino acid alterations,

the one or two amino acid alterations being preferably conservative substitutions.

~~1510.~~ An antibody according to claim ~~914~~, comprising

(i) the QUEL-0201 VH domain SEQ ID NO: 12 comprising the QUEL-0201 set of HCDRs HCDR1 SEQ ID NO: 13, HCDR2 SEQ ID NO: 14 and HCDR3 SEQ ID NO: 15, optionally with one or two amino acid alterations in the VH domain framework, and

the QUEL-0201 VL domain SEQ ID NO: 17 comprising the QUEL-0201 set of LCDRs LCDR1 SEQ ID NO: 18, LCDR2 SEQ ID NO: 19 and LCDR3 SEQ ID NO: 20, optionally with one or two amino acid alterations in the VL domain framework,

(ii) the QUEL-0301 VH domain SEQ ID NO: 22 comprising the QUEL-0301 set of HCDRs HCDR1 SEQ ID NO: 23, HCDR2 SEQ ID NO: 24 and HCDR3 SEQ ID NO: 25, optionally with one or two amino acid alterations in the VH domain framework, and

the QUEL-0301 VL domain SEQ ID NO: 27 comprising the QUEL-0301 set of LCDRs LCDR1 SEQ ID NO: 28, LCDR2 SEQ ID NO: 29 and LCDR3 SEQ ID NO: 30, optionally with one or two amino acid alterations in the VL domain framework, or

(iii) the QUEL-0101 VH domain SEQ ID NO: 2 comprising the QUEL-0101 set of HCDRs HCDR1 SEQ ID NO: 3, HCDR2 SEQ ID NO: 4 and HCDR3 SEQ ID NO: 5, optionally with one or two amino acid alterations in the VH domain framework, and

the QUEL-0101 VL domain SEQ ID NO: 7 comprising the QUEL-0101 set of LCDRs LCDR1 SEQ ID NO: 8, LCDR2 SEQ ID NO: 9 and LCDR3 SEQ ID NO: 10, optionally with one or two amino acid alterations in the VL domain framework,

the one or two amino acid alterations being preferably conservative substitutions.

~~16. An antibody according to claim 14 or claim 15, wherein the one or two amino acid alterations are conservative substitutions.~~

~~1711.~~ An antibody according to any ~~preceding claim~~ one of claims 1 to 10, comprising

(i) the QUEL-0201 VH domain SEQ ID NO: 12 and the QUEL-0201 VL domain SEQ ID NO: 17,

(ii) the QUEL-0301 VH domain SEQ ID NO: 22 and the QUEL-0301 VL domain SEQ ID NO: 27, or

(iii) the QUEL-0101 VH domain SEQ ID NO: 2 and the QUEL-0101 VL domain SEQ ID NO: 7.

~~18. An antibody that binds human GFRAL, comprising an antibody heavy chain variable (VH) domain and an antibody light chain variable (VL) domain,~~

~~the VH domain comprising a set of heavy chain complementarity determining regions (HCDRs), wherein HCDR1 is SEQ ID NO: 23 or SEQ ID NO: 133, HCDR2 is SEQ ID NO: 24,~~

~~SEQ ID NO: 124, SEQ ID NO: 134 or SEQ ID NO: 142, and HCDR3 is SEQ ID NO: 25, SEQ ID NO: 125, SEQ ID NO: 135 or SEQ ID NO: 143, and~~

~~—— the VL domain comprising a set of light chain complementarity determining regions (LCDRs), wherein LCDR1 is SEQ ID NO: 28, SEQ ID NO: 128 or SEQ ID NO: 138, LCDR2 is SEQ ID NO: 29 or SEQ ID NO: 129 and LCDR3 is SEQ ID NO: 30, SEQ ID NO: 130, SEQ ID NO: 139 or SEQ ID NO: 146.~~

~~19. — An antibody that binds human GFRAL, comprising an antibody heavy chain variable (VH) domain and an antibody light chain variable (VL) domain,~~

~~—— the VH domain comprising the QUEL-0301 set of heavy chain complementarity determining regions (HCDRs) HCDR1 SEQ ID NO: 23, HCDR2 SEQ ID NO: 24 and HCDR3 SEQ ID NO: 25, and~~

~~—— the VL domain comprising the QUEL-0301 set of light chain complementarity determining regions (LCDRs) LCDR1 SEQ ID NO: 28, LCDR2 SEQ ID NO: 29 and LCDR3 SEQ ID NO: 30.~~

~~20. — An antibody that binds human GFRAL, comprising a VH domain and a VL domain, the VH domain comprising the QUEL-0302 set of HCDRs HCDR1 SEQ ID NO: 23, HCDR2 SEQ ID NO: 124 and HCDR3 SEQ ID NO: 125, and~~

~~the VL domain comprising the QUEL-0302 set of LCDRs LCDR1 SEQ ID NO: 128, LCDR2 SEQ ID NO: 129 and LCDR3 SEQ ID NO: 130.~~

~~21. — An antibody that binds human GFRAL, comprising a VH domain and a VL domain, the VH domain comprising the QUEL-0303 set of HCDRs HCDR1 SEQ ID NO: 133, HCDR2 SEQ ID NO: 134 and HCDR3 SEQ ID NO: 135, and~~

~~the VL domain comprising the QUEL-0303 set of LCDRs LCDR1 SEQ ID NO: 138, LCDR2 SEQ ID NO: 29 and LCDR3 SEQ ID NO: 139.~~

~~22. — An antibody that binds human GFRAL, comprising a VH domain and a VL domain, the VH domain comprising the QUEL-0304 set of HCDRs HCDR1 SEQ ID NO: 133, HCDR2 SEQ ID NO: 142 and HCDR3 SEQ ID NO: 143, and~~

~~the VL domain comprising the QUEL-0304 set of LCDRs LCDR1 SEQ ID NO: 138, LCDR2 SEQ ID NO: 29 and LCDR3 SEQ ID NO: 146.~~

~~23. — An antibody that binds human GFRAL, comprising~~

a VH domain having at least 90 % amino acid sequence identity to the QUEL-0301 VH domain SEQ ID NO: 22 and

a VL domain having at least 90 % amino acid sequence identity to the QUEL-0301 VL domain SEQ ID NO: 27.

24. — An antibody that binds human GFRAL comprising

a VH domain encoded by a nucleotide sequence produced by recombination of gene segmentsIGHV3-7 (e.g., IGHV3-7*01) and IGHJ4 (e.g., IGHJ4*02), and

a VL domain encoded by a nucleotide sequence produced by recombination of gene segments IGLV1-44 (e.g., IGLV1-44*01) and IGLJ3 (e.g., IGLJ3*02).

25. — An antibody according to claim 24, wherein the VH domain is encoded by a nucleotide sequence produced by recombination of gene segments IGHV3-7 (e.g., IGHV3-7*01), IGHD1-7 (e.g., IGHD1-7*01) and IGHJ4 (e.g., IGHJ4*02).

26. — An antibody that binds human GFRAL comprising

a VH domain encoded by a nucleotide sequence produced by recombination of gene segments IGHV3-7 (e.g., IGHV3-7*01) and IGHJ4 (e.g., IGHJ4*02), and

a VL domain encoded by a nucleotide sequence produced by recombination of gene segments IGLV1-47 (e.g., IGLV1-47*01) and IGLJ3 (e.g., IGLJ3*02).

27. — An antibody according to claim 26, wherein the VH domain is encoded by a nucleotide sequence produced by recombination of gene segments IGHV3-7 (e.g., IGHV3-7*01), IGHD1-20 (e.g., IGHD1-20*01) and IGHJ4 (e.g., IGHJ4*02).

28. — An antibody that competes for binding human GFRAL with a QUEL-0301 IgG comprising QUEL-0301 VH domain SEQ ID NO: 22 and QUEL-0301 VL domain SEQ ID NO: 27.

29. — An antibody according to any of claims 18 to 28 which binds human GFRAL with an affinity of 1 nM or stronger as determined by surface plasmon resonance.

30. — An antibody according to claim 29 which binds human GFRAL with an affinity of 1 pM or stronger as determined by surface plasmon resonance.

31. — An antibody according to claim 29 which binds human GFRAL with an affinity in the range 0.5 pM — 2 pM.

~~32. — An antibody according to any of claims 18 to 31 which cross-reacts with mouse GFRAL, having an affinity for mouse GFRAL of 10 nM or stronger as determined by surface plasmon resonance.~~

~~33. — An antibody according to any of claims 18 to 32 which inhibits GFRAL with a potency of 15 nM or stronger, wherein the potency is determined as IC₅₀ in an in vitro assay of ERK phosphorylation in response to GDF15.~~

~~34. — An antibody according to claim 33, wherein the potency is 10 nM or stronger.~~

~~35. — An antibody according to any of claims 18 to 34, comprising
— a VH domain having at least 95 % amino acid sequence identity to the QUEL-0301 VH domain SEQ ID NO: 22 and
a VL domain having at least 95 % amino acid sequence identity to the QUEL-0301 VL domain SEQ ID NO: 27.~~

~~36. — An antibody according to any preceding claim, comprising
a VH domain having at least 98 % amino acid sequence identity to the QUEL-0301 VH domain SEQ ID NO: 22 and
a VL domain having at least 98 % amino acid sequence identity to the QUEL-0301 VL domain SEQ ID NO: 27.~~

~~37. — An antibody according to claim 36, comprising
the QUEL-0301 VH domain SEQ ID NO: 22, optionally with one or two amino acid alterations and
the QUEL-0301 VL domain SEQ ID NO: 27, optionally with one or two amino acid alterations.~~

~~38. — An antibody according to claim 37, comprising
— the QUEL-0301 VH domain SEQ ID NO: 22 comprising the QUEL-0301 set of HCDRs HCDR1 SEQ ID NO: 23, HCDR2 SEQ ID NO: 24 and HCDR3 SEQ ID NO: 25, optionally with one or two amino acid alterations in the VH domain framework, and~~

—— the QUEL-0301 VL domain SEQ ID NO: 27 comprising the QUEL-0301 set of LCDRs LCDR1 SEQ ID NO: 28, LCDR2 SEQ ID NO: 29 and LCDR3 SEQ ID NO: 30, optionally with one or two amino acid alterations in the VL domain framework.

39. — An antibody according to claim 37 or claim 38, wherein the one or two amino acid alterations are conservative substitutions.

40. — An antibody according to any of claims 18 to 39, comprising the QUEL-0301 VH domain SEQ ID NO: 22 and the QUEL-0301 VL domain SEQ ID NO: 27.

41. — An antibody according to any of claims 18, 20 and 23-28, comprising the QUEL-0302 VH domain SEQ ID NO: 123 and the QUEL-0302 VL domain SEQ ID NO: 127.

42. — An antibody according to any of claims 18, 21 and 23-28, comprising the QUEL-0303 VH domain SEQ ID NO: 132 and the QUEL-0303 VL domain SEQ ID NO: 137.

43. — An antibody according to any of claims 18 and 22-28, comprising the QUEL-0304 VH domain SEQ ID NO: 141 and the QUEL-0304 VL domain SEQ ID NO: 145.

44. — An antibody that binds human GFRAL, comprising an antibody heavy chain variable (VH) domain and an antibody light chain variable (VL) domain,
 the VH domain comprising a set of HCDRs HCDR1, HCDR2 and HCDR3, wherein
 HCDR1 is SEQ ID NO: 3, SEQ ID NO: 99, SEQ ID NO: 107 or SEQ ID NO: 118,
 HCDR2 is SEQ ID NO: 4, SEQ ID NO: 100 or SEQ ID NO: 108 and
 HCDR3 is SEQ ID NO: 5, SEQ ID NO: 101, SEQ ID NO: 113 or SEQ ID NO: 119, and
 the VL domain comprising a set of LCDRs LCDR1, LCDR2 and LCDR3, wherein
 LCDR1 is SEQ ID NO: 8,
 LCDR2 is SEQ ID NO: 9 and
 LCDR3 is SEQ ID NO: 10 or SEQ ID NO: 104.

45. — An antibody that binds human GFRAL, comprising an antibody heavy chain variable (VH) domain and an antibody light chain variable (VL) domain,
 —— the VH domain comprising the QUEL-0101 set of heavy chain complementarity determining regions (HCDRs) HCDR1 SEQ ID NO: 3, HCDR2 SEQ ID NO: 4 and HCDR3 SEQ ID NO: 5, and

—— the VL domain comprising the QUEL-0101 set of light chain complementarity determining regions (LCDRs) LCDR1 SEQ ID NO: 8, LCDR2 SEQ ID NO: 9 and LCDR3 SEQ ID NO: 10.

46. — An antibody that binds human GFRAL, comprising a VH domain and a VL domain, the VH domain comprising the QUEL-0102 set of HCDRs HCDR1 SEQ ID NO: 99, HCDR2 SEQ ID NO: 100 and HCDR3 SEQ ID NO: 101, and the VL domain comprising the QUEL-0102 set of LCDRs LCDR1 SEQ ID NO: 8, LCDR2 SEQ ID NO: 9 and LCDR3 SEQ ID NO: 104.

47. — An antibody that binds human GFRAL, comprising a VH domain and a VL domain, the VH domain comprising the QUEL-0103 set of HCDRs HCDR1 SEQ ID NO: 107, HCDR2 SEQ ID NO: 108 and HCDR3 SEQ ID NO: 5, and the VL domain comprising the QUEL-0103 set of LCDRs LCDR1 SEQ ID NO: 8, LCDR2 SEQ ID NO: 9 and LCDR3 SEQ ID NO: 104.

48. — An antibody that binds human GFRAL, comprising a VH domain and a VL domain, the VH domain comprising the QUEL-0104 set of HCDRs HCDR1 SEQ ID NO: 107, HCDR2 SEQ ID NO: 108 and HCDR3 SEQ ID NO: 113, and the VL domain comprising the QUEL-0104 set of LCDRs LCDR1 SEQ ID NO: 8, LCDR2 SEQ ID NO: 9 and LCDR3 SEQ ID NO: 104.

49. — An antibody that binds human GFRAL, comprising a VH domain and a VL domain, the VH domain comprising the QUEL-0105 set of HCDRs HCDR1 SEQ ID NO: 118, HCDR2 SEQ ID NO: 108 and HCDR3 SEQ ID NO: 119, and the VL domain comprising the QUEL-0105 set of LCDRs LCDR1 SEQ ID NO: 8, LCDR2 SEQ ID NO: 9 and LCDR3 SEQ ID NO: 104.

50. — An antibody that binds human GFRAL, comprising
a VH domain having at least 90 % amino acid sequence identity to the QUEL-0101 VH domain SEQ ID NO: 2 and
a VL domain having at least 90 % amino acid sequence identity to the QUEL-0101 VL domain SEQ ID NO: 7.

51. — ~~An antibody that binds human GFRAL comprising~~
~~a VH domain encoded by a nucleotide sequence produced by recombination of gene~~
~~segmentsIGHV3-30 (e.g., IGHV3-30*18) and IGHJ6 (e.g., IGHJ6*02), and~~
~~a VL domain encoded by a nucleotide sequence produced by recombination of gene~~
~~segmentsIGKV1-27 (e.g., IGKV1-27*01) and IGKJ4 (e.g., IGKJ4*01).~~
52. — ~~An antibody according to claim 51, wherein the VH domain is encoded by a nucleotide~~
~~sequence produced by recombination of gene segmentsIGHV3-30*18 (e.g., IGHV3-30),~~
~~IGHD3-10 (e.g., IGHJ6*01) and IGHJ6 (e.g., IGHJ6*02).~~
53. — ~~An antibody that competes for binding human GFRAL with a QUEL-0101 IgG comprising~~
~~QUEL-0101 VH domain SEQ ID NO: 2 and QUEL-0101 VL domain SEQ ID NO: 7.~~
54. — ~~An antibody according to any of claims 44 to 53 which binds human GFRAL with an~~
~~affinity of 1 nM or stronger as determined by surface plasmon resonance.~~
55. — ~~An antibody according to claim 54 which binds human GFRAL with an affinity of 200 pM~~
~~or stronger as determined by surface plasmon resonance.~~
56. — ~~An antibody according to claim 54 which binds human GFRAL with an affinity in the~~
~~range 100 pM—400 pM.~~
57. — ~~An antibody according to any of claims 44 to 56 which cross-reacts with mouse GFRAL,~~
~~having an affinity for mouse GFRAL within 10-fold of its affinity for human GFRAL.~~
58. — ~~An antibody according to any of claims 44 to 57 which inhibits GFRAL with a potency of~~
~~15 nM or stronger, wherein the potency is determined as IC50 in an in vitro assay of ERK~~
~~phosphorylation in response to GDF15.~~
59. — ~~An antibody according to claim 58, wherein the potency is 10 nM or stronger.~~
60. — ~~An antibody according to claim 59, wherein the potency is 5 nM or stronger.~~
61. — ~~An antibody according to any of claims 44 to 60, comprising~~
~~—— a VH domain having at least 95 % amino acid sequence identity to the QUEL-0101 VH~~
~~domain SEQ ID NO: 2 and~~

a VL domain having at least 95 % amino acid sequence identity to the QUEL-0101 VL domain SEQ ID NO: 7.

62. ~~An antibody according to any of claims 44 to 61, comprising~~
~~a VH domain having at least 98 % amino acid sequence identity to the QUEL-0101 VH domain SEQ ID NO: 2 and~~
~~a VL domain having at least 98 % amino acid sequence identity to the QUEL-0101 VL domain SEQ ID NO: 7.~~

63. ~~An antibody according to claim 62, comprising~~
~~the QUEL-0101 VH domain SEQ ID NO: 2, optionally with one or two amino acid alterations and~~
~~the QUEL-0101 VL domain SEQ ID NO: 7, optionally with one or two amino acid alterations.~~

64. ~~An antibody according to claim 63, comprising~~
~~the QUEL-0101 VH domain SEQ ID NO: 2 comprising the QUEL-0101 set of HCDRs HCDR1 SEQ ID NO: 3, HCDR2 SEQ ID NO: 4 and HCDR3 SEQ ID NO: 5, optionally with one or two amino acid alterations in the VH domain framework, and~~
~~the QUEL-0101 VL domain SEQ ID NO: 7 comprising the QUEL-0101 set of LCDRs LCDR1 SEQ ID NO: 8, LCDR2 SEQ ID NO: 9 and LCDR3 SEQ ID NO: 10, optionally with one or two amino acid alterations in the VL domain framework.~~

65. ~~An antibody according to claim 63 or claim 64, wherein the one or two amino acid alterations are conservative substitutions.~~

66. ~~An antibody according to any of claims 44 to 65, comprising the QUEL-0101 VH domain SEQ ID NO: 2 and the QUEL-0101 VL domain SEQ ID NO: 7.~~

67. ~~An antibody according to any of claims 44, 46 and 50-53, comprising the QUEL-0102 VH domain SEQ ID NO: 98 and the QUEL-0102 VL domain SEQ ID NO: 103.~~

68. ~~An antibody according to any of claims 44, 47 and 50-53, comprising the QUEL-0103 VH domain SEQ ID NO: 106 and the QUEL-0103 VH domain SEQ ID NO: 110.~~

69. ~~An antibody according to any of claims 44, 48 and 50-53, comprising the QUEL-0104 VH domain SEQ ID NO: 112 and the QUEL-0104 VL domain SEQ ID NO: 115.~~

~~70. — An antibody according to any of claims 44 and 49-53, comprising the QUEL-0105 VH domain SEQ ID NO: 117 and the QUEL-0105 VH domain SEQ ID NO: 121.~~

~~71~~12. An antibody according to any preceding claim, comprising a heavy chain Fc region.

~~72~~13. An antibody according to claim ~~71~~12, which is a human IgG.

~~73~~14. An antibody according to claim ~~72~~13, which is a human IgG4.

~~74~~15. An antibody according to claim ~~73-14~~ comprising heavy chain constant region SEQ ID NO: 60.

~~75~~16. Nucleic acid encoding an antibody as defined in any preceding claim.

~~76~~17. A host cell in vitro comprising nucleic acid as defined in claim ~~75~~16.

~~77~~18. A composition comprising an antibody according to any of claims 1 to ~~74-15~~ or nucleic acid according to claim ~~75~~16, formulated with a pharmaceutically acceptable excipient, preferably formulated for intravenous or subcutaneous injection.

~~78. — A composition according to claim 77, formulated for intravenous or subcutaneous injection.~~

~~79. — A method of treating a medical condition associated with the GDF15-GFRAL pathway in a patient, comprising administering a composition according to claim 77 or claim 78 to the patient.~~

~~80~~19. A composition according to claim ~~77-18 or claim 78~~ for use in treating a medical condition associated with the GDF15-GFRAL pathway in a patient.

~~81~~20. Use of a composition according to claim ~~77-18 or claim 78~~ for the manufacture of a medicament for treating a medical condition associated with the GDF15-GFRAL pathway in a patient.

~~8221.~~ A method ~~according to claim 79~~, a composition for use according to claim ~~80-19~~ or use of a composition according to claim ~~81-20~~, wherein the medical condition is hyperemesis gravidarum, anorexia, cachexia, conditioned taste aversion and/or a side effect of chemotherapy treatment for cancer.

~~8322.~~ A method, composition or use according to claim ~~8221~~, wherein the patient is also to receive, or has received, treatment with an anti-cancer chemotherapeutic agent.

~~8423.~~ A method, composition or use according to claim ~~82-21~~ or claim ~~8322~~, wherein the medical condition is anorexia or cachexia, in a cancer patient.

~~85.~~ A method, composition or use according to claim ~~82~~ or claim ~~83~~, wherein the medical condition is cachexia in a cancer patient.

~~8624.~~ A method, composition or use according to any of claims ~~82-21~~ to ~~8523~~, wherein the medical condition is a side effect of treatment with an anti-cancer chemotherapeutic agent and, optionally, wherein the treatment comprises preventing conditioned taste aversion caused by treatment with an anti-cancer chemotherapeutic agent.

~~87.~~ A method, composition or use according to claim ~~86~~, wherein the treatment comprises preventing conditioned taste aversion caused by treatment with an anti-cancer chemotherapeutic agent.

~~8825.~~ A method, composition or use according to any of claims ~~82-21~~ to ~~8724~~, wherein the treatment comprises reducing body weight loss and extending survival in a cancer patient.

~~89.~~ A method of reducing glucocorticoid (e.g., cortisol) level in a patient, comprising administering an inhibitor of GDF15 signalling to the patient.

~~9026.~~ An inhibitor of GDF15 signalling for use in reducing glucocorticoid (e.g., cortisol) levels in a patient, wherein the inhibitor is an anti-GFRAL antibody as defined in any one of claims 1 to 15.

~~9127.~~ Use of an inhibitor of GDF15 signalling for the manufacture of a medicament for reducing glucocorticoid (e.g., cortisol) levels in a patient, wherein the inhibitor is an anti-GFRAL antibody as defined in any one of claims 1 to 15.

~~9228.~~ ~~A method according to claim 89, a~~An inhibitor for use according to claim ~~9026~~, or use of an inhibitor according to claim ~~9127~~, for normalising the blood level of glucocorticoid (e.g., cortisol) in a patient who has been determined to have an elevated blood glucocorticoid level.

~~9329.~~ ~~A method according to claim 89, a~~An inhibitor for use according to claim ~~9026~~ or use of an inhibitor according to claim ~~9127~~, wherein the patient is a cancer patient.

~~9430.~~ ~~A method, a~~An inhibitor for use, or use of an inhibitor according to any of claims ~~8925~~ to ~~9329~~, wherein the patient is also to receive, or has received, treatment with a cytotoxic and/or antineoplastic agent.

~~95.~~ ~~A method, an inhibitor for use, or use of an inhibitor according to any of claims 89 to 94, wherein the inhibitor inhibits the GDF15-GFRAL-RET signalling complex.~~

~~96.~~ ~~A method, an inhibitor for use, or use of an inhibitor according to claim 95, wherein the inhibitor is an anti-GFRAL antibody.~~

~~97.~~ ~~A method, an inhibitor for use, or use of an inhibitor according to claim 96, wherein the anti-GFRAL antibody is an antibody as defined in any of claims 1 to 74.~~