Claims

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 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,

(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 according to claim 1 or 2, 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.

4. An antibody according to claim 3, 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.

7. An antibody according to any of claims 1 to 6, 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.

8. 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.

9. An antibody according to claim 8, 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.

10. An antibody according to claim 9, 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.

11. An antibody according to any 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.

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

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

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

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

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

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

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

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

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

21. A composition for use according to claim 19 or use of a composition according to claim20, wherein the medical condition is hyperemesis gravidarum, anorexia, cachexia, conditioned taste aversion and/or a side effect of chemotherapy treatment for cancer.

22. A composition or use according to claim 21, wherein the patient is also to receive, or has received, treatment with an anti-cancer chemotherapeutic agent.

23. A composition or use according to claim 21 or claim 22, wherein the medical condition is anorexia or cachexia, in a cancer patient.

24. A composition or use according to any of claims 21 to 23, 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.

25. A composition or use according to any of claims 21 to 24, wherein the treatment comprises reducing body weight loss and extending survival in a cancer patient.

26. 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.

27. 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.

28. An inhibitor for use according to claim 26, or use of an inhibitor according to claim 27, for normalising the blood level of glucocorticoid (e.g., cortisol) in a patient who has been determined to have an elevated blood glucocorticoid level.

29. An inhibitor for use according to claim 26 or use of an inhibitor according to claim27, wherein the patient is a cancer patient.

30. An inhibitor for use, or use of an inhibitor according to any of claims 25 to 29, wherein the patient is also to receive, or has received, treatment with a cytotoxic and/or antineoplastic agent.