

CLAIMS

1. An antibody variant binding to human CD38, the antibody variant comprising
 - (a) an antigen-binding region comprising a variable heavy (VH) region comprising the sequence of SEQ ID NO:1 and a variable light (VL) region comprising the sequence of SEQ ID NO:5, and
 - (b) a variant Fc region comprising a mutation in amino acid residue E430 of a human IgG1 heavy chain, wherein the amino acid residues are numbered according to the EU index, wherein said mutation consists of E430G and wherein the variant Fc region is, except for the recited mutation, a human IgG1 Fc region.
2. The antibody variant according to claim 1, wherein the variant Fc region is, except for the recited mutation, a human IgG1m(f), IgG1m(a), IgG1m(x), IgG1m(z) allotype or a mixed allotype of any two or more thereof.
3. The antibody variant according to any one of the preceding claims, which is a bivalent antibody.
4. The antibody variant according to any one of the preceding claims, which is a full-length antibody.
5. The antibody variant according to any one of the preceding claims, wherein the antibody variant is, except for the recited mutation, a human antibody.
6. The antibody variant according to any one of the preceding claims, which is a monoclonal antibody.
7. The antibody variant according to any one of the preceding claims, wherein the antibody variant is, except for the recited mutation, an IgG1 antibody.
8. The antibody variant according to any one of the preceding claims, wherein the antibody variant is, except for the recited mutation, a human monoclonal full-length bivalent IgG1m(f), κ antibody.

9. The antibody variant according to any one of the preceding claims, comprising a human IgG1 CH region which comprises, except for the recited mutation, the sequence of SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23 or SEQ ID NO:45.
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10. The antibody variant according to claim 9, wherein Lys (K) at position 447 according to Eu numbering is deleted.
11. The antibody variant according to any one of the preceding claims, comprising a human IgG1 CH region which comprises an amino acid sequence selected from the group consisting of SEQ ID NO:24 and SEQ ID NO: 46.
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12. The antibody variant according to claim 11, wherein the light chain comprises a CL comprising SEQ ID NO:37.
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13. The antibody variant according to any of the preceding claims comprising a heavy chain comprising a variable heavy chain (VH) region comprising SEQ ID NO:1, and a CH region comprising SEQ ID NO: 46, and a light chain comprising a variable light chain (VL) region comprising SEQ ID NO:5 and a CL comprising SEQ ID NO:37.
14. The antibody variant according to any one of the preceding claims, which is a bivalent antibody.
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15. The antibody variant according to any one of the preceding claims, wherein the antibody variant is a monospecific or bispecific antibody.
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16. The antibody variant according to any one of the preceding claims, which
- (a) has an inhibitory effect on the cyclase activity of human CD38;
- (b) induces apoptosis in the presence, but not in the absence, of an Fc-cross-linking antibody; and/or
- (c) induces CDC, ADCC, antibody-dependent cell-phagocytosis (ADCP), trogocytosis, or any combination thereof, of cells expressing human CD38.
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17. The antibody variant according to claim 16, which inhibits the cyclase activity of human CD38 by at least 40%, such as at least 50%, such as at least 60%, optionally wherein the inhibition of cyclase activity is determined by an assay comprising the steps of:
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- (a) seeding 200,000 Daudi or Wien133 cells in 100 μ L 20 mM Tris-HCL per well; or seeding 0.6 μ g/mL His-tagged soluble human CD38 (SEQ ID NO:39) in 100 μ L 20 mM Tris-HCL per well in a multi-well plate;
 - (b) adding 1 μ g/mL CD38 antibody and 80 μ M NGD to each well;
 - 5 (c) measuring fluorescence until a plateau is reached (e.g.; 5, 10 or 30 minutes); and
 - (d) determining the percentage inhibition as compared to a control, such as a well incubated with an isotype control antibody.
18. The antibody variant according to any one of the preceding claims, wherein the
- 10 antibody variant induces CDC of cells expressing human CD38.
19. The antibody variant according to any one of the preceding claims, wherein the antibody variant induces CDC against Daudi cells (ATCC No. CCL-213) or Ramos cells (ATCC No. CRL-1596) resulting in a maximum lysis at least 50%, such at least 60%, such as at
- 15 least 70% higher than that obtained with a reference antibody variant differing only in the absence of the one or more mutations in the Fc region.
20. The antibody variant according to claim 19, wherein the CDC is determined by an assay comprising the steps of:
- 20 (a) plating 100,000 CD38-expressing cells in 40 μ L culture medium supplemented with 0.2% BSA per well in a multi-well plate;
- (b) preincubating cells for 20 minutes with 40 μ L of serially diluted CD38 antibody (0.0002-10 μ g/mL);
- (c) incubating each well for 45 minutes at 37°C with 20 percent of pooled normal human
- 25 serum;
- (d) adding a viability dye and measuring the percentage of cell lysis on a flow cytometer;
- (e) determining the maximum lysis using non-linear regression.
21. An antibody variant according to any one of the preceding claims, wherein the
- 30 antibody variant is conjugated to a cytotoxic agent, a radioisotope or a drug.
22. A nucleic acid or combination of nucleic acids encoding the antibody variant according to any one of the preceding claims.
23. An expression vector comprising the nucleic acid or combination of nucleic acids
- 35 according to claim 22.

24. A delivery vehicle comprising the nucleic acid(s) according to claim 22.
25. A delivery vehicle according to claim 24, wherein said delivery vehicle is a particle.
- 5 26. A delivery vehicle according to claim 25, wherein said particle is a lipid nanoparticle (LNP).
- 10 27. A delivery vehicle according to claim 26, wherein said LNP comprises lipids, ionizable aminolipids, PEG-lipids, cholesterol or any combination thereof.
- 15 28. A recombinant host cell which produces an antibody variant as defined in any one of claim 1 to 20, optionally wherein the host cell comprises the nucleic acid(s) of claim 22 or the expression vector of claim 23.
- 20 29. The recombinant host cell according to claim 28, which is a eukaryotic or prokaryotic cell.
- 30 30. A method of producing an antibody variant according to any one of claims 1 to 20, comprising cultivating the recombinant host cell of claim 28 or 29 in a culture medium and under conditions suitable for producing the antibody variant.
- 25 31. The method of claim 30, comprising the further step of purifying or isolating the antibody variant from the culture medium.
- 30 32. A method of increasing at least one effector function of a parent antibody comprising an Fc region and an antigen-binding region binding to CD38, which method comprises introducing into the Fc region a mutation in amino acid residue E430 of the Fc region of a human IgG1 heavy chain, wherein the amino acid residues are numbered according to the EU index, wherein said mutation consists of E430G;
- 35 wherein the antigen-binding region comprises a variable heavy (VH) region comprising the sequence of SEQ ID NO:1 and a variable light (VL) region comprising the sequence of SEQ ID NO:5, and wherein Fc region of the parent antibody is a human IgG1 Fc region; and wherein the effector function is CDC, trogocytosis, or both.
33. A method of producing a variant of a parent antibody comprising an Fc region and an antigen-binding region binding to CD38, the variant having an increased effector function as compared to the parent antibody, which method comprises

- (a) introducing into the Fc region a mutation in amino acid residue E430 of the Fc region of a human IgG1 heavy chain to obtain a variant antibody, wherein said mutation consists of E430G,
- (b) selecting any variant antibody having an increased effector function as compared
5 to the parent antibody, and
- (c) producing said variant antibody in a recombinant host cell,
wherein the antigen-binding region comprises a variable heavy (VH) region comprising the sequence of SEQ ID NO:1 and a variable light (VL) region comprising the sequence of SEQ ID NO:5, and wherein Fc region of the parent antibody is a human IgG1 Fc region; and
10 wherein the effector function is CDC, trogocytosis, or both.
34. The method according to claim 32 or 33, wherein the parent antibody is a human full-length IgG1 antibody, optionally a human monoclonal full-length bivalent IgG1, κ antibody.
- 15 35. The method according to any one of claims 32 to 34, wherein the parent antibody is a monospecific or bispecific antibody.
36. A composition comprising an antibody variant according to any one of claims 1 to 20, a nucleic acid or a combination of nucleic acids according to claim 22, an expression vector
20 according to claim 23, a delivery vehicle according to any one of claims 24-27, or a host cell according to any one of claims 28-29.
37. A pharmaceutical composition comprising an antibody variant as defined in any one of claims 1 to 20, a nucleic acid or a combination of nucleic acids according to claim 22, an
25 expression vector according to claim 23, or a delivery vehicle according to any one of claims 24-27, and a pharmaceutically acceptable carrier.
38. An (i) antibody variant according to any one of claims 1 to 20, (ii) a nucleic acid or a combination of nucleic acids according to claim 22, (iii) an expression vector according to
30 claim 23, (iv) a delivery vehicle according to any one of claims 24-27, (v) a composition according to claim 36, or (vi) a pharmaceutical composition according to claim 37 for use as a medicament.
39. Use of
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- i. an antibody variant according to any one of claims 1 to 20,
 - ii. a nucleic acid or a combination of nucleic acids according to claim 22,
 - iii. an expression vector according to claim 23,
 - iv. a delivery vehicle according to any one of claims 24-27,
 - v. a composition according to claim 36, or

vi. a pharmaceutical composition according to claim 37
in the manufacture of a medicament for:

- a) the treatment of a disease involving cells expressing CD38, wherein said disease is selected from the group consisting of cancer, inflammatory disease,
5 autoimmune disease or metabolic disorder involving cells expressing CD38 ;
- b) inducing a CDC-response against a tumor comprising cells expressing CD38;
- c) treating a cancer in a subject comprising cells expressing CD38;
- d) treating a cancer refractory to a prior therapy comprising a CD38 antibody;
- e) treating a cancer relapsed after a prior therapy comprising a CD38 antibody.

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40. The use according to claim 39, wherein the CD38 antibody is daratumumab.

41. The use according to claim 39 or claim 40, wherein the cancer is a hematological cancer.

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42. The use according to claim 41, wherein the hematological cancer is selected from the group consisting of multiple-myeloma (MM), chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (adults) (AML), mantle cell lymphoma, follicular lymphoma (FL), and diffuse large B-cell lymphoma (DLBCL).

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43. The use according to claim 41, wherein the cancer is:

- a) MM
- b) CLL;
- c) mantle cell lymphoma;
- 25 d) DLBCL;
- e) FL; or
- f) acute myelogenous leukemia (adults) (AML).

44. The use according to any one of claims 39 to 40, wherein the cancer comprises a solid
30 tumor.

45. The use according to claim 44, wherein the solid tumor is melanoma, lung cancer, squamous non-small cell lung cancer (NSCLC), non-squamous NSCLC, colorectal cancer, prostate cancer, castration-resistant prostate cancer, stomach cancer, ovarian cancer, gastric
35 cancer, liver cancer, pancreatic cancer, thyroid cancer, squamous cell carcinoma of the head and neck, carcinoma of the esophagus or gastrointestinal tract, breast cancer, fallopian tube cancer, brain cancer, urethral cancer, genitourinary cancer, endometrial cancer, cervical cancer, lung adenocarcinoma, renal cell carcinoma (RCC) (e.g., a kidney clear cell carcinoma or a kidney papillary cell carcinoma), mesothelioma, nasopharyngeal carcinoma (NPC), a

carcinoma of the esophagus or gastrointestinal tract, or a metastatic lesion of any one thereof.

46. The use according to claim 44, wherein the solid tumor is:

- 5 a) lung cancer;
- b) squamous non-small cell lung cancer (NSCLC);
- c) non-squamous NSCLC;
- d) melanoma;
- 10 e) colorectal cancer;
- f) prostate cancer;
- g) castration-resistant prostate cancer;
- h) stomach cancer;
- i) ovarian cancer;
- 15 j) gastric cancer;
- k) liver cancer;
- l) pancreatic cancer;
- m) thyroid cancer;
- n) squamous cell carcinoma of the head and neck;
- 20 o) carcinoma of the esophagus or gastrointestinal tract;
- p) breast cancer;
- q) fallopian tube cancer;
- r) brain cancer;
- s) urethral cancer;
- 25 t) genitourinary cancer;
- u) endometrial cancer; or
- v) cervical cancer.

30 47. The use according to any one of claims 39 to 46, wherein the cancer is in a patient comprising T regulatory cells expressing CD38.

48. Use of an antibody variant according to any one of claims 1 to 20 in the manufacture of a medicament for treating rheumatoid arthritis.