

CLAIMS

1. An isolated antibody or antigen binding fragment thereof that binds to human TMEM219 receptor and inhibits or reduces the binding of IGFBP3 to said TMEM219 receptor.
- 5 2. The isolated antibody or antigen binding fragment thereof according to claim 1 that inhibits, reduces, or neutralizes the activation of the TMEM219 receptor induced by binding of IGFBP3.
3. The isolated antibody or antigen binding fragment thereof according to claim 1 or 2 that does not activate TMEM219 pathway upon binding to human TMEM219.
- 10 4. The isolated antibody or antigen binding fragment thereof according to any one of previous claims that is effective in preserving beta cells in diabetic subject and/or in preventing islet destruction, and/or in controlling blood glucose levels in an in vivo model.
5. The isolated antibody or antigen binding fragment thereof according to any one of previous claims that is effective in reducing acute colitis in an in vivo model.
- 15 6. The isolated antibody or antigen binding fragment thereof according to any one of previous claims that has at least one activity selected from:
 - a- increase in IGFBP3 treated healthy subject minigut growth;
 - b- increase in IBD-patient minigut growth;
 - c- increase in diabetic enteropathy serum treated healthy subject minigut growth;
 - 20 d- increase in expression of EphB2 and/or LGR5 in IGFBP3 treated healthy subject minigut;
 - e- decrease in Caspase 8 expression in IGFBP3 treated healthy subject minigut;
 - f- decrease in β -cell loss in IGFBP3 treated β -cell;
 - g- increase in expression of insulin in IGFBP3 treated β -cell;
 - 25 h- inhibits or decreases DSS-induced intestinal cells apoptosis;
 - i- restores expression of PCNA in DSS-treated colon;
 - j- decrease in apoptosis of β -cell in IGFBP3 treated β -cell;
 - k- decrease in insulinitis score in an animal model of diabetes;
 - l- decrease in diabetes onset in an animal model of diabetes;
 - 30 m- protects beta cell injury in an animal model of diabetes;
 - n- prevents beta cell loss in an animal model of diabetes.
7. The isolated antibody or antigen binding fragment thereof according to claim 6 wherein the increase in a), b) and c) is by at least 20 %; the increase in d) and e) is by at least 30 %, preferably by at least 50 %; the decrease in f) and the increase in g) is by

35 at least 10 %.

8. The isolated antibody or antigen binding fragment thereof according any one of previous claims comprising:

a. a heavy chain variable domain (VH) comprising:

i. a CDR1 sequence of the amino acid sequence selected from the group consisting of: SEQ ID NO: 4, 1, 8, 10, 56, 59, 62, 65 and 68;

ii. a CDR2 sequence of the amino acid sequence selected from the group consisting of : SEQ ID NO: 5, 2, 11, 57, 60, 63, 66 and 69; and

iii. a CDR3 sequence of the amino acid sequence selected from the group consisting of : SEQ ID NO:6, 3, 7, 9, 12, 13, 58, 61, 64, 67 and 70; and/or

b. a light chain variable domain (VL) comprising:

i. a CDR1 sequence of the amino acid sequence selected from the group consisting of: SEQ ID NO:17, 14, 20, 23, 26, 29, 71, 77, 80, 82 and 85;

ii. a CDR2 sequence of the amino acid sequence selected from the group consisting of : SEQ ID NO:18, 15, 21, 24, 27, 30, 72, 78, 83 and 86; and

iii. a CDR3 sequence of the amino acid sequence selected from the group consisting of: SEQ ID NO:19, 16, 22, 25, 28, 31, 73, 74, 75, 76, 79, 81, 84, 87, 166 and 167.

9. The isolated antibody or antigen binding fragment thereof according any one of claims 1 to 8 comprising:

- SEQ ID NO: 4 and SEQ ID NO: 5 and SEQ ID NO: 6 and SEQ ID NO: 17 and SEQ ID NO: 18 and SEQ ID NO: 19 or Kabat, IMGT, Chothia, AbM, or Contact CDRs of TC01 or of TC05 or

- SEQ ID NO: 4 and SEQ ID NO: 5 and SEQ ID NO: 6 and SEQ ID NO: 17 and SEQ ID NO: 18 and SEQ ID NO: 166 or Kabat, IMGT, Chothia, AbM, or Contact CDRs of TC03 or

- SEQ ID NO: 4 and SEQ ID NO: 5 and SEQ ID NO: 6 and SEQ ID NO: 17 and SEQ ID NO: 18 and SEQ ID NO: 167 or Kabat, IMGT, Chothia, AbM, or Contact CDRs of TC04 or

- SEQ ID NO: 68 and SEQ ID NO: 69 and SEQ ID NO: 70 and SEQ ID NO: 85 and SEQ ID NO: 86 and SEQ ID NO: 87 or Kabat, IMGT, Chothia, AbM, or Contact CDRs of TM1.

10. The isolated antibody or antigen binding fragment thereof according any one of claims 1 to 9 comprising:

a. a heavy chain variable domain (VH) comprising:

i. a CDR1 sequence of the amino acid sequence selected from the group consisting of a sequence as defined using abysis tool analysis (www.abysis.org);

ii. a CDR2 sequence of the amino acid sequence selected from the group consisting of a sequence as defined using abysis tool analysis (www.abysis.org); and

iii. a CDR3 sequence of the amino acid sequence selected from the group consisting of a sequence as defined using abysis tool analysis (www.abysis.org); and/or

b. a light chain variable domain (VL) comprising:

i. a CDR1 sequence of the amino acid sequence selected from the group consisting of a sequence as defined using abysis tool analysis (www.abysis.org);

ii. a CDR2 sequence of the amino acid sequence selected from the group consisting of a sequence as defined using abysis tool analysis (www.abysis.org); and

iii. a CDR3 sequence of the amino acid sequence selected from the group consisting of a sequence as defined using abysis tool analysis (www.abysis.org).

11. The isolated antibody or antigen binding fragment thereof according to any one of previous claims comprising:

a. a heavy chain variable domain sequence of the amino acid sequence selected from the group consisting of: SEQ ID NO:32 to SEQ ID NO:37 or of SEQ ID NO:88 to SEQ ID NO:95, or of SEQ ID NO:168, SEQ ID NO:169 and SEQ ID NO:170 ;

or

b. a light chain variable domain sequence of the amino acid sequence selected from the group consisting of: SEQ ID NO: 38 to SEQ ID NO:43; or of SEQ ID NO: 96 to SEQ ID NO: 103 or of SEQ ID NO: 171, SEQ ID NO: 172 or SEQ ID NO: 173; or

c. the heavy chain variable domain of (a) and the light chain variable domain of (b).

12. The isolated antibody or antigen binding fragment thereof according to any one of previous claims comprising VH and VL regions together selected from the group consisting of: TC01, TC03, TC04, TC05, TA02, TC02, TD01, TE01, TG02, TM1, TE02.1, TE02.2, TE02.3, TE03, TE04, TE07, TE10.

13. The isolated antibody or antigen binding fragment thereof according to any one of the previous claims, wherein, preferably the isolated antibody or antigen binding fragment thereof comprises the VH and VL regions of antibody TC01, TC03, TC04, TC05 or TM1.

14. The isolated antibody or antigen binding fragment thereof according to claim 10, said antibody comprising VH CDR1, CDR2 and CDR3 selected from Table 3.3 and VL CDR1, CDR2 and CDR3 selected from Table 3.4.

15. The isolated antibody or antigen binding fragment thereof according to any one of previous claims having an affinity constant lower than or equal to 10^{-7} M for human TMEM.

16. An isolated antibody or antigen binding fragment thereof that:

(a) binds specifically to an epitope on TMEM, said epitope being the same or similar epitope as the epitope recognized by the monoclonal antibody TC01, TC03, TC04, TC05, TA02, TC02, TD01, TE01, TG02, TM1, TE02.1, TE02.2, TE02.3, TE03, TE04, TE07, TE10 as defined in Tables 2-19 and Tables 3.1-3.4; or

(b) cross-competes for binding with the monoclonal antibody TC01, TC03, TC04, TC05, TA02, TC02, TD01, TE01, TG02, TM1, TE02.1, TE02.2, TE02.3, TE03, TE04, TE07, TE10 as defined in Tables 2-19 and Tables 3.1-3.4; or

€ shows the same or similar binding affinity or specificity, or both, as any of TC01, TC03, TC04, TC04, TA02, TC02, TD01, TE01, TG02, TM1, TE02.1, TE02.2, TE02.3, TE03, TE04, TE07, TE10 as defined in Tables 2-19 and Tables 3.1-3.4; or

(d) has one or more biological properties of an antibody molecule described herein, e.g., an antibody molecule chosen from, e.g., any of TC01, TC03, TC04, TC04, TA02, TC02, TD01, TE01, TG02, TM1, TE02.1, TE02.2, TE02.3, TE03, TE04, TE07, TE10 as defined in Tables 2-19 and Tables 3.1-3.4; or

€ has one or more pharmacokinetic properties of an antibody molecule described herein, e.g., an antibody molecule chosen from, e.g., any of TC01, TC03, TC04, TC04, TA02, TC02, TD01, TE01, TG02, TM1, TE02.1, TE02.2, TE02.3, TE03, TE04, TE07, TE10 as defined in Tables 2-19 and Tables 3.1-3.4.

17. The isolated antibody or antigen binding fragment thereof according to any one of previous claims being a human or a humanized antibody.

18. The isolated antibody or antigen binding fragment thereof according to any one of previous claims being an IgG2 or IgG4 antibody, preferably an IgG2 kappa antibody, an IgG2 lambda antibody, an IgG4 kappa antibody or an IgG4 lambda antibody, preferably said IgG2 or IgG4 is human IgG2 or human IgG4 .

~~18~~19. An isolated polynucleotide comprising at least one sequence that encodes the antibody or antigen binding fragment thereof according to any one of previous claims, preferably said polynucleotide being a cDNA.

~~19~~20. A vector comprising the polynucleotide according to claim ~~18~~19.

5 ~~21.~~ The vector of claim 20, wherein~~preferably~~ said vector ~~being is~~ selected from the group consisting of a plasmid, a viral vector, a non-episomal mammalian vector, an expression vector and a recombinant expression vector.

~~20~~22. An isolated cell comprising the polynucleotide according to claim ~~18-19~~ or the vector according to any one of claims ~~19~~20-21.

10 ~~23.~~ The isolated cell of claim 22, wherein~~preferably~~ said isolated cell ~~being is~~ a hybridoma or a Chinese Hamster Ovary (CHO) cell or a Human Embryonic Kidney cells (HEK293).

~~24~~24. The antibody or antigen binding fragment thereof according to any one of claims ~~1 to 17-18~~ or the polynucleotide according to claim ~~18-19~~ or the vector according to any one of claims ~~19-20-21~~ or the cell according to any one of claims ~~20~~22-23, for use as a medicament.

15 ~~25.~~ The antibody or antigen binding fragment thereof according to any one of claims 1 to 18 or the polynucleotide according to claim 19 or the vector according to any one of claims 20-21 or the cell according to any one of claims 22-23, ~~preferably~~ for use in the treatment of: diabetes, intestinal and/or bowel disorder, malabsorption syndrome, cachexia or diabetic enteropathy, preferably diabetes is Type I or Type II diabetes, preferably the intestinal and/or bowel disorder is inflammatory bowel disease, celiac disease, ulcerative colitis, Crohn's disease or intestinal obstruction.

20 ~~22~~26. A pharmaceutical composition comprising the isolated antibody or antigen binding fragment thereof according to any one of claims ~~1 to 17-18~~ or the polynucleotide according to claim ~~18-19~~ or the vector according to any one of claims ~~19~~20-21 or the cell according to any one of claims ~~20~~22-23 and pharmaceutically acceptable carrier.

25 ~~27.~~ The pharmaceutical composition of claim 26, ~~preferably~~ for use in the treatment of: diabetes, intestinal and/or bowel disorder, malabsorption syndrome, cachexia or diabetic enteropathy, preferably the intestinal and/or bowel disorder is inflammatory bowel disease, celiac disease, ulcerative colitis, Crohn's disease or intestinal obstruction.

30 ~~23.~~ A method of inhibiting the binding of IGFBP3 to TMEM219 receptor, comprising contacting TMEM219 with the antibody according to any one of claims 1 to 17, or with the composition according to claim 22.

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28. Use of the antibody according to any one of claims 1 to 18, or the composition according to any one of claims 26-27, in the preparation of a medicament for inhibiting the binding of IGFBP3 to TMEM219 receptor, comprising contacting TMEM219 with the antibody or the composition.

- 5 29. Use of the antibody or antigen binding fragment thereof according to any one of claims 1 to 18 or 28, or the polynucleotide according to claim 19, or the vector according to any one of claims 20-21, or the cell according to any one of claims 22-23, or the pharmaceutical composition of any one of claims 26-28, in the preparation of a medicament for the treatment of: diabetes, intestinal and/or bowel disorder,
- 10 malabsorption syndrome, cachexia or diabetic enteropathy, preferably diabetes is Type I or Type II diabetes, preferably the intestinal and/or bowel disorder is inflammatory bowel disease, celiac disease, ulcerative colitis, Crohn's disease or intestinal obstruction.