CLAIMS (Marked-up)

1. (Currently amended) An antibody or antigen binding fragment capable of binding to Chemokine (C-X-C motif) receptor 3 (CXCR3), the antibody or antigen binding fragment comprising six complementarity determining regions (CDRs): heavy chain variable domain (VH) CDR1, VH CDR2, VH CDR3, light chain variable domain (VL) CDR1, VL CDR2, and VL CDR3,

wherein:

VH CDR1 is selected from the group consisting of:

GISFNDAA (SEQ ID NO: 116),

GFTFTSYA (SEQ ID NO: 172),

GFTFSNYA (SEQ ID NO: 228),

GFTFTSYA (SEQ ID NO: 368), and

GYTFTDYA (SEQ ID NO: 543);

VH CDR2 is selected from the group consisting of:

IRSKINDYGT (SEQ ID NO: 118),

ISHGGSYT (SEQ ID NO: 174),

ISNGGSYT (SEQ ID NO: 230),

~~ISNLGSYT (SEQ ID NO: 314),~~

ISHGGTYT (SEQ ID NO: 370), and

ISTYNGNT (SEQ ID NO: 545),

VH CDR3 is selected from the group consisting of:

VIDGYGSLAY (SEQ ID NO: 120),

ARHPFYSGNYQGYFDY (SEQ ID NO: 176),

SRPSERSHYYATSQFAY (SEQ ID NO: 232),

ARHPIYSGNYQGYFDY (SEQ ID NO: 372), and

ARFLSLRYFDV (SEQ ID NO: 547),

VL CDR1 is selected from the group consisting of:

SSVISSY (SEQ ID NO: 123),

SGVNY (SEQ ID NO: 179),

SSVSY (SEQ ID NO: 235),

SGVNY (SEQ ID NO: 375), and

SSVIY (SEQ ID NO: 550),

VL CDR2 is selected from the group consisting of:

STS (SEQ ID NO: 125),

FTS (SEQ ID NO: 181),

DTS (SEQ ID NO: 237),

FTS (SEQ ID NO: 377), and

ATS (SEQ ID NO: 552),

and

VL CDR3 is selected from the group consisting of:

QQYSGYPLT (SEQ ID NO: 127),

QQFTSSPYT (SEQ ID NO: 183),

QQWSSSPLT (SEQ ID NO: 239),

QQFTSSPYT (SEQ ID NO: 379), and

QQWSSEPLT (SEQ ID NO: 554).

2. (Previously presented) The antibody or fragment of claim 1, wherein the antibody or fragment is chimeric, CDR grafted, mutated, mutated to remove one or more deamidation site, human, humanized, humanized and back-mutated, synthetic, or recombinant.

3. (Currently amended) The antibody or fragment of ~~any one of claims 1-2~~ claim 1, wherein the antibody or fragment is capable of binding to a polypeptide comprising a peptide selected from the group consisting of:

a) a peptide comprising residues 1-58 of SEQ ID NO:1;

b) a peptide comprising residues 1-16 of SEQ ID NO:1; and

c) a peptide comprising residues 1-37 of SEQ ID NO:1.

4. (Currently amended) The antibody or fragment of ~~any one of claims 1-3~~ claim 1, wherein the antibody or fragment is capable of binding to a polypeptide comprising a peptide selected from the group consisting of:

a) a peptide comprising the amino acid sequence SDHQVLNDAE (SEQ ID NO:71);

b) a peptide comprising the amino acid sequence SDHQVLND (SEQ ID NO:72);

c) a peptide comprising the amino acid sequence DHQVLND (SEQ ID NO:73);

d) a peptide comprising the amino acid sequence VLNDAE (SEQ ID NO:74);

e) a peptide comprising the amino acid sequence VLND (SEQ ID NO:75);

f) a peptide comprising the amino acid sequence XDXXVXNDXX (SEQ ID NO:76);

g) a peptide comprising the amino acid sequence XDXXVXND (SEQ ID NO:77);

h) a peptide comprising the amino acid sequence DXXVXND (SEQ ID NO:78);

i) a peptide comprising the amino acid sequence VXNDXX (SEQ ID NO:79); and

j) a peptide comprising the amino acid sequence VXND (SEQ ID NO:80),

wherein X indicates any amino acid.

5. (Currently amended) The antibody or fragment of ~~any one of claims 1-4~~ claim 1, comprising a heavy chain variable region and a light chain variable region, wherein[[:]] the heavy chain variable region comprises a sequence at least about [[85%,]] 90%~~, 95%, or 99%~~ identical to a sequence selected from the group consisting of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26-33, 38, 40, 42, 44, 46-48, 63-66, 55, 57, 59, and 61; and ~~wherein~~ the light chain variable region comprises a sequence at least about [[85%]], 90%~~, 95%, or 99%~~ identical to a sequence selected from the group consisting of SEQ ID NO: 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 34-37, 39, 41, 43, 45, 49-54, 67-70, 56, 58, 60, and 62.

6. (Currently amended) The antibody or fragment of ~~any one of claims 1-5~~ claim 1, wherein the heavy chain variable region comprises a sequence selected from the group consisting of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26-33, 38, 40, 42, 44, 46-48, 63-66, 55, 57, 59, and 61; and wherein the light chain variable region comprises a sequence selected from the group consisting of SEQ ID NO: 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 34-37, 39, 41, 43, 45, 49-54, 67-70, 56, 58, 60, and 62.

7. (Currently amended) The antibody or fragment of ~~any one of claims 1-6~~ claim 1, wherein said antibody or fragment comprises 3 CDRs selected from the group of variable domain CDR sets consisting of:
Clone 12 VH CDR set: SEQ ID NO: 116, SEQ ID NO: 118, and SEQ ID NO: 120;
Clone 12 VL CDR set: SEQ ID NO: 123, SEQ ID NO: 125, and SEQ ID NO: 127;
Clone 135 VH CDR set: SEQ ID NO: 172, SEQ ID NO: 174, and SEQ ID NO: 176;
Clone 135 VL CDR set: SEQ ID NO: 179, SEQ ID NO: 181, and SEQ ID NO: 183;
Clone 4 VH CDR set: SEQ ID NO: 228, SEQ ID NO: 230, and SEQ ID NO: 232;
Clone 4 VL CDR set: SEQ ID NO: 235, SEQ ID NO: 237, and SEQ ID NO: 239;
~~Clone 4.8 VH CDR set: SEQ ID NO: 228, SEQ ID NO: 314, and SEQ ID NO: 232;~~
~~Clone 4.8 VL CDR set: SEQ ID NO: 235, SEQ ID NO: 237, and SEQ ID NO: 239;~~
Clone 53 VH CDR set: SEQ ID NO: 368, SEQ ID NO: 370, and SEQ ID NO: 372;
Clone 53 VL CDR set: SEQ ID NO: 375, SEQ ID NO: 377, and SEQ ID NO: 379;
Clone 82 VH CDR set: SEQ ID NO: 543, SEQ ID NO: 545, and SEQ ID NO: 547; and
Clone 82 VL CDR set: SEQ ID NO: 550, SEQ ID NO: 552, and SEQ ID NO: 554.

8. (Currently amended) The antibody or fragment of claim 7, comprising two variable domain CDR sets selected from a group consisting of:
Clone 12 VH CDR set and Clone 12 VL CDR set;
Clone 135 VH CDR set and Clone 135 VL CDR set;
Clone 4 VH CDR set and Clone 4 VL CDR set;
~~Clone 4.8 VH CDR set and Clone 4.8 VL CDR set;~~
Clone 53 VH CDR set and Clone 53 VL CDR set; and
Clone 82 VH CDR set and Clone 82 VL CDR set.

9. (Currently amended) The antibody or fragment of ~~any one of claims 1-8~~ claim 1, wherein the antibody or fragment comprises a combination of heavy chain and light chain variable regions selected from the group consisting of:
SEQ ID NOs: 18 and 19; SEQ ID NOs: 20 and 21; SEQ ID NOs: 22 and 23; SEQ ID NOs: 24 and 25; SEQ ID NOs: 22 and 25; SEQ ID NOs: 24 and 23; SEQ ID NOs: 26 and 34; SEQ ID NOs: 26 and 37; SEQ ID NOs: 27 and 35; SEQ ID NOs: 27 and 36; SEQ ID NOs: 28 and 34; SEQ ID NOs: 22 and 21; SEQ ID NOs: 20 and 23; SEQ ID NOs: 24 and

21; SEQ ID NOs: 20 and 25; SEQ ID NOs: 29 and 23; SEQ ID NOs: 30 and 23; SEQ ID NOs: 31 and 23; SEQ ID NOs: 32 and 23; SEQ ID NOs: 33 and 23; SEQ ID NOs: 2 and 3; SEQ ID NOs: 4 and 5; SEQ ID NOs: 6 and 7; SEQ ID NOs: 8 and 9; SEQ ID NOs: 55 and 56; SEQ ID NOs: 57 and 58; SEQ ID NOs: 59 and 60; SEQ ID NOs: 61 and 62; SEQ ID NOs: 10 and 11; SEQ ID NOs: 12 and 13; SEQ ID NOs: 14 and 15; SEQ ID NOs: 16 and 17; SEQ ID NOs: 38 and 39; SEQ ID NOs: 40 and 41; SEQ ID NOs: 42 and 43 SEQ ID NOs: 44 and 45; SEQ ID NOs: 40 and 43; SEQ ID NOs: 42 and 41; SEQ ID NOs: 42 and 49; SEQ ID NOs: 42 and 50; SEQ ID NOs: 42 and 51; SEQ ID NOs: 42 and 52; SEQ ID NOs: 42 and 53; SEQ ID NOs: 42 and 54; SEQ ID NOs: 46 and 43; SEQ ID NOs: 47 and 43; SEQ ID NOs: 48 and 43; SEQ ID NOs: 40 and 49; SEQ ID NOs: 40 and 51; SEQ ID NOs: 48 and 49; SEQ ID NOs: 48 and 51; SEQ ID NOs: 63 and 67; SEQ ID NOs: 63 and 68.

10. (Currently amended) The antibody or fragment of ~~any one of claims 1-9~~ claim 1, wherein the antibody ~~or fragment~~ is capable of ~~preferentially~~ binding to ~~A isoform of~~ CXCR3 with an affinity constant of from about $1x10^{8}$ M^{-1} to about $1x10^{11}$ M^{-1}.

11. (Currently amended) ~~An isolated nucleic acid encoding the amino acid sequence of the~~ The antibody or fragment of ~~any one of claims 1-10~~ claim 1, wherein the antibody or fragment is capable of neutralizing CXCR3 activity.

12. (Cancel) ~~A method of producing the antibody or fragment of any one of claims 1-1110, comprising culturing a host cell comprising the nucleic acid of claim 11 in a culture medium under conditions suitable to produce the antibody or fragment.~~

~~13~~12. (Currently amended) Use of a CXCR3 neutralizing antibody or fragment thereof for ~~the antibody or fragment according to any one of claims 1-10 to prevent, treat, or reduce method of~~ preventing, treating or reducing the progression of new onset type 1 diabetes (T1D) in a subject, wherein the antibody or fragment thereof comprises the antibody or fragment of claim 1. ~~comprising:~~

~~a) identifying a subject at risk for developing T1D or who has new onset T1D; and~~

~~b) administering an effective amount of the antibody or fragment of any one of claims 1-9[[10]], to the subject.~~

14. (Cancel) ~~The method of claim 13, wherein the antibody or fragment thereof is administered at a dose of about 0.03-3.7 mg/kg/dose.~~

15. (Cancel) ~~The method of any one of claims 13-14, wherein the antibody or fragment thereof is administered at a total dose over all administrations of about 0.16-18 mg/kg.~~

16. (Cancel) ~~A method of treating or reducing the progression of new-onset type 1 diabetes (T1D) comprising:~~

~~a) identifying a human subject having new-onset T1D and having a basal serum C-peptide level of greater than or equal to about 0.2 nmol/L, and/or having a fasting integrated serum C-peptide level during C-peptide stimulation of between about 0.033 and 1.0 nmol/L x min; and~~

~~b) administering about 0.03-3.7 mg/kg/dose of an antibody or fragment of any one of claims 1-10.~~

~~17~~13. (Currently amended) A conjugate comprising the antibody or fragment of ~~any one of claims 1-10~~ claim 1 and at least one additional agent~~, wherein said additional agent is a therapeutic agent, a solubilizing agent, a stabilizing agent, an immunosuppressant, a receptor, or an antigen binding peptide~~.

14. (New) The conjugate of claim 13, wherein the additional agent is a therapeutic agent, a solubilizing agent, a stabilizing agent, an immunosuppressant, a receptor, or an antigen binding peptide.

~~18~~15. (Currently amended) A pharmaceutical composition comprising the antibody or fragment of ~~any one of claims 1-10, or the nucleic acid of claim 11~~ claim 1, and a pharmaceutically acceptable carrier.

~~19~~16. (Currently amended) The pharmaceutical composition of claim ~~18~~15, wherein the composition further comprises at least one additional therapeutic agent ~~selected from the group consisting of a β-cell stimulating agent and, insulin, and an insulin-producing cell~~.

17. (New) The pharmaceutical composition of claim 16, wherein the at least one additional therapeutic agent comprises a β-cell stimulating agent, or insulin.

~~20~~18. (Currently amended) An *in vitro* method of detecting the presence or concentration of CXCR3 in a test sample, comprising contacting the test sample with the antibody or fragment of ~~any one of claims 1-10~~ claim 1 and a detectable label, wherein the presence or concentration of CXCR3 is directly or indirectly correlated with a signal generated by the detectable label.

CLAIMS

1. An antibody or antigen binding fragment capable of binding to Chemokine (C-X-C motif) receptor 3 (CXCR3), the antibody or antigen binding fragment comprising six complementarity determining regions (CDRs): heavy chain variable domain (VH) CDR1, VH CDR2, VH CDR3, light chain variable domain (VL) CDR1, VL CDR2, and VL CDR3,

wherein:

VH CDR1 is selected from the group consisting of:

GISFNDAA (SEQ ID NO: 116),

GFTFTSYA (SEQ ID NO: 172),

GFTFSNYA (SEQ ID NO: 228),

GFTFTSYA (SEQ ID NO: 368), and

GYTFTDYA (SEQ ID NO: 543);

VH CDR2 is selected from the group consisting of:

IRSKINDYGT (SEQ ID NO: 118),

ISHGGSYT (SEQ ID NO: 174),

ISNGGSYT (SEQ ID NO: 230),

ISHGGTYT (SEQ ID NO: 370), and

ISTYNGNT (SEQ ID NO: 545),

VH CDR3 is selected from the group consisting of:

VIDGYGSLAY (SEQ ID NO: 120),

ARHPFYSGNYQGYFDY (SEQ ID NO: 176),

SRPSERSHYYATSQFAY (SEQ ID NO: 232),

ARHPIYSGNYQGYFDY (SEQ ID NO: 372), and

ARFLSLRYFDV (SEQ ID NO: 547),

VL CDR1 is selected from the group consisting of:

SSVISSY (SEQ ID NO: 123),

SGVNY (SEQ ID NO: 179),

SSVSY (SEQ ID NO: 235),

SGVNY (SEQ ID NO: 375), and

SSVIY (SEQ ID NO: 550),

VL CDR2 is selected from the group consisting of:

STS (SEQ ID NO: 125),

FTS (SEQ ID NO: 181),

DTS (SEQ ID NO: 237),

FTS (SEQ ID NO: 377), and

ATS (SEQ ID NO: 552),

and

VL CDR3 is selected from the group consisting of:

QQYSGYPLT (SEQ ID NO: 127),

QQFTSSPYT (SEQ ID NO: 183),

QQWSSSPLT (SEQ ID NO: 239),

QQFTSSPYT (SEQ ID NO: 379), and

QQWSSEPLT (SEQ ID NO: 554).

2. The antibody or fragment of claim 1, wherein the antibody or fragment is chimeric, CDR grafted, mutated, mutated to remove one or more deamidation site, human, humanized, humanized and back-mutated, synthetic, or recombinant.

3. The antibody or fragment of claim 1, wherein the antibody or fragment is capable of binding to a polypeptide comprising a peptide selected from the group consisting of:

a) a peptide comprising residues 1-58 of SEQ ID NO:1;

b) a peptide comprising residues 1-16 of SEQ ID NO:1; and

c) a peptide comprising residues 1-37 of SEQ ID NO:1.

4. The antibody or fragment of claim 1, wherein the antibody or fragment is capable of binding to a polypeptide comprising a peptide selected from the group consisting of:

a) a peptide comprising the amino acid sequence SDHQVLNDAE (SEQ ID NO:71);

b) a peptide comprising the amino acid sequence SDHQVLND (SEQ ID NO:72);

c) a peptide comprising the amino acid sequence DHQVLND (SEQ ID NO:73);

d) a peptide comprising the amino acid sequence VLNDAE (SEQ ID NO:74);

e) a peptide comprising the amino acid sequence VLND (SEQ ID NO:75);
f) a peptide comprising the amino acid sequence XDXXVXNDXX (SEQ ID NO:76);
g) a peptide comprising the amino acid sequence XDXXVXND (SEQ ID NO:77);
h) a peptide comprising the amino acid sequence DXXVXND (SEQ ID NO:78);
i) a peptide comprising the amino acid sequence VXNDXX (SEQ ID NO:79); and
j) a peptide comprising the amino acid sequence VXND (SEQ ID NO:80),
wherein X indicates any amino acid.

5. The antibody or fragment of claim 1, comprising a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises a sequence at least about 90% identical to a sequence selected from the group consisting of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26-33, 38, 40, 42, 44, 46-48, 63-66, 55, 57, 59, and 61; and the light chain variable region comprises a sequence at least about 90% identical to a sequence selected from the group consisting of SEQ ID NO: 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 34-37, 39, 41, 43, 45, 49-54, 67-70, 56, 58, 60, and 62.

6. The antibody or fragment of claim 1, wherein the heavy chain variable region comprises a sequence selected from the group consisting of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26-33, 38, 40, 42, 44, 46-48, 63-66, 55, 57, 59, and 61; and wherein the light chain variable region comprises a sequence selected from the group consisting of SEQ ID NO: 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 34-37, 39, 41, 43, 45, 49-54, 67-70, 56, 58, 60, and 62.

7. The antibody or fragment of claim 1, wherein said antibody or fragment comprises 3 CDRs selected from the group of variable domain CDR sets consisting of:
Clone 12 VH CDR set: SEQ ID NO: 116, SEQ ID NO: 118, and SEQ ID NO: 120;
Clone 12 VL CDR set: SEQ ID NO: 123, SEQ ID NO: 125, and SEQ ID NO: 127;
Clone 135 VH CDR set: SEQ ID NO: 172, SEQ ID NO: 174, and SEQ ID NO: 176;
Clone 135 VL CDR set: SEQ ID NO: 179, SEQ ID NO: 181, and SEQ ID NO: 183;
Clone 4 VH CDR set: SEQ ID NO: 228, SEQ ID NO: 230, and SEQ ID NO: 232;

Clone 4 VL CDR set: SEQ ID NO: 235, SEQ ID NO: 237, and SEQ ID NO: 239;
Clone 53 VH CDR set: SEQ ID NO: 368, SEQ ID NO: 370, and SEQ ID NO: 372;
Clone 53 VL CDR set: SEQ ID NO: 375, SEQ ID NO: 377, and SEQ ID NO: 379;
Clone 82 VH CDR set: SEQ ID NO: 543, SEQ ID NO: 545, and SEQ ID NO: 547; and
Clone 82 VL CDR set: SEQ ID NO: 550, SEQ ID NO: 552, and SEQ ID NO: 554.

8. The antibody or fragment of claim 7, comprising two variable domain CDR sets selected from a group consisting of:

Clone 12 VH CDR set and Clone 12 VL CDR set;
Clone 135 VH CDR set and Clone 135 VL CDR set;
Clone 4 VH CDR set and Clone 4 VL CDR set;
Clone 53 VH CDR set and Clone 53 VL CDR set; and
Clone 82 VH CDR set and Clone 82 VL CDR set.

9. The antibody or fragment of claim 1, wherein the antibody or fragment comprises a combination of heavy chain and light chain variable regions selected from the group consisting of:

SEQ ID NOs: 18 and 19; SEQ ID NOs: 20 and 21; SEQ ID NOs: 22 and 23; SEQ ID NOs: 24 and 25; SEQ ID NOs: 22 and 25; SEQ ID NOs: 24 and 23; SEQ ID NOs: 26 and 34; SEQ ID NOs: 26 and 37; SEQ ID NOs: 27 and 35; SEQ ID NOs: 27 and 36; SEQ ID NOs: 28 and 34; SEQ ID NOs: 22 and 21; SEQ ID NOs: 20 and 23; SEQ ID NOs: 24 and 21; SEQ ID NOs: 20 and 25; SEQ ID NOs: 29 and 23; SEQ ID NOs: 30 and 23; SEQ ID NOs: 31 and 23; SEQ ID NOs: 32 and 23; SEQ ID NOs: 33 and 23; SEQ ID NOs: 2 and 3; SEQ ID NOs: 4 and 5; SEQ ID NOs: 6 and 7; SEQ ID NOs: 8 and 9; SEQ ID NOs: 55 and 56; SEQ ID NOs: 57 and 58; SEQ ID NOs: 59 and 60; SEQ ID NOs: 61 and 62; SEQ ID NOs: 10 and 11; SEQ ID NOs: 12 and 13; SEQ ID NOs: 14 and 15; SEQ ID NOs: 16 and 17; SEQ ID NOs: 38 and 39; SEQ ID NOs: 40 and 41; SEQ ID NOs: 42 and 43 SEQ ID NOs: 44 and 45; SEQ ID NOs: 40 and 43; SEQ ID NOs: 42 and 41; SEQ ID NOs: 42 and 49; SEQ ID NOs: 42 and 50; SEQ ID NOs: 42 and 51; SEQ ID NOs: 42 and 52; SEQ ID NOs: 42 and 53; SEQ ID NOs: 42 and 54; SEQ ID NOs: 46 and 43; SEQ ID NOs: 47 and 43; SEQ ID NOs: 48 and 43; SEQ ID NOs: 40 and 49; SEQ ID NOs: 40 and 51; SEQ

ID NOs: 48 and 49; SEQ ID NOs: 48 and 51; SEQ ID NOs: 63 and 67; SEQ ID NOs: 63 and 68.

10. The antibody or fragment of claim 1, wherein the antibody is capable of binding to CXCR3 with an affinity constant of from about $1x10^{8}$ M^{-1} to about $1x10^{11}$ M^{-1}.

11. The antibody or fragment of claim 1, wherein the antibody or fragment is capable of neutralizing CXCR3 activity.

12. A CXCR3 neutralizing antibody or fragment thereof for preventing, treating or reducing the progression of new onset type 1 diabetes (T1D) in a subject, wherein the antibody or fragment thereof comprises the antibody or fragment of claim 1.

13. A conjugate comprising the antibody or fragment of claim 1 and at least one additional agent.

14. The conjugate of claim 13, wherein the additional agent is a therapeutic agent, a solubilizing agent, a stabilizing agent, an immunosuppressant, a receptor, or an antigen binding peptide.

15. A pharmaceutical composition comprising the antibody or fragment of claim 1, and a pharmaceutically acceptable carrier.

16. The pharmaceutical composition of claim 15, wherein the composition further comprises at least one additional therapeutic agent.

17. The pharmaceutical composition of claim 16, wherein the at least one additional therapeutic agent comprises a β-cell stimulating agent, or insulin.

18. An *in vitro* method of detecting the presence or concentration of CXCR3 in a test sample, comprising contacting the test sample with the antibody or fragment of claim 1

and a detectable label, wherein the presence or concentration of CXCR3 is directly or indirectly correlated with a signal generated by the detectable label.