

Thus, antagonistic antibodies specific for TIGIT that could inhibit TIGIT receptor activity represent an opportunity to decrease the immunosuppressive effect associated with tumour microenvironments and thereby increase antitumor immune response against tumour cells.

SUMMARY

- 5 The present disclosure provides anti-TIGIT antibodies that can decrease the immunosuppressive effect of TIGIT-mediated signalling. In particular, antibodies or antigen binding fragments of the disclosure can inhibit TIGIT-mediated immunosuppression through prevention of ligand binding on T cells (conventional $\alpha\beta$ T cells and non-conventional $\gamma\delta$ T cells) and NK cells and/or depletion of TIGIT positive Treg cells, and/or by inducing internalisation of the TIGIT receptor.
- 10 In one example, the present disclosure provides an isolated antibody or antigen binding fragment thereof which binds to human TIGIT and which comprises a heavy chain variable domain comprising a heavy chain CDR1 (HCDR1), a heavy chain CDR2 (HCDR2), and a heavy chain CDR3 (HCDR3) selected from the HCDR1, HCDR2 and HCDR3 sequences shown in Figure 1 and which further comprises a light chain variable domain comprising a light chain CDR1 (LCDR1), a light chain CDR2 (LCDR2), and a light chain CDR3 (LCDR3) selected from the LCDR1, LCDR2, and LCDR3 sequences shown in Figure 2.

- In certain examples the antibody or antigen binding fragment comprises a combination of HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3, wherein the combination is selected from the group of combinations formed by the HCDRs from each antibody in Figure 1 taken with the LCDRs from the corresponding antibody in Figure 2.

- In certain examples, an antibody or antigen binding fragment according to the disclosure may comprise a heavy chain variable domain having an amino acid sequence selected from the group consisting of: SEQ ID Nos: 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 239, 327, 329, and 331 and amino acid sequences exhibiting at least 90%, 95%, 97%, 98% or 99% sequence identity thereto; and optionally comprise a light chain variable domain having an amino acid sequence selected from the group consisting of: the amino acid sequences of SEQ ID Nos: 212, 214, 216, 218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, 328, 330, and 332 and amino acid sequences exhibiting at least 90%, 95%, 97%, 98% or 99% sequence identity thereto.

- In certain examples the antibody or antigen binding fragment comprises a combination of a heavy chain variable domain and a light chain variable domain, wherein the combination is selected from the group of combinations formed by the VH from each antibody in Figure 5, or an amino acid sequence exhibiting at least 90%, 95%, 97%, 98% or 99% sequence identity thereto, taken with the VL from the same antibody in Figure 5, or an amino acid sequence exhibiting at least 90%, 95%, 97%, 98% or 99% sequence identity thereto.

The most-preferred antibodies and antigen binding fragments provided herein are those based on the CDRs or complete variable domains of antibody 31282 provided herein.

As demonstrated herein, these preferred anti-TIGIT antibodies and antigen binding fragments based on antibody 31282 have particularly surprising and advantageous properties. These properties include: a higher affinity for TIGIT expressed on CD8 T cells (from healthy donors or from cancer patients) compared to each previously described anti-TIGIT antibody tested; a better IC₅₀ for competition with CD155/PVR compared to each previously described anti-TIGIT antibody tested; a better EC₅₀ in T cell activation assays compared to each previously described anti-TIGIT antibody tested; and potentially increasing activity in T cells from cancer patient peripheral blood, and importantly in tumour infiltrating lymphocytes. Furthermore, it is surprisingly shown herein that antibodies and antigen binding fragments according to the disclosure, especially those based on antibody 31282, preferentially deplete Treg cells. That is, TIGIT-expressing Treg cells exposed to the provided anti-TIGIT antibodies undergo lysis to a greater proportion compared to conventional CD4 and CD8 T cells. This is surprising because conventional CD4 and CD8 T cells also express TIGIT, but do not undergo cell lysis to the same extent when contacted with the antibodies. It is further surprisingly shown that antibodies and antigen binding fragments according to the disclosure, especially those based on antibody 31282 not only promote conventional T cell pro-inflammatory activity, but also increase activity of non-conventional $\gamma\delta$ T cells.

Thus, in certain preferred examples, provided herein is an antibody or antigen binding fragment comprising HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 wherein:

HCDR1 comprises or consists of SEQ ID NO: 16 (YTFTSYMH),
HCDR2 comprises or consists of SEQ ID NO: 17 (VIGPSGASTSYAQKFQG),
HCDR3 comprises or consists of SEQ ID NO: 18 (ARDHSDYWWSGIMEV),
LCDR1 comprises or consists of SEQ ID NO: 61 (RASQSVRSSYLA),
LCDR2 comprises or consists of SEQ ID NO: 62 (GASSRAT), and
LCDR3 comprises or consists of SEQ ID NO: 63 (QQYFSPWT).

In one aspect, provided herein is an isolated antibody or antigen binding fragment thereof which binds to human TIGIT, wherein the antibody or antigen binding fragment comprises a combination of HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3, wherein:

HCDR1 comprises SEQ ID NO: 16 (YTFTSYMH),
HCDR2 comprises SEQ ID NO: 17 (VIGPSGASTSYAQKFQG),
HCDR3 comprises SEQ ID NO: 18 (ARDHSDYWWSGIMEV),
LCDR1 comprises SEQ ID NO: 61 (RASQSVRSSYLA),
LCDR2 comprises SEQ ID NO: 62 (GASSRAT), and
LCDR3 comprises SEQ ID NO: 63 (QQYFSPWT).

In certain such examples, the heavy chain variable domain comprises or consists of an amino acid sequence according to SEQ ID NO: 221 or an amino acid sequence exhibiting at least 90%, 95%,

97%, 98% or 99% sequence identity thereto, and the light chain variable domain comprises or consists of an amino acid sequence according to SEQ ID NO: 222 or an amino acid sequence exhibiting at least 90%, 95%, 97%, 98% or 99% sequence identity thereto.

In certain preferred examples the anti-TIGIT antibody is antibody 31282 described herein.

- 5 In a further example the disclosure provides an isolated antibody or antigen binding fragment thereof, which cross-competes for binding to human TIGIT with an antibody according to the first example of the disclosure, for example an antibody exemplified herein.

- In a further example, the disclosure provides an isolated antibody or antigen binding fragment thereof, which binds to the same epitope as an antibody according to the first example of the disclosure, for
10 example an antibody exemplified herein.

- In a further example, the disclosure provides an antibody or antigen binding fragment thereof which binds to an epitope of human TIGIT comprising TIGIT residues Q56, and I109, optionally comprising residues Q56, N58 and I109. In preferred examples is provided an antibody or antigen binding fragment thereof which binds to an epitope of human TIGIT comprising TIGIT residues Q56, N58,
15 E60, I68, L73, H76, and I109.

In certain examples, the antibody or antigen binding fragment thereof binds to an epitope of human TIGIT consisting of TIGIT residues Q56, N58, E60, I68, L73, H76, and I109.

In a further example, the disclosure provides an isolated antibody or antigen binding fragment thereof which binds to human TIGIT and which does not compete with CD155 for TIGIT binding.

- 20 In certain examples, the antibody or antigen binding fragment which binds to human TIGIT and which does not compete with CD155 for TIGIT binding comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 wherein HCDR1 comprises or consists of SEQ ID NO: 280, HCDR2 comprises or consists of SEQ ID NO: 281, HCDR3 comprises or consists of SEQ ID NO: 282, and LCDR1 comprises or consists of SEQ ID NO: 292, LCDR2 comprises or consists of SEQ ID NO: 293, and
25 LCDR3 comprises or consists of SEQ ID NO: 294.

- In certain such examples, the heavy chain variable domain comprises or consists of the amino acid sequence shown as SEQ ID NO: 333 or an amino acid sequence exhibiting at least 90%, 95%, 97%, 98% or 99% sequence identity thereto, and the light chain variable domain comprises or consists of the amino acid sequence shown as SEQ ID NO: 334 or an amino acid sequence exhibiting at least
30 90%, 95%, 97%, 98% or 99% sequence identity thereto.

In certain preferred examples, the antibody which binds to human TIGIT and which does not compete with CD155 for TIGIT binding comprises a heavy chain variable domain and a light chain variable domain wherein HCDR1 comprises SEQ ID NO: 353, HCDR2 comprises SEQ ID NO: 354, HCDR3

comprises SEQ ID NO: 355, and LCDR1 comprises SEQ ID NO: 356, LCDR2 comprises SEQ ID NO: 357, and LCDR3 comprises SEQ ID NO: 358.

In certain such examples, the heavy chain variable domain may comprise the amino acid sequence shown as SEQ ID NO: 367 or an amino acid sequence exhibiting at least 90%, 95%, 97%, 98% or 99% sequence identity thereto, and the light chain variable domain may comprise the amino acid sequence shown as SEQ ID NO: 368 or an amino acid sequence exhibiting at least 90%, 95%, 97%, 98% or 99% sequence identity thereto.

In a further example, the disclosure provides an isolated anti-TIGIT antibody or antigen binding fragment thereof which preferentially depletes TIGIT-expressing Treg cells, optionally wherein the antibody or antigen binding fragment is an antibody or antigen binding fragment according to the first example of the disclosure, for example an antibody exemplified herein..

In a further example the disclosure provides an affinity variant of an antibody according to other examples of the disclosure, for example an antibody exemplified herein.

In a further example the disclosure provides an isolated polynucleotide or combination of isolated polynucleotides encoding an antibody or antigen binding fragment according to any other example of the disclosure, for example an antibody exemplified herein.

In one aspect, provided herein is an isolated polynucleotide or combination of isolated polynucleotides encoding an antibody or antigen binding fragment which binds to human TIGIT, wherein the antibody or antigen binding fragment comprises a combination of HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3, wherein:

HCDR1 comprises SEQ ID NO: 16 (YTFTSYMH),
HCDR2 comprises SEQ ID NO: 17 (VIGPSGASTSYAQKFQG),
HCDR3 comprises SEQ ID NO: 18 (ARDHSDYWSGIMEV),
LCDR1 comprises SEQ ID NO: 61 (RASQSVRSSYLA),
LCDR2 comprises SEQ ID NO: 62 (GASSRAT), and
LCDR3 comprises SEQ ID NO: 63 (QQYFSPWT).

In one aspect, provided herein is an isolated polynucleotide or combination of isolated polynucleotides encoding a VH domain and a VL domain of an anti-TIGIT antibody, wherein the isolated polynucleotide or combination of isolated polynucleotides comprises SEQ ID NO: 251 and SEQ ID NO: 252.

In a further example the disclosure provides an isolated polynucleotide encoding a VH and/or a VL domain of an anti-TIGIT antibody, wherein the polynucleotide comprises one or more sequences selected from the group consisting of SEQ ID Nos: 241-270, 335-342 and 369-370.

In a further example the disclosure provides an expression vector comprising a polynucleotide or combination of polynucleotides according to the disclosure operably linked to regulatory sequences which permit expression of the antigen binding polypeptide in a host cell or cell-free expression system.

- 5 In a further example the disclosure provides a host cell or cell-free expression system containing an expression vector according to the disclosure.

- In a further example the disclosure provides a method of producing a recombinant antibody or antigen binding fragment thereof which comprises culturing a host cell or cell free expression system according to the disclosure under conditions which permit expression of the antibody or antigen
10 binding fragment and recovering the expressed antibody or antigen binding fragment.

In a further example the disclosure provides a pharmaceutical composition comprising an antibody or antigen binding fragment according to the disclosure, for example an antibody exemplified herein, and at least one pharmaceutically acceptable carrier or excipient.

- 15 In a further aspect the disclosure provides an antibody or antigen-binding fragment according to the disclosure or pharmaceutical composition according to the disclosure for use in therapy.

In a further example, the disclosure provides an antibody or antigen-binding fragment according to the disclosure (for example an antibody exemplified herein) or pharmaceutical composition according to the disclosure for use in a method of treating cancer.

- 20 In one aspect, provided herein is a use of an isolated antibody or antigen binding fragment thereof as described herein in the manufacture of a medicament for treating cancer.

In a further example, the disclosure provides an antibody or antigen-binding fragment according to the disclosure (for example an antibody exemplified herein) or pharmaceutical composition according to the disclosure for use in a method of treating viral infection, optionally CMV infection.

- 25 In a further example the disclosure provides a method of treating cancer in a subject comprising administering an effective amount of an antibody or antigen-binding fragment according to the disclosure (for example an antibody exemplified herein) or pharmaceutical composition according to the disclosure to the subject, thereby treating the cancer.

- In a further example is provided a method of treating viral infection in a subject comprising administering an effective amount of an antibody or antigen-binding fragment according to the
30 disclosure or pharmaceutical composition according to the disclosure to the subject,

thereby treating the viral infection. In preferred examples the viral infection is CMV infection.

In a further example is provided a method of promoting T cell activity comprising contacting a population of T cells with an antibody or antigen binding fragment according to the disclosure. In certain examples the method promotes $\alpha\beta$ T cell activity. In certain examples the method promotes $\gamma\delta$ T cell activity. In certain examples the method is performed *in vitro*. In certain examples the method is performed *in vivo*, for example in a human subject.

In certain examples is provided a method according to the disclosure, or an antibody or antigen-binding fragment or pharmaceutical composition for use in a method according to the disclosure, wherein the method further comprises administration of one or more additional therapeutic agents. In certain preferred examples, the one or more additional agents are selected from: a chemotherapeutic agent, an anti-PD1 antibody, an anti-PD-L1 antibody, an anti-41BB antibody, an anti-OX40 antibody, an anti-GITR antibody, and an anti-ICOS antibody.

In a further example is provided a combination comprising an anti-TIGIT antibody or antigen binding fragment thereof and one or more of a chemotherapeutic agent, an anti-PD1 antibody, an anti-PD-L1 antibody, an anti-41BB antibody, an anti-OX40 antibody, an anti-GITR antibody, and an anti-ICOS antibody. In a further example is provided a combination according to the disclosure for use in therapy. In a further example is provided a combination according to the disclosure for use in a method of treating cancer or for use in a method of treating viral infection. In a further example is provided a combination according to the disclosure for use in a method according to the disclosure. In a preferred example the anti-TIGIT antibody or antigen binding fragment thereof is an antibody of the disclosure or an antigen binding fragment thereof.

In all relevant examples, it is preferred that any subject to be treated is a human subject. In all relevant examples it is preferred that cells (e.g. T cells) contacted with antibodies according to the disclosure are human cells (e.g. human T cells).

Unless technically incompatible or indicated to the contrary, any preferred example described can optionally be used in combination with one or more of all other preferred examples.

CLAIMS

1. An isolated antibody or antigen binding fragment thereof which binds to human TIGIT, wherein the antibody or antigen binding fragment comprises a combination of HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3, wherein:

HCDR1 comprises SEQ ID NO: 16 (YTFTSYMH),

HCDR2 comprises SEQ ID NO: 17 (VIGPSGASTSYAQKFQG),

HCDR3 comprises SEQ ID NO: 18 (ARDHSDYWSGIMEV),

LCDR1 comprises SEQ ID NO: 61 (RASQSVRSSYLA),

LCDR2 comprises SEQ ID NO: 62 (GASSRAT), and

LCDR3 comprises SEQ ID NO: 63 (QQYFSPWT).

2. An isolated antibody or antigen binding fragment according to claim 1 comprising a combination of a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain comprises the amino acid sequence shown as SEQ ID NO: 221 or an amino acid sequence exhibiting at least 90%, 95%, 97%, 98% or 99% sequence identity thereto, and the light chain variable domain comprises the amino acid sequence shown as SEQ ID NO: 222 or an amino acid sequence exhibiting at least 90%, 95%, 97%, 98% or 99% sequence identity thereto.
3. An isolated antibody or antigen binding fragment according to claim 1 comprising a combination of a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain comprises the amino acid sequence shown as SEQ ID NO: 219 or an amino acid sequence exhibiting at least 90%, 95%, 97%, 98% or 99% sequence identity thereto, and the light chain variable domain comprises the amino acid sequence shown as SEQ ID NO: 220 or an amino acid sequence exhibiting at least 90%, 95%, 97%, 98% or 99% sequence identity thereto.
4. An antibody or antigen binding fragment according to any one of claims 1-3 which is a human IgG antibody, preferably a human IgG1 antibody.
5. An antibody or antigen binding fragment according to any one of claims 1-4 which selectively depletes TIGIT-expressing Treg cells.

6. An antibody or antigen binding fragment according to any one of claims 1-5 which decreases expression of TIGIT on CD8 T cells and/or on Treg cells by inducing internalization of TIGIT.
7. An isolated polynucleotide or combination of isolated polynucleotides encoding an antibody or antigen binding fragment which binds to human TIGIT, wherein the antibody or antigen binding fragment comprises a combination of HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3, wherein:

HCDR1 comprises SEQ ID NO: 16 (YTFTSYMH),
HCDR2 comprises SEQ ID NO: 17 (VIGPSGASTSYAQKFQG),
HCDR3 comprises SEQ ID NO: 18 (ARDHSDYWSGIMEV),
LCDR1 comprises SEQ ID NO: 61 (RASQSVRSSYLA),
LCDR2 comprises SEQ ID NO: 62 (GASSRAT), and
LCDR3 comprises SEQ ID NO: 63 (QQYFSPWT).
8. An isolated polynucleotide or combination of isolated polynucleotides encoding a VH domain and a VL domain of an anti-TIGIT antibody, wherein the isolated polynucleotide or combination of isolated polynucleotides comprises SEQ ID NO: 251 and SEQ ID NO: 252.
9. An isolated antibody or antigen binding fragment thereof according to any one of claims 1-6, for use in therapy.
10. Use of an isolated antibody or antigen binding fragment thereof according to any one of claims 1-6, in the manufacture of a medicament for treating cancer.
11. The use according to claim 10, wherein the antibody or antigen binding fragment is to be administered to a subject in need thereof and wherein one or more additional therapeutic agents are to be further administered.
12. The use according to claim 11, wherein the one or more therapeutic agents are selected from: a chemotherapeutic agent, an anti-PD1 antibody, an anti-PD-L1

antibody, an anti-41BB antibody, an anti-OX40 antibody, an anti-GITR antibody, and an anti-ICOS antibody.