

WO2020/136218 also discloses fragments derived from Fab fragment of an anti-BTN3A antibody mAb103.2 and their use as BTN3A activating antibody for inducing the proliferation and cytokine secretion of V γ 9V δ 2 T cells

5 However, to the knowledge of the inventors, there is no evidence of a plausible use of an activating compound of V γ 9V δ 2 T cells, and in particular, BTN3A activating antibodies, as for treating infectious disorders caused by *Coxiella burnetii* or SARS-Cov2.

The inventors have now surprisingly found that treatments with BTN3A activating antibodies such as treatment with mAb 20.1 enhances V γ 9V δ 2 T cell responses against SARS-CoV-2 and *Coxiella burnetii* infected cells in particular to diminish viral and bacterial load,
10 respectively.

SUMMARY

A first aspect of the disclosure relates to an isolated BTN3A activating antibody comprising a variable heavy chain polypeptide VH at least 95% identical to SEQ ID NO:1 and a variable light chain polypeptide VL at least 95% identical to SEQ ID NO:2 and comprising HCDRs1-3 of SEQ
15 ID NO:5-7 and LCDRs1-3 of SEQ ID NO:8-10.

Another aspect of the disclosure relates to a nucleic acid molecule encoding the heavy and light chains of a BTN3A activating antibody according to any one of claims 1 to 3.

A further aspect of the disclosure relates to an expression vector comprising at least one nucleic acid as described herein.

20 Yet another aspect of the disclosure relates to a host cell comprising an expression vector as described herein.

Another aspect of the disclosure relates to a pharmaceutical composition comprising an anti-BTN3A antibody as described herein, in combination with one or more of a pharmaceutically acceptable excipient, diluent or carrier, optionally comprising other active ingredients, for
25 example a cytokine, such as IL-2 or IL-15, or their functional derivatives and pegylated versions.

Yet another aspect of the disclosure relates to use of a BTN3A activating antibody in the manufacture of a medicament for treating infectious disorders in a human subject in need thereof, preferably selected from the group consisting of (i)

disorder caused by SARS-Cov2 infection, typically COVID-19, and (ii) disorder caused by *Coxiella Burnetii* infection, typically Q fever.

In specific examples, said BTN3A activating antibody is mAb 20.1 or a humanized form of mAb 20.1.

- 5 Another example of the disclosure relates to novel humanized forms of mAb 20.1 or their pharmaceutical compositions, in particular for their use in treating disorders caused by SARS-Cov2 infection or *Coxiella Burnetii* infection.

Other specific aspects and specific embodiments are disclosed hereafter.

LEGENDS OF THE FIGURES

- 10 **Figure 1. Expression BTN2A and BTN3A in response to SARS-CoV-2- infection in monocytes, MDMs and lung epithelial cell lines**

(A, B) Monocytes, MDMs, BEAS-2B and MRC-5 cells were stimulated with SARS-CoV-2 IHU-MI6 strain (1 MOI) for 24 hours. Mean fluorescence intensity (MFI) of BTN2A (**A**) and BTN3A (**B**) expression was investigated on healthy donor monocytes and MDMs, as well as lung epithelial cell lines BEAS-2B and MRC-5 (n=3). The gene expression of the two BTN2A isoforms (A1, A2) (**A**) and the three BTN3A isoforms (A1, A2, A) (**B**) was investigated by qRT-PCR after normalization with housekeeping gene as endogenous control. Relative expression

CLAIMS

1. An isolated BTN3A activating antibody comprising a variable heavy chain polypeptide VH at least 95% identical to SEQ ID NO:1 and a variable light chain polypeptide VL at least 95% identical to SEQ ID NO:2 and comprising HCDRs1-3 of SEQ ID NO:5-7 and LCDRs1-3 of SEQ ID NO:8-10.
2. The BTN3A activating antibody of claim 1, comprising a variable heavy chain polypeptide VH of SEQ ID NO: 1 and a variable light chain polypeptide VL of SEQ ID NO: 2.
3. The BTN3A activating antibody of claim 1 or 2, comprising a heavy chain polypeptide of SEQ ID NO:23 and a light chain polypeptide of SEQ ID NO:24.
4. A nucleic acid molecule encoding the heavy and light chains of a BTN3A activating antibody according to any one of claims 1 to 3.
5. An expression vector comprising at least one nucleic acid according to claim 4.
6. A host cell comprising an expression vector according to claim 5.
7. A pharmaceutical composition comprising an anti-BTN3A antibody according to any one of claims 1 to 4, in combination with one or more of a pharmaceutically acceptable excipient, diluent or carrier, optionally comprising other active ingredients, for example a cytokine, such as IL-2 or IL-15, or their functional derivatives and pegylated versions.
8. The BTN3A activating antibody of any one of claims 1 to 4 or the pharmaceutical composition of claim 7, for use as a therapeutic.
9. Use of a BTN3A activating antibody in the manufacture of a medicament for treating infectious disorders in a human subject in need thereof, preferably selected from the group consisting of (i) disorder caused by SARS-Cov2 infection, typically COVID-19, and (ii) disorder caused by *Coxiella burnetii* infection, typically Q fever.
10. The use according to claim 9, wherein said BTN3A activating antibody has one or more of the following properties:
 - (i) it binds to human PBMCs with an EC₅₀ of 50 µg/ml or below, preferably of 10 µg/ml or below, as measured in a flow cytometry assay;
 - (ii) it induces in vitro the activation of γδ-T cells, typically Vγ9Vδ2 T cells, in co-culture with BTN3A expressing cells, with an EC₅₀ below 5 µg/ml, preferably of 1 µg/ml or below, as measured with a degranulation assay;

- (iii) it potentiates in vitro the reduction of *C. burnetii* bacterial load, as measured in vitro with co-cultures of monocytes in the presence of V γ 9V δ 2 T cells;
- (iv) it increases in vitro cytotoxic activity of V γ 9V δ 2 T cells towards *C. burnetii* infected cells, as measured in vitro with co-cultures of infected monocytes, typically after 4 hours of co-culture; and/or
- (v) it increases in vitro cytotoxic activity of V γ 9V δ 2 T cells towards SARS-Cov2 infected cells as measured in vitro in co-cultures of infected cells with V γ 9V δ 2 T cells.

11. The use according to claim 9 or 10, wherein said BTN3A activating antibody either

- (i) comprises HCDRs1-3 of SEQ ID NO:5-7 and LCDRs1-3 of SEQ ID NO:8-10;
- (ii) comprises HCDRs1-3 of SEQ ID NO:11-13 and LCDRs1-3 of SEQ ID NO:14-16;
- (iii) comprises HCDRs1-3 of SEQ ID NO:17-19 and LCDRs1-3 of SEQ ID NO:20-22;
- (iv) comprises a variable heavy chain (VH) polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:1, and a variable light chain (VL) polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to of SEQ ID NO: 2;
- (v) comprises a variable heavy chain (VH) polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:3, and a variable light chain (VL) polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to of SEQ ID NO: 4;
- (vi) comprises a heavy chain of SEQ ID NO: 23 and a light chain of SEQ ID NO: 24;
- (vii) competes for binding with mAb 20.1 as produced by the hybridoma deposited at the CNCM under deposit number I-4401, or
- (viii) competes for binding with mAb 7.2 as produced by the hybridoma deposited at the CNCM under deposit number I-4402.

12. The use according to any one of claims 9-11, wherein said BTN3A activating antibody comprises a mutant or chemically modified IgG1 constant region, wherein said mutant or chemically modified IgG1 constant region confers no or decreased binding to Fc γ receptors when compared to a corresponding antibody with wild type IgG1 isotype constant region, preferably wherein said BTN3A activating antibody comprises mutant IgG1 constant region which is an IgG1 triple mutant Fc with mutations L247F L248E and P350S.

13. The use according to any one of claims 9-12, wherein the infectious disorder is a disorder caused by SARS-Cov2 infection, wherein:

- said BTN3A activating antibody is to be administered in combination, simultaneously or separately with a second drug substance such as an antiviral treatment, an anti-inflammatory treatment or a cell therapy product, preferably wherein the second drug substance is selected from the group consisting of remdesivir, baricitinib, bamlanivimab, bamlanivimab/etesevimab, casirivimab/imdevimab, dexamethasone, budesonide and tocilizumab;
- said subject is a human subject who had been diagnosed as being SARS-Cov2 positive; and/or
- said subject is a human subject who has mild or moderate COVID-19, or is at high risk of progressing to severe COVID-19, or is having severe COVID-19.

14. The use according to any one of claims 9-12, wherein the infectious disorder is a disorder caused by *Coxiella Burnetii* infection, wherein:

- said BTN3A antibody is to be administered in combination, simultaneously or separately with a second drug substance, such as an antibacterial treatment or a cell therapy product, in particular wherein the second drug substance is selected from antibiotics, preferably selected from doxycycline, tetracycline, chloramphenicol, ciprofloxacin, ofloxacin, and hydroxychloroquine;
- said subject had been diagnosed as being positive for *Coxiella Burnetii* infection; and/or
- said subject has Q fever.

15. The use according to any one of claims 9-14, wherein said medicament is to be administered to the subject in need thereof, by intravenous infusion, preferably at a dose comprised between 1mg and 1 g, for example at a dose comprised between 1 mg and 200 mg.