

January 18, 2021

The European Patent Office
International Searching Authority
P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
The Netherlands

Submitted online

Re: PCT Application No. PCT/IL2020/050889
Filed: August 12, 2020
Our Ref.: BDB-P-002-PCT
Applicant: BIOND BIOLOGICS LTD.

Dear Sirs,

We hereby request correction of the following obvious errors according to Rule 91.1 under the PCT in the above referenced PCT application.

Rectification of the Description and Sequence Listing:

- The correct sequence of SEQ ID NO: 28 is:
DVQLQGSGPGLVKPSETLSLTCSVTGYSITSGYYWNWIRQFPGKKLEWMGYISYDGS
NNYNPSLKNRITISRDTSKNQFSLKLNSVTAADTATYYCAHGYSYYYAMDAWGQGT
SVTVSS. This sequence has an S at position 75 and not a D, it has only a single S at position 114 and not a second S directly after, and it ends in SS at positions 118 and 119.
This exact sequence is provided in Figure 6 (Figure 6 continued_1, top sequence) and is called “15G8 heavy chain variable region (Human)”. Within Figure 6 this sequence is labeled as SEQ ID NO: 28. Paragraph [0208] of the instant application states that “The sequences of the selected antibodies are indicated in **Figure 6**.” This heavy chain is the heavy chain of the 15G8 antibody that is used throughout the experimental section of the application.

Instances in the application in which SEQ ID NO: 28 was incorrectly written with a D at position 75, with an extra S after position 114 and without the SS at positions 118 and 119

were typos caused by confusion between antibody sequences of the other antibodies of the invention and the murine version of this antibody. Applicants deeply regret these typos.

- The correct sequence of SEQ ID NO: 23 is:
DVQLQGSGPGLVKPSETLSLTCSVTGYSITSGYYWNWIRQFPGKKLEWMGYISYDGS
NNYNPSLKNRITISRDTSKNQFSLKLNSVTAADTATYYCAHGYSYYYAMDXWGQGT
SVTVSS. This sequence is identical to the corrected SEQ ID NO: 28 except that amino acid 108 is an X and not an A and that the X can be any of C, A and S.
Paragraph [0208] of the instant application describes the generation of the antibodies. It states that “The sequences of the selected antibodies are indicated in **Figure 6**.” It further states that during humanization “The final humanized 15G8 also contained a single amino acid change, removing the cysteine in CDR-H3 and replace it with alanine or serine.” This means that there were three variants of the 15G8 antibody, all with the same backbone and one each with a C, an A or an S within CDR-H3. The sequence of CDR-H3, SEQ ID NO: 15, is given in many places in the application, and it is clear that the variable amino acid in question is amino acid 108. The 15G8 variant with an A at position 108 is given in Figure 6 (SEQ ID NO: 28). It is therefore clear from a combination of Figure 6 and paragraph [0208] that SEQ ID NO: 23 should have the same sequence as SEQ ID NO: 28, but with an X at position 108. Thus, the corrected sequence provided above is fully supported.

Applicants regret the typos that were also included in SEQ ID NO: 23. The same typos occur in both sequences as they are essentially the same sequence but with a single amino acid change.

- The correct sequence for SEQ ID NO: 29 is:
DVQLQGSGPGLVKPSETLSLTCSVTGYSITSGYYWNWIRQFPGKKLEWMGYISYDGS
NNYNPSLKNRITISRDTSKNQFSLKLNSVTAADTATYYCAHGYSYYYAMDSWGQGT
SVTVSS. This sequence is identical to the corrected SEQ ID NO: 28 except that amino acid 108 is an S and not an A.
The support for this sequence is the same as for SEQ ID NO: 23 as explained above. SEQ ID NO: 23 was the generic sequence with the option of three different amino acids at position 108. SEQ ID NO: 29 is the specific variant with an S at this position.

We hereby submit a corrected version of the Sequence Listing in TXT and replacement sheets of pages 3, 21, 22 of the description and 66 of the claims, embodying the requested rectifications.

The applicant states that at the applicable date and with respect to the amended sections as described herein above, it is clear that something else was intended than what appears in the application as filed and that nothing else could have been intended than the proposed rectifications.

Yours sincerely,

A handwritten signature in blue ink, appearing to read 'D. Kesten'.

Dov Kesten

GEYRA KESTEN

Attorneys at Law, Patent Attorneys

Encl.:

Corrected version of the Sequence Listing in TXT

Marked up pages 3, 21, 22, 66

Replacement pages 3, 21, 22, 66

(QVQLQQSDAELVKPGASVKISCKVSGYTFTDHTIHWMKQRPEQGLEWIGYIYPRDGSTK
YNEKFKGKATLTADKSSSTAYMQLNSLTSEDSAVYFCARTWDYFDYWGQGTTTLTVSS),

SEQ ID NO: 21

(QVQLQQSGAELARPGASVKLSCKASGYTFTSYGISWVKQRTGQGLEWVGEIYPGSGNSY
YNEKFKGKATLTADKSSSTAYMELRSLTSEDSAVYFCARSNDGYPDYWGQGTTTLTVSS)

and SEQ ID NO: 23

(DVQLQGSGPGLVKPSETLSLTCSVTGYSITSGYYWNWIRQFPGKKLEWMGYISYDGSNN
YNPSLKNRITISRDTSDKNQFSLKLNSVTAADTATYYCAHGYSYYYAMDXWGQGTSSVT
VSS) , wherein the X is selected from A, C and S.

[008] According to some embodiments, the antibody or antigen binding fragment of the invention comprises a light chain comprising an amino acid sequence selected from: SEQ ID NO: 20
(DIVLTQSPASLAVSLGQRATISCRASESVDSYGNFMHWYQQKPGQPPKLLIYRASNLES
GIPARFSGSGSRTDFTLTINPVEADDVATYYCQQSNEDPYTFGGGTKLEIK), SEQ ID NO:
22

(DIQMTQSSSYLSVSLGGRVTITCKASDHINNWLAWYQQKPGNAPRLLISGATSLETGVPS
RFSGSGSGKDYTLSTSLQTEDVATYYCQQYWSTPWTFGGGTKLEIK), SEQ ID NO: 24
(DIQMTQSPSSLSASVGDRVTITCRTSQDISNYLNWYQQKPGKAVKLLISYTSRLHSGVPSR
FSGSGSGTDYTLTISSLQPEDFATYYCQQGNTLPTFGGGTKLEIK) and SEQ ID NO: 45
(DIQMTQTTSSLSASLGDRVTISCRTSQDISNYLNWYQQKPDGTVKLLISYTSRLHSGVPSR
FSGSGSGTDYSLTISNLEQEDIATYFCQQGNTLPTFGSGGTKLEIK).

[009] According to some embodiments, the antibody or antigen binding fragment is humanized, and the X is selected from A and S.

[010] According to some embodiments, the X is A, SEQ ID NO: 15 is GYSYYYAMDA (SEQ ID
NO: 25) and SEQ ID NO: 23 is
DVQLQGSGPGLVKPSETLSLTCSVTGYSITSGYYWNWIRQFPGKKLEWMGYISYDGSNN
YNPSLKNRITISRDTSDKNQFSLKLNSVTAADTATYYCAHGYSYYYAMDAWGQGTSSVT
VSS (SEQ ID NO: 28).

[011] According to another aspect, there is provided a monoclonal antibody or antigen binding fragment that binds a human leukocyte immunoglobulin-like receptor subfamily B member 1 (ILT2) epitope within a sequence of human ILT2 selected from VKKGQFPIPSITWEH (SEQ ID NO: 41), LELVVTGAYIKPTLS (SEQ ID NO: 42), VILQCDSQVAFDGFS (SEQ ID NO: 43) and WYRCYAYDSNSPYEW (SEQ ID NO: 44).

disclosed herein can be said to bind a target antigen with an affinity of 10^{-6} M or greater, whereas most antibodies have typical affinities of 10^{-9} M.

[0101] In some embodiments, the antibody or antigen binding fragment comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 19 (QVQLQQSDAELVKPGASVKISCKVSGYTFTDHTIHWMKQRPEQGLEWIGYIYPRDGSTKYNEKFKGKATLTADKSSSTAYMQLNSLTSEDSAVYFCARTWDYFDYWGQGTTTLTVSS).

In some embodiments, the antibody or antigen binding fragment comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 21 (QVQLQQSGAELARPGASVKLSCKASGYTFTSYGISWVKQRTGQGLEWVGEIYPGSGNSY YNEKFKGKATLTADKSSSTAYMELRSLTSEDSAVYFCARSNDGYPDYWGQGTTTLTVSS).

In some embodiments, the antibody or antigen binding fragment comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 23 (DVQLQGSGPGLVKPSETLSLTCSVTGYSTITSGYYWNWIRQFPGKKLEWMGYISYDGSNN YNPSLKNRITISRDTSDKNQFSLKLNSVTAADTATYYCAHGYSYYYAMDXWGQGTSSVT VSS), wherein X is selected from A, C and S.

[0102] In some embodiments, the antibody or antigen binding fragment comprises a light chain comprising the amino acid sequence of SEQ ID NO: 20 (DIVLTQSPASLAVSLGQRATISCRASESVDSYGNSFMHWYQQKPGQPPLLIYRASNLSEGI PARFSGSGSRTDFTLTINPVEADDVATYYCQQSNEDPYTFGGGTKLEIK). In some

embodiments, the antibody or antigen binding fragment comprises a light chain comprising the amino acid sequence of SEQ ID NO: 22 (DIQMTQSSSYLSVSLGGRVTITCKASDHINNWLAWYQQKPGNAPRLLISGATSLETGVPS RFGSGSGGKDYTLTSLQTEDVATYYCQQYWSTPWFPGGTKLEIK). In some

embodiments, the antibody or antigen binding fragment comprises a light chain comprising the amino acid sequence of SEQ ID NO: 24 (DIQMTQSPSSLSASVGDRVTITCRTSQDISNYLNWYQQKPGKAVKLLISYTSRLHSGVPSRF SGSGSGTDYTLTISSLQPEDFATYYCQQGNTLPTFGQGTKLEIK). In some embodiments, the

antibody or antigen binding fragment comprises a light chain comprising the amino acid sequence of SEQ ID NO: 45 (DIQMTQTTSSLSASLGDRVTISCRTSQDISNYLNWYQQKPDGTVKLLISYTSRLHSGVPSRF SGSGSGTDYSLTISNLEQEDIATYFCQQGNTLPTFGSGGTKLEIK).

[0103] In some embodiments, SEQ ID NO: 23 is DVQLQGSGPGLVKPSETLSLTCSVTGYSTITSGYYWNWIRQFPGKKLEWMGYISYDGSNN

YNPSLKNRITISRDT~~S~~DKNQFSLKLNSVTAADTATYYCAHGYSYYYAMDAWGQGTSSVT
VSS (SEQ ID NO: 28). In some embodiments, SEQ ID NO: 23 is SEQ ID NO: 28 and the antibody
or antigen binding fragment is humanized. In some embodiments, SEQ ID NO: 23 is
DVQLQGSGPGLVKPSETLSLTCSVTGYSITSGYYWNWIRQFPGKKLEWMGYISYDGSNN
YNPSLKNRITISRDT~~S~~DKNQFSLKLNSVTAADTATYYCAHGYSYYYAMDSWGQGTSSVT
VSS (SEQ ID NO: 29). In some embodiments, SEQ ID NO: 23 is SEQ ID NO: 29 and the antibody
or antigen binding fragment is humanized. In some embodiments, SEQ ID NO: 23 is
DVQLQGSGPGLVKPSQSLSLTCSVTGYSITSGYYWNWIRQFPGNKLEWMGYISYDGSNN
YNPSLKNRISITRDTSKNQFFLKLNSVTSEDTATYYCAHGYSYYYAMDCWGQGTSTVTVSS
(SEQ ID NO: 30). In some embodiments, SEQ ID NO: 23 is SEQ ID NO: 30 and the antibody or
antigen binding fragment is murine.

[0104] In some embodiments, the antibody or antigen binding fragment of the invention is for use
in treating or ameliorating cancer in a subject in need thereof. In some embodiments, the cancer is
an HLA-G positive cancer. In some embodiments, the cancer is an MHC-I positive cancer. In some
embodiments, the cancer is an HLA-G expressing cancer. In some embodiments, the cancer is an
MHC-I expressing cancer. In some embodiments, an antibody or antigen binding fragment of the
invention is for use in shifting a tumor microenvironment from immunosuppressive to immuno-
stimulatory. In some embodiments, said shifting the tumor microenvironment comprises one or
more of: inducing/enhancing an anti-tumor T-cell response, increasing T-cell proliferation, reducing
cancer-induced suppressor myeloid activity, increasing dendritic cell (DC) activation, increasing
dendritic cell homing to the tumor, increasing macrophage phagocytosis, increasing generation of
M1 macrophages, decreasing generation of M2 macrophages and increasing NK cell activity. In
some embodiments, antibody or antigen binding fragment of the invention is for use in increasing a
T-cell response against a cancer cell. In some embodiments, the T cell response comprises increased
pro-inflammatory cytokine secretion. In some embodiments, T cell response comprises increased
cytotoxicity. In some embodiments, the T cell response comprises increased T cell proliferation. In
some embodiments, antibody or antigen binding fragment of the invention is for use in increasing
macrophage phagocytosis of a cancer cell. In some embodiments, antibody or antigen binding
fragment of the invention is for use increasing dendritic cell homing to a tumor or cancer. In some
embodiments, antibody or antigen binding fragment of the invention is for use in increasing
macrophage phagocytosis. In some embodiments, antibody or antigen binding fragment of the
invention is for use increasing macrophage phagocytosis of the cancer. In some embodiments,
antibody or antigen binding fragment of the invention is for use in increasing generation of M1

(DVQLQGSGPGLVKPSETLSLTCSVTGYSITSGYYWNWIRQFPGKKLEWMGYISYDGSNN YNPSLKNRITISRDT~~S~~DKNQFSLKLNSVTAADTATYYCAHGYSYYYAMDXWGQGTSS~~V~~TVSS) , wherein said X is selected from A, C and S.

3. The antibody or antigen binding fragment of claim 1 or 2, comprising a light chain comprising an amino acid sequence selected from: SEQ ID NO: 20 (DIVLTQSPASLAVSLGQRATISCRASESVDSYGNSFMHWYQQKPGQPPLLIYRASNLSEGI PARFSGSGSRTDFTLTINPVEADDVATYYCQQSNEDPYTFGGGTKLEIK), SEQ ID NO: 22 (DIQMTQSSSYLSVSLGGRVTITCKASDHINNWLAWYQQKPGNAPRLISGATSLETGVPS RFSGSGSGKDYTLSTSLQTEDVATYYCQQYWSTPWTFGGGTKLEIK), SEQ ID NO: 24 (DIQMTQSPSSLSASVGDRVTITCRTSQDISNYLNWYQQKPGKAVKLLISYTSRLHSGVPSRF SGSGSGTDYTLTISSLQPEDFATYYCQQGNTLPTFGQGTKLEIK) and SEQ ID NO: 45 (DIQMTQTTSSLSASLGDRVTISCRTSQDISNYLNWYQQKPDGTVKLLISYTSRLHSGVPSRF SGSGSGTDYSLTISNLEQEDIATYFCQQGNTLPTFGSGGTKLEIK).

4. The antibody or antigen binding fragment of any one of claims 1 to 3, wherein said antibody or antigen binding fragment is humanized and said X is selected from A and S.

5. The antibody or antigen binding fragment of any one of claim 4, wherein said X is A, SEQ ID NO: 15 is GYSYYYAMDA (SEQ ID NO: 25) and SEQ ID NO: 23 is DVQLQGSGPGLVKPSETLSLTCSVTGYSITSGYYWNWIRQFPGKKLEWMGYISYDGSNN YNPSLKNRITISRDT~~S~~DKNQFSLKLNSVTAADTATYYCAHGYSYYYAMDAWGQGTSS~~V~~TVSS (SEQ ID NO: 28).

6. A monoclonal antibody or antigen binding fragment that binds a human leukocyte immunoglobulin-like receptor subfamily B member 1 (ILT2) epitope within a sequence of human ILT2 selected from VKKGQFPIPSITWEH (SEQ ID NO: 41), LELVVTGAYIKPTLS (SEQ ID NO: 42), VILQCDSQVAFDGFs (SEQ ID NO: 43) and WYRCYAYDSNSPYEW (SEQ ID NO: 44).

7. The antibody or antigen binding fragment of claim 6, wherein said epitope is a 3-dimensional epitope comprising SEQ ID NO: 41, 42, 43 and 44.

8. A monoclonal antibody or antigen binding fragment that binds ILT2 and inhibits direct interaction between said ILT2 and beta-2-microglobulin (B2M).

9. The antibody or antigen binding fragment of claim 8, wherein said antibody or antigen binding fragment inhibits interaction of said ILT2 and an HLA protein or MHC-I protein via said inhibition of ILT2 direct interaction with B2M.

(QVQLQQSDAELVKPGASVKISCKVSGYTFTDHTIHWMKQRPEQGLEWIGYIYPRDGSTK
YNEKFKGKATLTADKSSSTAYMQLNSLTSEDSAVYFCARTWDYFDYWGQGTTTLTVSS),

SEQ ID NO: 21

(QVQLQQSGAELARPGASVKLSCKASGYTFTSYGISWVKQRTGQGLEWVGEIYPGSGNSY
YNEKFKGKATLTADKSSSTAYMELRSLTSEDSAVYFCARSNDGYPDYWGQGTTTLTVSS)

and SEQ ID NO: 23

(DVQLQGSGPGLVKPSETLSLTCSVTGYSITSGYYWNWIRQFPGKKLEWMGYISYDGSNN
YNPSLKNRITISRDTSKNQFSLKLNSVTAADTATYYCAHGYSYYYAMDXWGQGTSTVTS

S) , wherein the X is selected from A, C and S.

[008] According to some embodiments, the antibody or antigen binding fragment of the invention comprises a light chain comprising an amino acid sequence selected from: SEQ ID NO: 20

(DIVLTQSPASLAVSLGQRATISCRASESVDSYGNFMHWYQQKPGQPPKLLIYRASNL
GIPARFSGSGSRTDFTLTINPVEADDVATYYCQQSNEDPYTFGGGTKLEIK), SEQ ID NO:

22

(DIQMTQSSSYLSVSLGGRVTITCKASDHINNWLAWYQQKPGNAPRLISGATSLETGVPS
RFSGSGSGKDYTLSTSLQTEDVATYYCQYWPWFPGGGGTKLEIK), SEQ ID NO: 24

(DIQMTQSPSSLSASVGDRVTITCRTSQDISNYLNWYQQKPGKAVKLLISYTSRLHSGVPSR
FSGSGSGTDYTLTISSLQPEDFATYYCQQGNTLPTFGGGTKLEIK) and SEQ ID NO: 45

(DIQMTQTTSSLSASLGDRVTISCRTSQDISNYLNWYQQKPDGTVKLLISYTSRLHSGVPSR
FSGSGSGTDYSLTISNLEQEDIATYFCQQGNTLPTFGSGGTKLEIK).

[009] According to some embodiments, the antibody or antigen binding fragment is humanized, and the X is selected from A and S.

[010] According to some embodiments, the X is A, SEQ ID NO: 15 is GYSYYYAMDA (SEQ ID NO: 25) and SEQ ID NO: 23 is

DVQLQGSGPGLVKPSETLSLTCSVTGYSITSGYYWNWIRQFPGKKLEWMGYISYDGSNN
YNPSLKNRITISRDTSKNQFSLKLNSVTAADTATYYCAHGYSYYYAMDAWGQGTSTVTS
S (SEQ ID NO: 28).

[011] According to another aspect, there is provided a monoclonal antibody or antigen binding fragment that binds a human leukocyte immunoglobulin-like receptor subfamily B member 1 (ILT2) epitope within a sequence of human ILT2 selected from VKKGQFPIPSITWEH (SEQ ID NO: 41), LELVVTGAYIKPTLS (SEQ ID NO: 42), VILQCDSQVAFDGFS (SEQ ID NO: 43) and WYRCYAYDSNSPYEW (SEQ ID NO: 44).

disclosed herein can be said to bind a target antigen with an affinity of 10^{-6} M or greater, whereas most antibodies have typical affinities of 10^{-9} M.

[0101] In some embodiments, the antibody or antigen binding fragment comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 19 (QVQLQQSDAELVKPGASVKISCKVSGYTFTDHTIHWMKQRPEQGLEWIGYIYPRDGSTKYNEKFKGKATLTADKSSSTAYMQLNSLTSEDSAVYFCARTWDYFDYWGQGTTTLTVSS).

In some embodiments, the antibody or antigen binding fragment comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 21 (QVQLQQSGAELARPGASVKLSCKASGYTFTSYGISWVKQRTGQGLEWVGEIYPGSGNSY YNEKFKGKATLTADKSSSTAYMELRSLTSEDSAVYFCARSNDGYPDYWGQGTTTLTVSS).

In some embodiments, the antibody or antigen binding fragment comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 23 (DVQLQGSGPGLVKPSETLSLTCSVTGYSTITSGYYWNWIRQFPGKKLEWMGYISYDGSNNYNPSLKNRITISRDTSKNQFSLKLNSVTAADTATYYCAHGYSYYYAMDXWGQGTSVTVSS), wherein X is selected from A, C and S.

[0102] In some embodiments, the antibody or antigen binding fragment comprises a light chain comprising the amino acid sequence of SEQ ID NO: 20 (DIVLTQSPASLAVSLGQRATISCRASESVDSYGNSFMHWYQQKPGQPPLLIYRASNLSEGI PARFSGSGSRTDFTLTINPVEADDVATYYCQQSNEDPYTFGGGTKLEIK). In some

embodiments, the antibody or antigen binding fragment comprises a light chain comprising the amino acid sequence of SEQ ID NO: 22 (DIQMTQSSSYLSVSLGGRVTITCKASDHINNWLAWYQQKPGNAPRLLISGATSLETGVPSRFSGSGSGKDYTLTSLQTEDVATYYCQQYWSTPWFPGGTKLEIK). In some

embodiments, the antibody or antigen binding fragment comprises a light chain comprising the amino acid sequence of SEQ ID NO: 24 (DIQMTQSPSSLSASVGDRVTITCRTSQDISNYLNWYQQKPGKAVKLLISYTSRLHSGVPSRFSGSGSGTDYTLTISSLQPEDFATYYCQQGNTLPTFGQGTKLEIK). In some embodiments, the

antibody or antigen binding fragment comprises a light chain comprising the amino acid sequence of SEQ ID NO: 45 (DIQMTQTTSSLSASLGDRVTISCRTSQDISNYLNWYQQKPDGTVKLLISYTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTLPTFGSGGTKLEIK).

[0103] In some embodiments, SEQ ID NO: 23 is DVQLQGSGPGLVKPSETLSLTCSVTGYSTITSGYYWNWIRQFPGKKLEWMGYISYDGSNN

YNPSLKNRITISRDTSKNQFSLKLNSVTAADTATYYCAHGYSYYYAMDAWGQGTSVTVS
S (SEQ ID NO: 28). In some embodiments, SEQ ID NO: 23 is SEQ ID NO: 28 and the antibody or antigen binding fragment is humanized. In some embodiments, SEQ ID NO: 23 is DVQLQGSGPGLVKPSETLSLTCSVTGYSITSGYYWNWIRQFPGKKLEWMGYISYDGSNN
YNPSLKNRITISRDTSKNQFSLKLNSVTAADTATYYCAHGYSYYYAMDSWGQGTSVTVS
S (SEQ ID NO: 29). In some embodiments, SEQ ID NO: 23 is SEQ ID NO: 29 and the antibody or antigen binding fragment is humanized. In some embodiments, SEQ ID NO: 23 is DVQLQGSGPGLVKPSQSLSLTCSVTGYSITSGYYWNWIRQFPGNKLEWMGYISYDGSNN
YNPSLKNRISITRDTSKNQFFLKLNSVTSEDTATYYCAHGYSYYYAMDCWGQGTSVTVSS
(SEQ ID NO: 30). In some embodiments, SEQ ID NO: 23 is SEQ ID NO: 30 and the antibody or antigen binding fragment is murine.

[0104] In some embodiments, the antibody or antigen binding fragment of the invention is for use in treating or ameliorating cancer in a subject in need thereof. In some embodiments, the cancer is an HLA-G positive cancer. In some embodiments, the cancer is an MHC-I positive cancer. In some embodiments, the cancer is an HLA-G expressing cancer. In some embodiments, the cancer is an MHC-I expressing cancer. In some embodiments, an antibody or antigen binding fragment of the invention is for use in shifting a tumor microenvironment from immunosuppressive to immunostimulatory. In some embodiments, said shifting the tumor microenvironment comprises one or more of: inducing/enhancing an anti-tumor T-cell response, increasing T-cell proliferation, reducing cancer-induced suppressor myeloid activity, increasing dendritic cell (DC) activation, increasing dendritic cell homing to the tumor, increasing macrophage phagocytosis, increasing generation of M1 macrophages, decreasing generation of M2 macrophages and increasing NK cell activity. In some embodiments, antibody or antigen binding fragment of the invention is for use in increasing a T-cell response against a cancer cell. In some embodiments, the T cell response comprises increased pro-inflammatory cytokine secretion. In some embodiments, T cell response comprises increased cytotoxicity. In some embodiments, the T cell response comprises increased T cell proliferation. In some embodiments, antibody or antigen binding fragment of the invention is for use in increasing macrophage phagocytosis of a cancer cell. In some embodiments, antibody or antigen binding fragment of the invention is for use increasing dendritic cell homing to a tumor or cancer. In some embodiments, antibody or antigen binding fragment of the invention is for use in increasing macrophage phagocytosis. In some embodiments, antibody or antigen binding fragment of the invention is for use increasing macrophage phagocytosis of the cancer. In some embodiments, antibody or antigen binding fragment of the invention is for use in increasing generation of M1

(DVQLQGSGPGLVKPSETLSLTCSVTGYSITSGYYWNWIRQFPGKKLEWMGYISYDGSNN YNPSLKNRITISRDTSKNQFSLKLNSVTAADTATYYCAHGYSYYYAMDXWGQGTSVTVS S) , wherein said X is selected from A, C and S.

3. The antibody or antigen binding fragment of claim 1 or 2, comprising a light chain comprising an amino acid sequence selected from: SEQ ID NO: 20 (DIVLTQSPASLAVSLGQRATISCRASESVDSYGNSFMHWYQQKPGQPPKLLIYRASNLSEGI PARFSGSGSRTDFTLTINPVEADDVATYYCQQSNEDPYTFGGGTKLEIK), SEQ ID NO: 22 (DIQMTQSSSYLSVSLGGRVTITCKASDHINNWLAWYQQKPGNAPRLLISGATSLETGVPS RFSGSGSGKDYTLSTSLQTEDVATYYCQQYWSTPWTFGGGTKLEIK), SEQ ID NO: 24 (DIQMTQSPSSLSASVGDRVTITCRTSQDISNYLNWYQQKPGKAVKLLISYTSRLHSGVPSRF SGSGSGTDYTLTISSLQPEDFATYYCQQGNTLPTFGQGTKLEIK) and SEQ ID NO: 45 (DIQMTQTTSSLSASLGDRVTISCRTSQDISNYLNWYQQKPDGTVKLLISYTSRLHSGVPSRF SGSGSGTDYSLTISNLEQEDIATYFCQQGNTLPTFGSGTKLEIK).

4. The antibody or antigen binding fragment of any one of claims 1 to 3, wherein said antibody or antigen binding fragment is humanized and said X is selected from A and S.

5. The antibody or antigen binding fragment of any one of claim 4, wherein said X is A, SEQ ID NO: 15 is GYSYYYAMDA (SEQ ID NO: 25) and SEQ ID NO: 23 is DVQLQGSGPGLVKPSETLSLTCSVTGYSITSGYYWNWIRQFPGKKLEWMGYISYDGSNN YNPSLKNRITISRDTSKNQFSLKLNSVTAADTATYYCAHGYSYYYAMDAWGQGTSVTVS S (SEQ ID NO: 28).

6. A monoclonal antibody or antigen binding fragment that binds a human leukocyte immunoglobulin-like receptor subfamily B member 1 (ILT2) epitope within a sequence of human ILT2 selected from VKKGQFPIPSITWEH (SEQ ID NO: 41), LELVVTGAYIKPTLS (SEQ ID NO: 42), VILQCDSQVAFDGFs (SEQ ID NO: 43) and WYRCYAYDSNSPYEW (SEQ ID NO: 44).

7. The antibody or antigen binding fragment of claim 6, wherein said epitope is a 3-dimensional epitope comprising SEQ ID NO: 41, 42, 43 and 44.

8. A monoclonal antibody or antigen binding fragment that binds ILT2 and inhibits direct interaction between said ILT2 and beta-2-microglobulin (B2M).

9. The antibody or antigen binding fragment of claim 8, wherein said antibody or antigen binding fragment inhibits interaction of said ILT2 and an HLA protein or MHC-I protein via said inhibition of ILT2 direct interaction with B2M.

18 de enero de 2021

The European Patent Office
International Searching Authority
P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
The Netherlands

Presentado en línea

Re: Solicitud PCT nº PCT/IL2020/050889
Presentada el 12 de agosto de 2020
Ntra. Ref.: BDB-P-002-PCT
Solicitante: BIOND BIOLOGICS LTD.

Estimados señores,

Por la presente solicitamos la corrección de los siguientes errores obvios de acuerdo con la Regla 91.1 bajo el PCT en la solicitud PCT mencionada anteriormente.

Rectificación de la Descripción y del Listado de Secuencias:

- La secuencia correcta de SEQ ID NO: 28 es:
DVQLQGSGPGLVKPSETLSLTCSVTGYSITSGYYWNWIRQFPGKKLEWMGYISYDGS
NNYNPSLKNRITISRDTSKNQFSLKLNSVTAADTATYYCAHGYSYYYAMDAWGQGT
SVTVSS. Esta secuencia tiene una S en la posición 75 y no una D, solo tiene una S en la posición 114 y no una segunda S inmediatamente después, y termina en SS en las posiciones 118 y 119. Esta secuencia exacta se proporciona en la **Figura 6** (Figura 6 continuación_1, secuencia superior) y se denomina "región variable de cadena pesada de 15G8 (humana)". Dentro de la Figura 6, esta secuencia está etiquetada como SEQ ID NO: 28. El párrafo [0208] de la presente solicitud establece que "Las secuencias de los anticuerpos seleccionados se indican en la Figura 6". Esta cadena pesada es la cadena pesada del anticuerpo 15G8 que se utiliza en toda la sección experimental de la solicitud.

Los casos en la solicitud en los que SEQ ID NO: 28 se escribió incorrectamente con una D en la posición 75, con una S adicional después de la posición 114 y sin la SS en las posiciones 118 y 119 fueron errores tipográficos causados por la confusión entre las

secuencias de anticuerpos de los otros anticuerpos de la invención y la versión murina de este anticuerpo. Los solicitantes lamentan profundamente estos errores tipográficos.

- La secuencia correcta de SEQ ID NO: 23 es:

DVQLQGSGPGLVKPSETLSLTCSVTGYSITSGYYWNWIRQFPGKKLEWMGYISYDGS
NNYNPSLKNRITISRDTSKNQFSLKLNSVTAADTATYYCAHGYSYYYAMDXWGQGT
SVTVSS. Esta secuencia es idéntica a la SEQ ID NO: 28 corregida excepto que el aminoácido 108 es una X y no una A y que la X puede ser cualquiera de C, A y S.

El párrafo [0208] de la presente solicitud describe la generación de los anticuerpos. Establece que "Las secuencias de los anticuerpos seleccionados se indican en la Figura 6". Además, afirma que durante la humanización "El 15G8 humanizado final también contenía un solo cambio de aminoácido, eliminando la cisteína en CDR-H3 y reemplazándola con alanina o serina". Esto significa que había tres variantes del anticuerpo 15G8, todas con el mismo esqueleto y cada una con una C, una A o una S dentro de CDR-H3. La secuencia de CDR-H3, SEQ ID NO: 15, se proporciona en muchos lugares de la solicitud, y está claro que el aminoácido variable en cuestión es el aminoácido 108. La variante 15G8 con una A en la posición 108 se proporciona en Figura 6 (SEQ ID NO: 28). Por lo tanto, es claro a partir de una combinación de la Figura 6 y el párrafo [0208] que SEQ ID NO: 23 debe tener la misma secuencia que SEQ ID NO: 28, pero con una X en la posición 108. Por lo tanto, la secuencia corregida proporcionada anteriormente está completamente soportada.

Los solicitantes lamentan los errores tipográficos que también se incluyeron en SEQ ID NO: 23. Los mismos errores tipográficos ocurren en ambas secuencias ya que son esencialmente la misma secuencia pero con un solo cambio de aminoácido.

- La secuencia correcta para SEQ ID NO: 29 es:

DVQLQGSGPGLVKPSETLSLTCSVTGYSITSGYYWNWIRQFPGKKLEWMGYISYDGS
NNYNPSLKNRITISRDTSKNQFSLKLNSVTAADTATYYCAHGYSYYYAMDSWGQGT
SVTVSS. Esta secuencia es idéntica a la SEQ ID NO: 28 corregida excepto que el aminoácido 108 es una S y no una A.

El soporte para esta secuencia es el mismo que para SEQ ID NO: 23 como se explicó anteriormente. SEQ ID NO: 23 era la secuencia genérica con la opción de tres aminoácidos diferentes en la posición 108. SEQ ID NO: 29 es la variante específica con una S en esta posición.

Presentamos una versión corregida del Listado de Secuencias en TXT y hojas de reemplazo de las páginas 3, 21, 22 de la descripción y 66 de las reivindicaciones, incorporando las rectificaciones solicitadas.

El solicitante manifiesta que a la fecha aplicable y con respecto a los artículos modificados descritos anteriormente, es claro que se pretendía otra cosa de lo que aparece en la solicitud tal como fue presentada y que no se podría haber pretendido otra cosa que las rectificaciones propuestas.

Le saluda atentamente,



Dov Kesten

GEYRA KESTEN

Abogados, Abogados de patentes