

LAP and TGF β that confers latency. LAP-TGF β binding is reversible and the isolated purified components can recombine to form an inactive SLC. Both the SLC and the larger complex are referred to herein as latent TGF β , as both are inactive.

[0005] In general, integrins are adhesion molecules and mediate the attachment of cells to extracellular matrix proteins. Integrin $\alpha\text{v}\beta 8$ binds to the LAP of TGF- β and mediates the activation of TGF- β 1 and 3 (Mu *et al.* (2002) *J. Cell Biol.* 159:493). Integrin $\alpha\text{v}\beta 8$ -mediated activation of TGF- β is required for *in vivo* activation of TGF- β (*i.e.*, release of the mature TGF- β polypeptide), thus $\alpha\text{v}\beta 8$ is a gatekeeper of TGF- β function. Integrin $\alpha\text{v}\beta 8$ is expressed in normal epithelia (*e.g.*, airway epithelia), mesenchymal cells, and neuronal tissues.

[0006] The integrin $\beta 8$ (Itgb8) has been associated with forkhead box P3 (Foxp3)-positive T cells and T-regulatory-specific epigenetic remodeling. See, *e.g.*, Vandenbon, *et al.*, *Proc. Natl. Acad. Sci. USA* vol. 113 no. 17 pp. E2393–E2402 (2016). FoxP3 is a transcription factor involved in the development of T-regulatory (Treg) cells. Human and mouse effector Treg cells express functional TGF- β -activating integrin $\alpha\text{v}\beta 8$. See, Worthington, *Immunity* Volume 42, Issue 5, pp. 903–915 (May 2015). Treg cell integrin $\alpha\text{v}\beta 8$ -mediated TGF- β activation is not needed for T cell homeostasis and integrin $\alpha\text{v}\beta 8$ expression by Treg cells suppresses active inflammation.

BRIEF SUMMARY ~~OF THE INVENTION~~

[0007] Antibodies that bind to $\alpha\text{v}\beta 8$ are provided as described herein. In some ~~embodimentsexamples~~, the disclosure provides an antibody that specifically binds human $\alpha\text{v}\beta 8$, wherein the antibody comprises:

a heavy chain complementary determining region (HCDR) 1 comprising TFTDYSMH (SEQ ID NO:1) or TFTKYSMH (SEQ ID NO:2);

a HCDR 2 comprising RINTETGEPTFADDFRG (SEQ ID NO:3);

a HCDR 3 comprising FYYGRD(S/T) (SEQ ID NO:4);

a light chain complementary determining region (LCDR) 1 comprising KSSQSLLNSRSRKNYLA (SEQ ID NO:5) or KSSQSLLHSRSRKNYLA (SEQ ID NO:6);

a LCDR2 comprising WASTRES (SEQ ID NO:7); and

a LCDR3 comprising KQSYNLLS (SEQ ID NO:8), wherein the antibody comprises one or none of SEQ ID NO:1 and SEQ ID NO:5, but not both of SEQ ID NO:1 and SEQ ID NO:5.

[007a] In some aspects, the disclosure provides an antibody that specifically binds human $\alpha\text{v}\beta 8$, wherein the antibody comprises: a heavy chain complementary determining region (HCDR) 1 comprising TFTDYSMH (SEQ ID NO:1) or TFTKYSMH (SEQ ID NO:2); a HCDR 2 comprising RINTETGEPTFADDFRG (SEQ ID NO:3); a HCDR 3 comprising FYYGRD(S/T) (SEQ ID NO:4); a light chain complementary determining region (LCDR) 1 comprising KSSQSLLNSRSRKNYLA (SEQ ID NO:5) or KSSQSLLHSRSRKNYLA (SEQ ID NO:6); a LCDR2 comprising WASTRES (SEQ ID NO:7); and a LCDR3 comprising KQSYNLLS (SEQ ID NO:8), wherein the antibody comprises one or none of SEQ ID NO:1 and SEQ ID NO:5, but not both of SEQ ID NO:1 and SEQ ID NO:5.

[007b] In some aspects, the disclosure provides an antibody that binds human $\alpha\text{v}\beta 8$ and $\alpha\text{v}\beta 6$, wherein the antibody comprises: a heavy chain complementary determining region (HCDR) 1 comprising TFTDYSMH (SEQ ID NO:1) or TFTKYSMH (SEQ ID NO:2); a HCDR 2 comprising RINTETGEPTFADDFRG (SEQ ID NO:3); a HCDR 3 comprising FYYGRD(S/T) (SEQ ID NO:4); a light chain complementary determining region (LCDR) 1 comprising KSSQSLLRRGDLATIHGNALA (SEQ ID NO:11); a LCDR2 comprising WASTRES (SEQ ID NO:7); and a LCDR3 comprising KQSYNLLS (SEQ ID NO:8).

[007c] In some aspects, the disclosure provides an antibody that binds human $\alpha\text{v}\beta 8$ and $\alpha\text{v}\beta 6$, wherein the antibody comprises: a heavy chain complementary determining region (HCDR) 1 comprising TFTKYSMH (SEQ ID NO:2); a HCDR 2 comprising RINTETGEPTFADDFRG (SEQ ID NO:3); a HCDR 3 comprising FYYGRD(S/T) (SEQ ID NO:4); a light chain complementary determining region (LCDR) 1 comprising a sequence selected from the group consisting of SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, and SEQ ID NO:59; a LCDR2 comprising WASTRES (SEQ ID NO:7); and a LCDR3 comprising KQSYNLLS (SEQ ID NO:8).

[007d] In some aspects, the disclosure provides a use of the antibody of the disclosure in the manufacture of a medicament for enhancing an immune response to cancer in a human individual.

[007e] In some aspects, the disclosure provides a use of the antibody of the disclosure in the manufacture of a medicament for enhancing an immune response to a viral infection in a human individual.

[007f] In some aspects, the disclosure provides a pharmaceutical composition comprising the antibody of the disclosure in a pharmaceutically acceptable excipient.

[007g] A method of detecting the presence, absence, or quantity of human in a sample, the method comprising, contacting the antibody of the disclosure to the sample, and detecting or quantifying binding of the antibody to the sample.

[0008] In some embodimentsexamples, the HCDR1 comprises SEQ ID NO:2 and the LCDR1 comprises SEQ ID NO:6. In some embodimentsexamples, the HCDR1 comprises SEQ ID NO:1 and the LCDR1 comprises SEQ ID NO:6. In some embodimentsexamples, the HCDR1 comprises SEQ ID NO:2 and the LCDR1 comprises SEQ ID NO:5.

[0009] In some embodimentsexamples, the antibody comprises a heavy chain variable region comprising SEQ ID NO:9. In some embodimentsexamples, the antibody comprises a light chain variable region comprising SEQ ID NO: 10. In some embodimentsexamples, the antibody comprises a light chain variable region comprising SEQ ID NO:39. In some embodimentsexamples, the antibody comprises a heavy chain variable region comprising SEQ ID NO:9 and a light chain variable region comprising SEQ ID NO: 10. In some embodimentsexamples, the antibody comprises a heavy chain variable region comprising SEQ ID NO:9 and a light chain variable region comprising SEQ ID NO:39.

[0010] In some embodimentsexamples, the antibody is humanized.

[0011] In some embodimentsexamples, the antibody is linked to a detectable label.

[0012] Also provided are antibodies that bind human $\alpha\text{v}\beta 8$ and $\alpha\text{v}\beta 6$. In some embodimentsexamples, the antibody comprises:

a heavy chain complementary determining region (HCDR) 1 comprising TFTDYSMH (SEQ ID NO:1) or TFTKYSMH (SEQ ID NO:2);

a HCDR 2 comprising RINTETGEPTFADDFRG (SEQ ID NO:3);

a HCDR 3 comprising FYYGRD(S/T) (SEQ ID NO:4);

5 a light chain complementary determining region (LCDR) 1 comprising KSSQSLLRRGDLATIHGNALA (SEQ ID NO:11);

a LCDR2 comprising WASTRES (SEQ ID NO:7); and

a LCDR3 comprising KQSYNLLS (SEQ ID NO:8).

[0013] In some [embodimentsexamples](#), the antibody comprises a heavy chain variable region comprising SEQ ID NO:9 or SEQ ID NO:37. In some [embodimentsexamples](#), the antibody comprises a light chain variable region comprising SEQ ID NO:12. In some [embodimentsexamples](#), the antibody comprises a heavy chain variable region comprising SEQ ID NO:9 or SEQ ID NO:37 and a light chain variable region comprising SEQ ID NO:12.

[0014] In some [embodimentsexamples](#), the antibody is humanized.

[0015] In some [embodimentsexamples](#), the antibody is linked to a detectable label.

[0016] Also provided are antibodies that bind human $\alpha\text{v}\beta 8$ and $\alpha\text{v}\beta 6$, wherein the antibody comprises:

10 a heavy chain complementary determining region (HCDR) 1 comprising TFTKYSMH (SEQ ID NO:2);

a HCDR 2 comprising RINTETGEPTFADDFRG (SEQ ID NO:3);

a HCDR 3 comprising FYYGRD(S/T) (SEQ ID NO:4);

15 a light chain complementary determining region (LCDR) 1 comprising a sequence selected from the group consisting of SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, and SEQ ID NO:59;

a LCDR2 comprising WASTRES (SEQ ID NO:7); and

20 a LCDR3 comprising KQSYNLLS (SEQ ID NO:8).

[0017] In some [embodimentsexamples](#), the HCDR1 comprises SEQ ID NO:2 and the LCDR1 comprises SEQ ID NO:40.

25 [0018] In some [embodimentsexamples](#), the antibody comprises a heavy chain variable region comprising SEQ ID NO:9. In some [embodimentsexamples](#), the antibody comprises a light chain variable region comprising SEQ ID NO:39. In some [embodimentsexamples](#), the antibody comprises both a heavy chain variable region comprising SEQ ID NO:9 and a light chain variable region comprising SEQ ID NO:39.

[0019] In some embodimentsexamples, the antibody is humanized. In some embodimentsexamples, the antibody is linked to a detectable label.

[0020] Also provided is a method of enhancing an immune response to cancer in a human individual, the method comprising administering a sufficient amount of an antibody as described above or elsewhere herein to the individual, thereby enhancing an immune response to the cancer. In some embodimentsexamples, the cancer is lung cancer. In some embodimentsexamples, the cancer is a metastatic cancer. In some embodimentsexamples, the cancer is a primary cancer.

[0021] Also provided is a method of enhancing an immune response to a viral infection in a human individual, the method comprising administering a sufficient amount of an antibody as described above or elsewhere herein to the individual, thereby enhancing an immune response to the viral infection. In some embodimentsexamples, the viral infection is a hepatitis infection. In some embodimentsexamples, the viral infection is a hepatitis B infection.

[0022] Also provided is a pharmaceutical composition comprising an antibody as described above or elsewhere herein in a pharmaceutically acceptable excipient.

[0023] Also provided is a method of detecting the presence, absence, or quantity of human in a sample, the method comprising, contacting an antibody as described above or elsewhere herein to the sample, and detecting or quantifying binding of the antibody to the sample.

BRIEF DESCRIPTION OF THE DRAWINGS

[0024] FIG. 1 depicts sequence alignments of antibody variable regions; heavy and light chains (Vh and Vk, respectively), with underlined amino acids indicating the mutations or substituted loops. The top portion of the figure depicts changes to antibody C6D4 to form C6-TGFβ1RGD Vk. The bottom portion of the figure depicts heavy and light chain changes to form antibody HuC6D4F12, which has improved binding characteristics compared to C6D4.

[0025] FIG. 2A-D depicts rational design of select potential mutants to improve or create binding interactions between C6D4 and αvβ8 (αvβ8 in grey, C6D4 in black, potential mutant positions in C6D4 in black sticks, potential new interacting residues in β8 in grey sticks). The dashed lines represent potential new or strengthened interactions. A) CDR1 Vh; D31 which is

WHAT IS CLAIMED IS:

- 1 1. An antibody that specifically binds human $\alpha\text{v}\beta 8$, wherein the antibody
2 comprises:
3 a heavy chain complementary determining region (HCDR) 1 comprising
4 TFTDYSMH (SEQ ID NO:1) or TFTKYSMH (SEQ ID NO:2);
5 a HCDR 2 comprising RINTETGEPTFADDFRG (SEQ ID NO:3);
6 a HCDR 3 comprising FYYGRD(S/T) (SEQ ID NO:4);
7 a light chain complementary determining region (LCDR) 1 comprising
8 KSSQSLLNSRSRKNYLA (SEQ ID NO:5) or KSSQSLLHSRSRKNYLA (SEQ ID NO:6);
9 a LCDR2 comprising WASTRES (SEQ ID NO:7); and
10 a LCDR3 comprising KQSYNLLS (SEQ ID NO:8), wherein the antibody
11 comprises one or none of SEQ ID NO:1 and SEQ ID NO:5, but not both of SEQ ID NO:1 and
12 SEQ ID NO:5.
- 1 2. The antibody of claim 1, wherein the HCDR1 comprises SEQ ID NO:2
2 and the LCDR1 comprises SEQ ID NO:6.
- 1 3. The antibody of claim 1, wherein the HCDR1 comprises SEQ ID NO:1
2 and the LCDR1 comprises SEQ ID NO:6.
- 1 4. The antibody of claim 1, wherein the HCDR1 comprises SEQ ID NO:2
2 and the LCDR1 comprises SEQ ID NO:5.
- 1 5. The antibody of claim 1, comprising a heavy chain variable region
2 comprising SEQ ID NO:9.
- 1 6. The antibody of claim 1 or 5, comprising a light chain variable region
2 comprising SEQ ID NO: 10.
- 1 7. The antibody of any of claims 1-6, wherein the antibody is humanized.
- 1 8. The antibody of any of claims 1-6, wherein the antibody is linked to a
2 detectable label.

3 9. An antibody that binds human $\alpha\text{v}\beta 8$ and $\alpha\text{v}\beta 6$, wherein the antibody
4 comprises:
5 a heavy chain complementary determining region (HCDR) 1 comprising
6 TFTDYSMH (SEQ ID NO:1) or TFTKYSMH (SEQ ID NO:2);
7 a HCDR 2 comprising RINTETGEPTFADDFRG (SEQ ID NO:3);
8 a HCDR 3 comprising FYYGRD(S/T) (SEQ ID NO:4);
9 a light chain complementary determining region (LCDR) 1 comprising
10 KSSQSLLRRGDLATIHGNALA (SEQ ID NO:11);
11 a LCDR2 comprising WASTRES (SEQ ID NO:7); and
12 a LCDR3 comprising KQSYNLLS (SEQ ID NO:8).

1 10. The antibody of claim 9, comprising a heavy chain variable region
2 comprising SEQ ID NO:9.

1 11. The antibody of claim 9 or 10, comprising a light chain variable region
2 comprising SEQ ID NO:12.

1 12. The antibody of claim 9, wherein the antibody is humanized.

1 13. The antibody of claim 9, wherein the antibody is linked to a detectable
2 label.

1 14. An antibody that binds human $\alpha\text{v}\beta 8$ and $\alpha\text{v}\beta 6$, wherein the antibody
2 comprises:
3 a heavy chain complementary determining region (HCDR) 1 comprising
4 TFTKYSMH (SEQ ID NO:2);
5 a HCDR 2 comprising RINTETGEPTFADDFRG (SEQ ID NO:3);
6 a HCDR 3 comprising FYYGRD(S/T) (SEQ ID NO:4);
7 a light chain complementary determining region (LCDR) 1 comprising a sequence
8 selected from the group consisting of SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID
9 NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ
10 ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54,
11 SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, and SEQ ID NO:59;

12 a LCDR2 comprising WASTRES (SEQ ID NO:7); and
13 a LCDR3 comprising KQSYNLLS (SEQ ID NO:8).

1 15. The antibody of claim 14, wherein the HCDR1 comprises SEQ ID NO:2
2 and the LCDR1 comprises SEQ ID NO:40.

1 16. The antibody of claim 14, comprising a heavy chain variable region
2 comprising SEQ ID NO:9.

1 17. The antibody of claim 14 or 16, comprising a light chain variable region
2 comprising SEQ ID NO:39.

1 18. The antibody of claim 14, wherein the antibody is humanized.

1 19. The antibody of claim 14, wherein the antibody is linked to a detectable
2 label.

1 20. ~~A method of enhancing an immune response to cancer in a human~~
2 ~~individual, the method comprising administering a sufficient amount~~ Use of the antibody of any
3 of claims 1-19 in the manufacture of a medicament for enhancing an immune response to cancer
4 in a human individual ~~to the individual, thereby enhancing an immune response to the cancer.~~

1 21. The ~~method-use~~ of claim 20, wherein the cancer is lung cancer.

1 22. The ~~use method~~ of claim 20, wherein the cancer is a metastatic cancer.

1 23. The ~~use method~~ of claim 20, wherein the cancer is a primary cancer.

1 24. ~~A method of enhancing an immune response to a viral infection in a~~
2 ~~human individual, the method comprising administering a sufficient amount~~ Use of the antibody
3 of any of claims 1-19 in the manufacture of a medicament for enhancing an immune response to
4 a viral infection in a human individual ~~to the individual, thereby enhancing an immune response~~
5 ~~to the viral infection.~~

1 25. The ~~use method~~ of claim 24, wherein the viral infection is a hepatitis
2 infection.

1 26. The ~~use method~~ of claim 25, wherein the viral infection is a hepatitis B
2 infection.

1 27. A pharmaceutical composition comprising the antibody of any of claims
2 1-19 in a pharmaceutically acceptable excipient.

1 28. A method of detecting the presence, absence, or quantity of human in a
2 sample, the method comprising,
3 contacting the antibody of any of claims 1-19 to the sample, and
4 detecting or quantifying binding of the antibody to the sample.