

CLAIMS

1. An antibody or antibody fragment thereof that specifically binds to the extracellular domain of human TGF- β RII, wherein the antibody or antibody fragment binds to an epitope of the extracellular domain of human TGF- β RII of which phenylalanine (F) at position 25 of isoform A of human TGF- β RII, or at position 50 of isoform B of human TGF- β RII, is a critical residue for binding.

2. The antibody or antibody fragment thereof as claimed in claim 1, wherein aspartate (D) at position 119 of the epitope of the extracellular domain of isoform A of human TGF- β RII, or at position 144 of isoform B of human TGF- β RII, is a further critical residue for binding.

3. The antibody or antibody fragment thereof as claimed in claim 1 or 2, wherein threonine (T) at position 52 of the epitope of the extracellular domain of isoform A of human TGF- β RII, or at position 77 of isoform B of human TGF- β RII, is a further critical residue for binding.

4. The antibody or antibody fragment thereof as claimed in claim 1 or 2, wherein isoleucine (I) at position 54 and glutamate (E) at position 120 of the epitope of the extracellular domain of isoform A of human TGF- β RII, or at position 79 and 145 of isoform B of human TGF- β RII, are further critical residues for binding.

5. The antibody or antibody fragment thereof as claimed in any one of claims 1-4, wherein the antibody or antibody fragment thereof comprises the VH-CDR1, VH-CDR2, and VH-CDR3 of a VH having an amino acid sequence set forth in any one of SEQ ID NO: 25, 29-31, 33-35, 37, 38, 41, 44-47, 49, 50, 54, 55, 57-59, 62, 64, 66, 68, 69, 71, 73, 75, 78, 80, 82, 84-86, 88-91, 94-96, and a light chain variable region (VL) having

(a) a VL-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 19,

(b) a VL-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 20,

and

(c) a VL-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 21.

6. An antibody or antibody fragment thereof comprising the VH-CDR1, VH-CDR2, and VH-CDR3 of a VH having an amino acid sequence set forth in any one of SEQ ID NO: 25, 29-31, 33-35, 37, 38, 41, 44-47, 49, 50, 54, 55, 57-59, 62, 64, 66, 68, 69, 71, 73, 75, 78, 80, 82, 84-86, 88-91, 94-96, , and a light chain variable region (VL) having

(a) a VL-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 19,

(b) a VL-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 20,

and

(c) a VL-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 21.

7. The antibody or antibody fragment thereof as claimed in any one of claims 1-6, wherein the antibody or antibody fragment thereof comprises a VH amino acid sequence selected from any one of SEQ ID NO: 25, 29-31, 33-35, 37, 38, 41, 44-47, 49, 50, 54, 55, 57-59, 62, 64, 66, 68, 69, 71, 73, 75, 78, 80, 82, 84-86, 88-91, 94-96, or a VH amino acid sequence having at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity thereto, wherein any variation from the indicated SEQ ID NOs is outside the CDRs.

8. The antibody or antibody fragment thereof as claimed in any one of claims 1-7, wherein the antibody or antibody fragment thereof comprises a VL amino acid sequence:

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFGSGSGGTDFTLTISSLQPEDFATYYCQQSYSTPPTFGQGTKVEIK (SEQ ID NO: 16), or a VL amino acid sequence having at least 80% identity thereto, wherein any variation from the indicated SEQ ID NO is outside the CDRs.

9. The antibody or antibody fragment thereof as claimed in any one of claims 6-8, wherein the antibody or antibody fragment thereof comprises a heavy chain variable region of any one of SEQ ID NO: 25, 29-31, 33-35, 37, 38, 41, 44-47, 49, 50, 54, 55, 57-59, 62, 64, 66, 68, 69, 71, 73, 75, 78, 80, 82, 84-86, 88-91, 94-96, and a light chain variable region of SEQ ID NO: 16.

10. The antibody or antibody fragment thereof as claimed in any one of claims 6-9, wherein the antibody or antibody fragment thereof comprises two heavy chain variable regions of any one of SEQ ID NO: 25, 29-31, 33-35, 37, 38, 41, 44-47, 49, 50, 54, 55, 57-59, 62, 64, 66, 68, 69, 71, 73, 75, 78, 80, 82, 84-86, 88-91, 94-96, and two light chain variable regions of SEQ ID NO: 16.

11. The antibody as claimed in any one of claims 1-10, wherein the antibody is an IgG antibody.

12. The antibody as claimed in any one of claims 1-11, wherein the antibody is an IgG1 antibody or an IgG4 antibody.

13. The antibody as claimed in any one of claims 1-12, wherein the antibody is an IgG1 antibody.

14. The antibody or antibody fragment thereof as claimed in any one of claims 6-13, wherein the antibody or antibody fragment thereof further comprises a heavy chain constant region comprising the amino acid sequence set forth in SEQ ID No. 17.

15. The antibody or antibody fragment thereof as claimed in any one of claims 6-14, wherein the antibody or antibody fragment thereof further comprises a light chain constant region comprising the amino acid sequence set forth in SEQ ID No. 18.

16. The antibody as claimed in any one of claims 1-15, wherein the binding of the antibody to an Fc receptor is eliminated or reduced.

17. An antibody that specifically binds to human TGF- β RII, wherein the antibody comprises:

(A) a heavy chain having a VH comprising the amino acid sequence set forth in any one selected from SEQ ID No. 25, 29-31, 33-35, 37, 38, 41, 44-47, 49, 50, 54, 55, 57-59, 62, 64, 66,

68, 69, 71, 73, 75, 78, 80, 82, 84-86, 88-91, 94-96, and a heavy chain constant region comprising the amino acid sequence set forth in SEQ ID No. 17; and

(B) a light chain having a VL comprising the amino acid sequence set forth in SEQ ID No. 16, and a light chain constant region comprising the amino acid sequence set forth in SEQ ID No. 18.

18. The antibody or antibody fragment thereof as claimed in any one of claims 1-17, wherein the antibody is a monoclonal antibody.

19. A binding domain that specifically binds to human TGF- β RII, wherein the binding domain comprises:

any one of the heavy chain variable regions (VH) selected from:

(A) a VH having a VH-CDR1, VH-CDR2, and VH-CDR3 of the VH having an amino acid sequence set forth in SEQ ID No. 30;

(B) a VH having a VH-CDR1, VH-CDR2, and VH-CDR3 of the VH having an amino acid sequence set forth in SEQ ID No. 85; and

(C) a VH having a VH-CDR1, VH-CDR2, and VH-CDR3 of the VH having an amino acid sequence set forth in SEQ ID No. 86;

and a light chain variable region (VL) having

(a) a VL-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 19,

(b) a VL-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 20,

and

(c) a VL-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 21.

20. The binding domain as claimed in claim 19, wherein the binding domain comprises a VH amino acid sequence selected from SEQ ID NO: 30, 85 and 86, or a VH amino acid sequence having at least 80% identity thereto.

21. The binding domain as claimed in claim 19 or 20, wherein the binding domain comprises a VL amino acid sequence:

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQS
 GVPSRFGSGSGTDFLTITSSLPEDFATYYCQQSYSTPPTFGGQGTKVEIK (SEQ ID NO:
 16), or a VL amino acid sequence having at least 80% identity thereto.

5 22. The binding domain as claimed claim 19, wherein the binding domain comprises a
 VH amino acid sequence selected from SEQ ID NO: 30, 85 and 86, and a VL amino acid
 sequence of SEQ ID NO: 16.

10 23. A vector comprising a polynucleotide encoding either or both the heavy chain and the
 light chain of the antibody or antibody fragment thereof as claimed in any one of claims 1-18, or
 a binding domain as claimed in any one of claims 19-22.

15 24. A cell producing the antibody or antibody fragment thereof as claimed in any one of
 claims 1-18, or a binding domain as claimed in any one of claims 19-22.

25 25. The cell as claimed in claim 24, wherein the cell is a recombinant cell, which has
 been transformed with the vector as claimed in claim 23.

20 26. A pharmaceutical composition comprising the antibody or antibody fragment thereof
 as claimed in any one of claims 1-18, or a binding domain as claimed in any one of claims 19-22,
 and a pharmaceutically acceptable carrier, diluent, or excipient.

25 27. A pharmaceutical agent for use in treating a TGF- β RII positive cancer, wherein the
 pharmaceutical agent comprises the antibody or antibody fragment thereof as claimed in any one
 of claims 1-18, or a binding domain as claimed in any one of claims 19-22, as an active
 ingredient.

30 28. Use of an antibody or antibody fragment thereof as claimed in any one of claims 1-
 18, or a binding domain as claimed in any one of claims 19-22, or the pharmaceutical
 composition as claimed in claim 26 in the manufacture of a medicament for treating a TGF- β RII
 positive cancer in a subject in need thereof.

29. Use of an antibody or antibody fragment thereof as claimed in any one of claims 1-18, or a binding domain as claimed in any one of claims 19-22, or the pharmaceutical composition as claimed in claim 26, in the manufacture of a medicament for inhibiting metastasis of a TGF- β RII positive cancer in a subject in need thereof.

30. The use as claimed in claim 28 or 29, wherein the cancer is a cancer-type correlated with higher than normal TGF- β signaling, in particular higher than normal TGF- β RII expression.

31. The use as claimed in any one of claims 28 to 30, wherein the cancer is selected from the group consisting of: breast cancer, colon cancer, colorectal cancer, gastric cancer, glioblastoma, neck cancer, hepatocellular carcinoma, non-small cell lung cancer, small cell lung cancer, melanoma, myelodysplastic syndrome, pancreatic cancer, prostate cancer and renal cancer.

32. An in vitro method of blocking binding of human TGF- β to human TGF- β RII on a cell, the method comprising: providing the antibody or antibody fragment thereof as claimed in any one of claims 1-18, or a binding domain as claimed in any one of claims 19-22, to the cell and allowing the antibody or antibody fragment thereof, or binding domain, to bind to the human TGF- β RII of the cell, to thereby block binding of human TGF- β to human TGF- β RII on the cell.

33. An in vitro method of inhibiting signal transduction into a cell induced by binding of a human TGF- β to a human TGF- β RII of the cell, the method comprising: providing the antibody or antibody fragment thereof as claimed in any one of claims 1-18, or a binding domain as claimed in any one of claims 19-22, to the cell and allowing the antibody or antibody fragment thereof, or binding domain, to bind to the human TGF- β RII of the cell, to thereby inhibit the signal transduction into the cell.