

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
5 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 as claimed in claim 1, wherein aspartate
10 (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 as claimed in claim 1 or 2, wherein
15 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 as claimed in claim 1 or 2, wherein
20 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 as claimed in any one of claims 1-4,
25 wherein the antibody or antibody fragment comprises any one of the heavy chain variable regions (VH) selected from:
- (A) a VH having
- (a) a VH-CDR1 comprising the amino acid sequence set forth in SEQ ID
No. 1,
- 30 (b) a VH-CDR2 comprising the amino acid sequence set forth in SEQ ID
No. 2, and

- (c) a VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 3;
- (B) a VH having
- (a) a VH-CDR1 comprising the amino acid sequence set forth in SEQ ID
- 5 No. 4,
- (b) a VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 5, and
- (c) a VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 6;
- 10 (C) a VH having
- (a) a VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 7,
- (b) a VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 8, and
- 15 (c) a VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 9,
- wherein one to five amino acid residue(s) may be substituted with conservative amino acid(s) thereof in any one or more of the CDR(s) selected from VH-CDR1, VH-CDR2 and VH-CDR3.
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6. An antibody or antibody fragment thereof that specifically binds to the extracellular domain of human TGF- β RII, wherein the antibody or antibody fragment comprises any one of the heavy chain variable regions (VH) selected from:
- (A) a VH having
- 25 (a) a VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 1,
- (b) a VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 2, and
- (c) a VH-CDR3 comprising the amino acid sequence set forth in SEQ ID
- 30 No. 3;
- (B) a VH having

- (a) a VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 4,
- (b) a VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 5, and
- 5 (c) a VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 6;
- (C) a VH having
- (a) a VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 7,
- 10 (b) a VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 8, and
- (c) a VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 9,
- wherein one to five amino acid residue(s) may be substituted with conservative amino acid(s) thereof in any one or more of the CDR(s) selected from VH-CDR1, VH-CDR2 and VH-CDR3.
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7. The antibody or an antibody fragment thereof as claimed in any one of claims 1-6, wherein the FR1, FR2, FR3 and FR4 regions of the VH correspond to amino acid sequences encoded by the germline V genes IGHV3-15 and IGHV3-23 which may comprise somatic mutation(s).

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

25 EVQLVESGGGLVQPGGSLRLSCAASGFTFDIYAMTWVRQAPGKGLEWV
SVISGSGGTTYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARRGQ
YRDIVGATDYWGQGT LVT VSS (SEQ ID NO: 10);

QVQLVESGGGLVEPGGSLRLSCAASGFTFSNAWMSWVRQAPGKGLEW
VGRIKTTISGGATDFAAPVKGRFTISRDD SKNTLYLQMNSLKTEDTAVYYCTLD
30 LRDYWGQGT LVT VSS (SEQ ID NO: 11);

QVQLVESGGGLVQPGGSLRLSCAVSGFTFRRYAMSWVRQAPGKGLEW
VSAISASGDRTHNTDSVKGRFSISRDN SKNTLYLQMNSLRAEDTAVYFCAKGIA
ASGKNYFDPWGQGTLVTVSS (SEQ ID NO: 12),

or a VH amino acid sequence having at least 80% identity thereto.

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9. The antibody or an antibody fragment thereof as claimed in any one of claims 1-8, wherein the antibody comprises a VH amino acid sequence selected from any one of SEQ ID NO: 22-91, or a VH amino acid sequence having at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity thereto.

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10. The antibody or an antibody fragment thereof as claimed in any one of claims 1-9, wherein the antibody or antibody fragment further comprises:

a light chain variable region (VL) having

(a) a VL-CDR1 comprising the amino acid sequence set forth in SEQ ID

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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,

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wherein one to five amino acid residue(s) may be substituted with conservative amino acid(s) thereof in any one or more of the CDR(s) selected from VL-CDR1, VL-CDR2 and VL-CDR3.

11. The antibody or an antibody fragment thereof as claimed in any one of claims 1-10, wherein the antibody comprises a VL amino acid sequence:

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

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12. The antibody or antibody fragment thereof as claimed in any one of claims 1-8, 10 or 11, wherein the antibody comprises a heavy chain variable region of SEQ ID NO: 10, 11 or 12, and a light chain variable region of SEQ ID NO: 16.

13. The antibody or antibody fragment thereof as claimed in any one of claims 1-12, wherein the antibody comprises a heavy chain variable region of any one of SEQ ID NO: 22-91, and a light chain variable region of SEQ ID NO: 16.

5 14. The antibody or antibody fragment thereof as claimed in any one of claims 1-8, or 10-12, wherein the antibody comprises two heavy chain variable regions of SEQ ID NO: 10 and two light chain variable regions of SEQ ID NO: 16, two heavy chain variable regions of SEQ ID NO: 11 and two light chain variable regions of SEQ ID NO: 16, or two heavy chain variable regions of SEQ ID NO: 12 and two light chain variable
10 regions of SEQ ID NO: 16.

15 15. The antibody or antibody fragment thereof as claimed in any one of claims 11-13, wherein the antibody comprises two heavy chain variable regions of any one of SEQ ID NO: 22-91 and two light chain variable regions of SEQ ID NO: 16.

16 16. The antibody as claimed in any one of claims 1-15, wherein the antibody is an IgG antibody.

20 17. The antibody as claimed in any one of claims 1-16, wherein the antibody is an IgG1 antibody or an IgG4 antibody.

18. The antibody as claimed in any one of claims 1-17, wherein the antibody is an IgG1 antibody.

25 19. The antibody or antibody fragment thereof as claimed in any one of claims 1-18, wherein the antibody or antibody fragment further comprises a heavy chain constant region comprising the amino acid sequence set forth in SEQ ID No. 17.

30 20. The antibody or antibody fragment thereof as claimed in any one of claims 1-19, wherein the antibody or antibody fragment further comprises a light chain constant region comprising the amino acid sequence set forth in SEQ ID No. 18.

21. The antibody as claimed in any one of claims 1-20, wherein the binding of the antibody to an Fc receptor is eliminated or reduced.

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

(A) a heavy chain having a VH comprising the amino acid sequence set forth in any one selected from SEQ ID No. 10-12 and SEQ ID No. 22-91, 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
10 SEQ ID No. 16, and a light chain constant region comprising the amino acid sequence set forth in SEQ ID No. 18.

23. The antibody or fragment thereof as claimed in any one of claims 1-22, wherein the antibody is a monoclonal antibody.

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24. 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
20 amino acid sequence set forth in SEQ ID No. 12;

(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. 26;

(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. 30;

(D) a VH having a VH-CDR1, VH-CDR2, and VH-CDR3 of the VH having an
25 amino acid sequence set forth in SEQ ID No. 40;

(E) 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. 61;

(F) a VH having a VH-CDR1, VH-CDR2, and VH-CDR3 of the VH having an
30 amino acid sequence set forth in SEQ ID No. 65;

(G) 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. 70;

(H) 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. 76;

(I) 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

5 (J) 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;

wherein one to five amino acid residue(s) may be substituted with conservative amino acid(s) thereof in any one or more of the CDR(s) selected from VH-CDR1, VH-CDR2 and VH-CDR3.

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25. The binding domain as claimed in claim 24, wherein the binding domain comprises a VH amino acid sequence selected from SEQ ID NO: 12, 26, 30, 40, 61, 65, 70, 76, 85 and 86,

or a VH amino acid sequence having at least 80% identity thereto.

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26. The binding domain as claimed in claim 24 or 25, wherein the antibody or antibody fragment, or binding domain, further comprises:

a light chain variable region (VL) having

20 (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,

25 wherein one to five amino acid residue(s) may be substituted with conservative amino acid(s) thereof in any one or more of the CDR(s) selected from VL-CDR1, VL-CDR2 and VL-CDR3.

30 27. The binding domain as claimed in any one of claims 24-26, wherein the antibody or binding domain comprises a VL amino acid sequence:

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

- 5 28. An antibody or antibody fragment monovalent for binding to TGF- β RII,
wherein the antibody or antibody fragment has at least comparable or equal, or higher,
receptor blocking activity at equimolar concentrations when compared to a bivalent
monospecific control antibody comprising two heavy chain variable regions having an
amino acid sequence as set forth in SEQ ID NO: 97 and two light chain variable regions
10 having an amino acid sequence as set forth in SEQ ID NO: 135, in the same assay.

29. The antibody as claimed in claim, wherein the antibody or antibody
fragment comprises a TGF- β RII binding domain as defined in any one of claims 24-27.

- 15 30. A vector comprising a polynucleotide encoding either or both the heavy
chain and the light chain of the antibody or antibody fragment as claimed in any one of
claims 1-23, 28 or 29, or a binding domain as claimed in any one of claims 24-27.

31. A cell producing the antibody or antibody fragment as claimed in any one of
20 claims 1-23, 28 or 29, or a binding domain as claimed in any one of claims 24-27.

32. The cell as claimed in claim 31, wherein the cell is a recombinant cell, which
has been transformed with the vector as claimed in claim 30.

- 25 33. A pharmaceutical composition comprising the antibody or antibody
fragment as claimed in any one of claims 1-23, 28 or 29, or a binding domain as
claimed in any one of claims 24-27, and a pharmaceutically acceptable carrier, diluent,
or excipient.

- 30 34. A pharmaceutical agent for use in preventing, suppressing symptom
progression or recurrence of, and/or treating cancer, wherein the pharmaceutical agent
comprises the antibody or antibody fragment thereof as claimed in any one of claims 1-

23, 28 or 29, or a binding domain as claimed in any one of claims 24-27, as an active ingredient.

35. The pharmaceutical agent as claimed in claim 34, wherein the cancer is a
5 cancer-type correlated with higher than normal TGF- β signaling, in particular higher than normal TGF- β RII expression.

36. The pharmaceutical agent as claimed in claim 34 or 35, wherein the cancer is
selected from the group consisting of: breast cancer, colon cancer, colorectal cancer,
10 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.

37. A method of treating cancer in a subject in need thereof, the method
15 comprising: administering an effective amount of the antibody or antibody fragment as claimed in any one of claims 1-23, 28 or 29, or a binding domain as claimed in any one of claims 24-27, or the pharmaceutical composition as claimed in claim 33, to the subject.

20 38. A 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 as claimed in any one of claims 1-23, 28 or 29, or a binding domain as claimed in any one of claims 24-27, to the cell and allowing the antibody or antibody fragment, or binding domain, to bind to the human TGF- β RII of the cell, to thereby block binding of human TGF- β to
25 human TGF- β RII on the cell.

39. A 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 as claimed in any one of claims 1-23, 28 or 29, or a
30 binding domain as claimed in any one of claims 24-27, to the cell and allowing the antibody or antibody fragment, or binding domain, to bind to the human TGF- β RII of the cell, to thereby inhibit the signal transduction into the cell.

40. A method of preventing or inhibiting metastasis in a subject in need thereof, the method comprising: administering an effective amount of the antibody or antibody fragment as claimed in any one of claims 1-23, 28 or 29, or a binding domain as claimed in any one of claims 24-27, or the pharmaceutical composition as claimed in claim 33, to the subject.
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