Claims

1. An anti-TGFbetaRII immunoglobulin single variable domain comprising an amino acid sequence as set forth in any one of SEQ ID NO:1-38, 204, 206, 208, 214, 234, 236, 238, 240, 263, 265, 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289 and 291, having up to 5 amino acid substitutions, deletions or additions, in any combination.
2. An anti-TGFbetaRII immunoglobulin single variable domain as claimed in claim 1, comprising an amino acid sequence as set forth in SEQ ID NO: 234 or 236, having up to 5 amino acid substitutions, deletions or additions, in any combination.
3. An anti-TGFbetaRII immunoglobulin single variable domain as claimed in claim 1 or claim 2, wherein the said amino acid substitutions, deletions or additions are not within CDR3.
4. An anti-TGFbetaRII immunoglobulin single variable domain as claimed in claim 1, 2 or 3, wherein the said amino acid substitutions, deletions or additions are not within any of the CDRs.
5. An anti-TGFbetaRII immunoglobulin single variable domain comprising of an amino acid sequence selected from the group consisting of SEQ ID NO:1-38, 204, 206, 208, 214, 234, 236, 238, 240, 263, 265, 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289 and 291.
6. An anti-TGFbetaRII immunoglobulin single variable domain as claimed in claim 5 comprising an amino acid sequence of SEQ ID NO: 234 or 236.
7. An anti-TGFbetaRII immunoglobulin single variable domain as claimed in any one of the preceding claims, wherein the anti-TGFbetaRII immunoglobulin single variable domain further comprises a C-terminal alanine residue.
8. An isolated polypeptide comprising an anti-TGFbetaRII immunoglobulin single variable domain as claimed in any one of the preceding claims, wherein said isolated polypeptide binds to TGFbetaRII.
9. An anti-TGFbetaRII immunoglobulin single variable domain as claimed in any of claims 1-7, or a polypeptide as claimed in claim 8, further comprising at least one of the following amino acids selected from the group: R at position 39, I at position 48, D at position 53, N at position 61, R at position 61, K at position 61, R at position 64, F at position 64, D at position 64, E at position 64, M at position 64, Y at position 64, H at position 102, or S at position 103 of the immunoglobulin single variable domain, said positions being according to the kabat numbering convention.
10. An anti-TGFbetaRII immunoglobulin single variable domain or a polypeptide as claimed in claim 9, comprising an R or a K at position 61.
11. An anti-TGFbetaRII immunoglobulin single variable domain as claimed in any of claims 1-7, or a polypeptide as claimed in claim 8, further comprising one of the following amino acid combinations selected from the group: N at position 61 and R at position 64; R at position 61 and E at position 64; R at position 61 and M at position 64; R at position 61 and F at position

64; R at position 61 and Y at position 64; and R at position 61 and D at position 64 of the immunoglobulin single variable domain.

12. An anti-TGFbetaRII immunoglobulin single variable domain or a polypeptide as claimed in claim 9, 10 or 11, comprising an isoleucine residue at position 48.
13. An anti-TGFbetaRII immunoglobulin single variable domain or polypeptide as claimed in any one of claims 1-12, wherein said anti-TGFbetaRII immunoglobulin single variable domain or polypeptide binds to human TGFbetaRII.
14. An anti-TGFbeta RII immunoglobulin single variable domain or polypeptide as claimed in claim 13, wherein said anti-TGFbetaRII immunoglobulin single variable domain or polypeptide also binds to mouse TGFbetaRII and/or cyno TGFbetaRII.
15. An immunoglobulin single variable domain or polypeptide as claimed in any one of claims 1-14, wherein said immunoglobulin single variable domain or polypeptide neutralises TGFbeta activity.
16. An immunoglobulin single variable domain or polypeptide as claimed in any one of claims 1-15, wherein said immunoglobulin single variable domain or polypeptide inhibits binding of TGFbeta to TGFbetaRII.
17. An isolated nucleic acid encoding an anti-TGFbetaRII immunoglobulin single variable domain or polypeptide as claimed in any one of claims 1-16.
18. An isolated nucleic acid molecule as claimed in claim 16, comprising at least one nucleic acid molecule selected from the group of: SEQ ID NOs: 39-76, 203, 205, 207, 212, 233, 235, 237, 239, 262, 264, 266, 268, 270, 272, 274, 276, 278, 280, 282, 284, 286, 288, 290.
19. A vector comprising a nucleic acid molecule as claimed in claim 17 or claim 18.
20. A host cell comprising a nucleic acid or a vector as claimed in any one of claims 17-19.
21. A method of producing a polypeptide comprising an anti-TGFbetaRII immunoglobulin single variable domain as claimed in any one of claims 1-16, the method comprising maintaining a host cell as claimed in claim 20 under conditions suitable for expression of said nucleic acid or vector, whereby a polypeptide comprising an immunoglobulin single variable is produced.
22. An anti-TGFbetaRII immunoglobulin single variable domain or polypeptide as claimed in any one of claims 1-16 for use as a medicament.
23. A pharmaceutical composition comprising an anti-TGFbetaRII immunoglobulin single variable domain or polypeptide as claimed in any one of claims 1-16.
24. An anti-TGFbetaRII immunoglobulin single variable domain or polypeptide as claimed in claim 22 or pharmaceutical composition as claimed in claim 23 for treatment of a disease associated with TGFbeta signaling.
25. An anti-TGFbetaRII immunoglobulin single variable domain, polypeptide or pharmaceutical composition as claimed in claim 24, wherein the disease associated with TGFbeta signalling is selected from the group of: tissue fibrosis, such as pulmonary fibrosis, including idiopathic pulmonary fibrosis; liver fibrosis, including cirrhosis and chronic hepatitis; rheumatoid arthritis; ocular disorders; fibrosis of the skin, including keloid of skin, and Dupuytren's Contracture;

kidney fibrosis such as nephritis and nephrosclerosis, wound healing; and a vascular condition, such as restenosis.

26. An anti-TGFbetaRII immunoglobulin single variable domain, polypeptide or pharmaceutical composition as claimed in claim 22, for use in treating tissue fibrosis or for use in wound healing and/or scarring reduction.
27. An anti-TGFbetaRII immunoglobulin single variable domain as claimed in claim 22, 24 or 25, wherein the disease is keloid disease or Dupuytren's Contracture.
28. Use of an anti-TGFbetaRII single variable domain or polypeptide as claimed in any one of claims 1-16 in the manufacture of a medicament for the treatment of a disease associated with TGFbeta signaling.
29. A method of treating and/or preventing a TGFbeta-mediated condition in a human patient, the method comprising the step of: administering a composition comprising an anti-TGFbetaRII immunoglobulin single variable domain or polypeptide as claimed in any one of claims 1-16 to the human patient.
30. A kit comprising an anti-TGFbetaRII single variable domain or polypeptide as claimed in any one of claims 1-16 and a device for applying said single variable domain or polypeptide to the skin.
31. A kit as claimed in claim 30, wherein the device is an intradermal delivery device.

Claims

1. An anti-TGFbetaRII immunoglobulin single variable domain comprising an amino acid sequence as set forth in SEQ ID NO: 267 having up to 5 amino acid substitutions, deletions or additions, in any combination.
2. An anti-TGFbetaRII immunoglobulin single variable domain as claimed in claim 1, wherein the said amino acid substitutions, deletions or additions are not within CDR3.
3. An anti-TGFbetaRII immunoglobulin single variable domain as claimed in claim 1 or 2, wherein the said amino acid substitutions, deletions or additions are not within any of the CDRs.
4. An anti-TGFbetaRII immunoglobulin single variable domain as claimed in claim 1 having the sequence of SEQ ID NO:267.
5. An isolated polypeptide comprising an anti-TGFbetaRII immunoglobulin single variable domain as claimed in any one of the preceding claims, wherein said isolated polypeptide binds to TGFbetaRII.
6. An anti-TGFbetaRII immunoglobulin single variable domain as claimed in any of claims 1-4, or a polypeptide as claimed in claim 5, further comprising at least one of the following amino acids selected from the group: R at position 39, I at position 48, D at position 53, N at position 61, R at position 61, K at position 61, R at position 64, F at position 64, D at position 64, E at position 64, M at position 64, Y at position 64, H at position 102, or S at position 103 of the immunoglobulin single variable domain, said positions being according to the Kabat numbering convention.
7. An anti-TGFbetaRII immunoglobulin single variable domain or a polypeptide as claimed in claim 6, comprising an R or a K at position 61 (Kabat numbering convention).
8. An anti-TGFbetaRII immunoglobulin single variable domain as claimed in any of claims 1-4, or a polypeptide as claimed in claim 5, further comprising one of the following amino acid combinations selected from the group: N at position 61 and R at position 64; R at position 61 and E at position 64; R at position 61 and M at position 64; R at position 61 and F at position 64; R at position 61 and Y at position 64; and R at position 61 and D at position 64 of the immunoglobulin single variable domain, said positions being according to the Kabat numbering convention.
9. An anti-TGFbetaRII immunoglobulin single variable domain or a polypeptide as claimed in claim 6, 7 or 8, comprising an isoleucine residue at position 48 (Kabat numbering convention).

10. An anti-TGFbetaRII immunoglobulin single variable domain or polypeptide as claimed in any one of claims 1-9, wherein said anti-TGFbetaRII immunoglobulin single variable domain or polypeptide binds to human TGFbetaRII.
11. An anti-TGFbeta RII immunoglobulin single variable domain or polypeptide as claimed in claim 10, wherein said anti-TGFbetaRII immunoglobulin single variable domain or polypeptide also binds to mouse TGFbetaRII and/or cyno TGFbetaRII.
12. An immunoglobulin single variable domain or polypeptide as claimed in any one of claims 1-11, wherein said immunoglobulin single variable domain or polypeptide neutralises TGFbeta activity.
13. An immunoglobulin single variable domain or polypeptide as claimed in any one of claims 1-12, wherein said immunoglobulin single variable domain or polypeptide inhibits binding of TGFbeta to TGFbetaRII.
14. An isolated nucleic acid encoding an anti-TGFbetaRII immunoglobulin single variable domain or polypeptide as claimed in any one of claims 1-13.
15. An isolated nucleic acid molecule as claimed in claim 14, comprising the nucleic acid molecule of: SEQ ID NO: 266.
16. A vector comprising a nucleic acid molecule as claimed in claim 14 or claim 15.
17. A host cell comprising a nucleic acid or a vector as claimed in any one of claims 14-16.
18. A method of producing a polypeptide comprising an anti-TGFbetaRII immunoglobulin single variable domain as claimed in any one of claims 1-13, the method comprising maintaining a host cell as claimed in claim 17 under conditions suitable for expression of said nucleic acid or vector, whereby a polypeptide comprising an immunoglobulin single variable is produced.
19. An anti-TGFbetaRII immunoglobulin single variable domain or polypeptide as claimed in any one of claims 1-13 for use as a medicament.
20. A pharmaceutical composition comprising an anti-TGFbetaRII immunoglobulin single variable domain or polypeptide as claimed in any one of claims 1-13.
21. An anti-TGFbetaRII immunoglobulin single variable domain or polypeptide as claimed in claim 19 or pharmaceutical composition as claimed in claim 20 for use in the treatment of a disease selected from the group of: tissue fibrosis, such as pulmonary fibrosis, including idiopathic pulmonary fibrosis; liver fibrosis, including cirrhosis and chronic hepatitis; rheumatoid arthritis; ocular disorders; fibrosis of the skin, including keloid of skin, and Dupuytren's Contracture; kidney fibrosis such as nephritis and nephrosclerosis, wound healing; and a vascular condition, such as restenosis.

22. An anti-TGFbetaRII immunoglobulin single variable domain or polypeptide as claimed in claim 19 or pharmaceutical composition as claimed in claim 20, for use in treating tissue fibrosis or for use in wound healing and/or scarring reduction.
23. An anti-TGFbetaRII immunoglobulin single variable domain as claimed in claim 19 or 21, wherein the disease is keloid disease or Dupuytren's Contracture.
24. Use of an anti-TGFbetaRII single variable domain or polypeptide as claimed in any one of claims 1-13 in the manufacture of a medicament for the treatment of a disease selected from the group of: tissue fibrosis, such as pulmonary fibrosis, including idiopathic pulmonary fibrosis; liver fibrosis, including cirrhosis and chronic hepatitis; rheumatoid arthritis; ocular disorders; fibrosis of the skin, including keloid of skin, and Dupuytren's Contracture; kidney fibrosis such as nephritis and nephrosclerosis, wound healing; and a vascular condition, such as restenosis.
25. A kit comprising an anti-TGFbetaRII single variable domain or polypeptide as claimed in any one of claims 1-13 and a device for applying said single variable domain or polypeptide to the skin.
26. A kit as claimed in claim 25, wherein the device is an intradermal delivery device.