

CLAIMS

1. An inhibitor of IGFBP5 and/or of at least one of its receptors, wherein said inhibitor has anti-fibrotic effect and/or an anti-fibrosis activity.
2. An inhibitor of IGFBP5 and/or of at least one of its receptors for use in the treatment and/or prevention of fibrosis and/or of a fibrotic condition.
3. Use of the inhibitor according to claim 1 in the preparation of a medicament for the treatment and/or prevention of fibrosis and/or a fibrotic condition.
- ~~34~~. The inhibitor according to claim 1 or 2 or the use according to claim 3, wherein said inhibitor is selected from the group consisting of:
 - a) a polypeptide;
 - b) a polynucleotide or a polynucleotide coding for said polypeptide;
 - c) a vector comprising or expressing said polynucleotide;
 - d) a host cell genetically engineered expressing said polypeptide or said polynucleotide;
 - e) a small molecule;
 - f) a peptide, a protein, an antibody, an antisense oligonucleotide, a siRNA, antisense expression vector or recombinant virus.
45. The inhibitor or the use according to any one of previous claim wherein said inhibitor is an isolated antibody or antigen binding fragment thereof that binds to human IGFBP5 or to at least one of its receptors, wherein said isolated antibody or antigen binding fragment thereof has anti-fibrotic effect.
56. The inhibitor or the use according to any one of previous claim wherein said inhibitor inhibits, reduces, or neutralizes the formation of α SMA induced by a pro-fibrotic mediator and /or that inhibits, reduces, or neutralizes the activation of FN1 expression induced by a pro-fibrotic mediator.
67. The inhibitor or the use according to any one of previous claim wherein said inhibitor is an isolated antibody or antigen binding fragment thereof that binds to human IGFBP5 and has anti-fibrotic effect.
78. The inhibitor or the use according to claim 6-7 comprising:
 - a. a heavy chain variable domain (VH) comprising:
 - i. a CDR1 sequence of the amino acid sequence selected from the group consisting of: SEQ ID NO: 1, 2, 3, 4 and 5;
 - ii. a CDR2 sequence of the amino acid sequence selected from the group consisting of: SEQ ID NO: 6, 7, 8, 9, 10 and 11; and

iii. a CDR3 sequence of the amino acid sequence selected from the group consisting of: SEQ ID NO: 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25 and 26; and/or

b. a light chain variable domain (VL) comprising:

i. a CDR1 sequence of the amino acid sequence selected from the group consisting of: SEQ ID NO: 27, 28, 29, 30, 31, 32, 33, 34, 35 and 36;

ii. a CDR2 sequence of the amino acid sequence selected from the group consisting of: SEQ ID NO: 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47; and

iii. a CDR3 sequence of the amino acid sequence selected from the group consisting of: SEQ ID NO: 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60.

89. The inhibitor or the use according to any one of claims ~~6 or 7~~ or 8 comprising:

a. a heavy chain variable domain (VH) comprising:

i. a CDR1 sequence of the amino acid sequence selected from the group consisting of a sequence as defined using abysis tool analysis

(www.abysis.org); ~~preferably as shown in Table 4.1;~~

ii. a CDR2 sequence of the amino acid sequence selected from the group consisting of a sequence as defined using abysis tool analysis (www.abysis.org) ~~preferably as shown in Table 4.1;~~ and

iii. a CDR3 sequence of the amino acid sequence selected from the group consisting of a sequence as defined using abysis tool analysis

(www.abysis.org) ~~preferably as shown in Table 4.1;~~ and

b. a light chain variable domain (VL) comprising:

i. a CDR1 sequence of the amino acid sequence selected from the group consisting of a sequence as defined using abysis tool analysis (www.abysis.org)

~~preferably as shown in Table 4.1;~~

ii. a CDR2 sequence of the amino acid sequence selected from the group consisting of a sequence as defined using abysis tool analysis (www.abysis.org)

~~preferably as shown in Table 4.1;~~ and

iii. a CDR3 sequence of the amino acid sequence selected from the group consisting of a sequence as defined using abysis tool analysis

(www.abysis.org) ~~preferably as shown in Table 4.1.~~

10. The inhibitor or the use according to claim 9 comprising:

a. a heavy chain variable domain (VH) comprising:

i. a CDR1 sequence of the amino acid sequence selected from the group consisting of a sequence as shown in Table 4.1;

ii. a CDR2 sequence of the amino acid sequence selected from the group consisting of a sequence as shown in Table 4.1; and

iii. a CDR3 sequence of the amino acid sequence selected from the group consisting of a sequence as shown in Table 4.1; and

b. a light chain variable domain (VL) comprising:

i. a CDR1 sequence of the amino acid sequence selected from the group consisting of a sequence as shown in Table 4.1;

ii. a CDR2 sequence of the amino acid sequence selected from the group consisting of a sequence as shown in Table 4.1; and

iii. a CDR3 sequence of the amino acid sequence selected from the group consisting of a sequence as shown in Table 4.1.

9-11. The inhibitor or the use according to any one of claims ~~6-8~~ 7 to 10 comprising:

a. a heavy chain variable domain (VH) comprising:

i. a CDR1 sequence of the amino acid sequence selected from the group consisting of a sequence as defined using abysis tool analysis (www.abysis.org); ~~preferably as shown in Table 5.1;~~

ii. a CDR2 sequence of the amino acid sequence selected from the group consisting of a sequence as defined using abysis tool analysis (www.abysis.org) ~~preferably as shown in Table 5.1; and~~

iii. a CDR3 sequence of the amino acid sequence selected from the group consisting of a sequence as defined using abysis tool analysis (www.abysis.org) ~~preferably as shown in Table 5.1; and~~

b. a light chain variable domain (VL) comprising:

i. a CDR1 sequence of the amino acid sequence selected from the group consisting of a sequence as defined using abysis tool analysis (www.abysis.org) ~~preferably as shown in Table 5.1;~~

ii. a CDR2 sequence of the amino acid sequence selected from the group consisting of a sequence as defined using abysis tool analysis (www.abysis.org) ~~preferably as shown in Table 5.1; and~~

iii. a CDR3 sequence of the amino acid sequence selected from the group consisting of a sequence as defined using abysis tool analysis (www.abysis.org) ~~preferably as shown in Table 5.1.~~

12. The inhibitor or the use according to claim 11 comprising:

a. a heavy chain variable domain (VH) comprising:

i. a CDR1 sequence of the amino acid sequence selected from the group consisting of a sequence as shown in Table 5.1;

ii. a CDR2 sequence of the amino acid sequence selected from the group consisting of a sequence as shown in Table 5.1; and

iii. a CDR3 sequence of the amino acid sequence selected from the group consisting of a sequence as shown in Table 5.1; and

b. a light chain variable domain (VL) comprising:

i. a CDR1 sequence of the amino acid sequence selected from the group consisting of a sequence as shown in Table 5.1;

ii. a CDR2 sequence of the amino acid sequence selected from the group consisting of a sequence as shown in Table 5.1; and

iii. a CDR3 sequence of the amino acid sequence selected from the group consisting of a sequence as shown in Table 5.1.

~~40~~13. The inhibitor or use according to any one of claims ~~6-7~~ to ~~12~~9 comprising:

a. a heavy chain variable domain sequence of the amino acid sequence selected from the group consisting of: SEQ ID NO:61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74 and 75 or

b. a light chain variable domain sequence of the amino acid sequence selected from the group consisting of: SEQ ID NO: 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, and 90, or

c. the heavy chain variable domain of (a) and the light chain variable domain of (b).

~~44~~14. The inhibitor or use according any one of claims ~~6-7~~ to ~~13~~4 selected from the group consisting of: A09, B06, C02, D10, F05, B09, B11, C11, C12, D12, E02, E03, E05, F04, G01, preferably the isolated antibody or antigen binding fragment thereof is the antibody B06 or B09.

~~42~~15. The inhibitor or use according to claim ~~14~~4, comprising VH CDR1, CDR2 and CDR3 selected from Table 2 and VL CDR1, CDR2 and CDR3 selected from Table 3.

~~43~~16. The inhibitor or use according to any one of claims ~~6-7~~ to ~~15~~4 having an affinity constant lower than or equal to 10^{-8} M for human IGFBP5.

~~44~~17. The inhibitor or use according to any one of claims ~~1~~ to ~~5~~6 being an isolated antibody or antigen binding fragment thereof that:

(a) binds specifically to an epitope on IGFBP5, said epitope being the same or similar epitope as the epitope recognized by the monoclonal antibody A09, B06, C02, D10, F05, B09, B11, C11, C12, D12, E02, E03, E05, F04, G01 as defined in Tables 2-8; or

5 (b) cross-competes for binding with the monoclonal antibody A09, B06, C02, D10, F05, B09, B11, C11, C12, D12, E02, E03, E05, F04, G01 as defined in Tables 2-8; or

(c) shows the same or similar binding affinity or specificity, or both, as any of A09, B06, C02, D10, F05, B09, B11, C11, C12, D12, E02, E03, E05, F04, G0 as defined in Tables 2-8; or

(d) has one or more biological properties of an antibody molecule described herein, e.g., an antibody molecule chosen from, e.g., any of A09, B06, C02, D10, F05, B09, B11, C11, C12, D12, E02, E03, E05, F04, G01 as defined in Tables 2-8 and; or

15 (e) has one or more pharmacokinetic properties of an antibody molecule described herein, e.g., an antibody molecule chosen from, e.g., any of A09, B06, C02, D10, F05, B09, B11, C11, C12, D12, E02, E03, E05, F04, G01 as defined in Tables 2-8.

18. The inhibitor or use according to claim 6-7 being an isolated antibody or antigen binding fragment thereof that:

(a) binds specifically to an epitope on IGFBP5, said epitope being the same or similar epitope as the epitope recognized by the monoclonal antibody A09, B06, C02, D10, F05, B09, B11, C11, C12, D12, E02, E03, E05, F04, G01 as defined in Tables 2-8; or

25 (b) cross-competes for binding with the monoclonal antibody A09, B06, C02, D10, F05, B09, B11, C11, C12, D12, E02, E03, E05, F04, G01 as defined in Tables 2-8; or

(c) shows the same or similar binding affinity or specificity, or both, as any of A09, B06, C02, D10, F05, B09, B11, C11, C12, D12, E02, E03, E05, F04, G0 as defined in Tables 2-8; or

(d) has one or more biological properties of an antibody molecule described herein, e.g., an antibody molecule chosen from, e.g., any of A09, B06, C02, D10, F05, B09, B11, C11, C12, D12, E02, E03, E05, F04, G01 as defined in Tables 2-8 and; or

(e) has one or more pharmacokinetic properties of an antibody molecule described herein, e.g., an antibody molecule chosen from, e.g., any of A09, B06, C02, D10, F05, B09, B11, C11, C12, D12, E02, E03, E05, F04, G01 as defined in Tables 2-8.

5 ~~46~~19. The inhibitor or use according to any one of previous claims being a human or a humanized antibody.

~~47~~20. The inhibitor or use according to any one of previous claims being an IgG2 or IgG4 antibody, preferably an IgG2 kappa antibody, an IgG2 lambda antibody, an IgG4 kappa antibody or an IgG4 lambda antibody.

10 ~~48~~21. The inhibitor or use according to any one of previous claims wherein said inhibitor reduces or inhibits the binding of IGFBP5 to at least one of its receptors, preferably the at least one receptor is the $\alpha 2\beta 1$ integrin or $\alpha \nu \beta 6$ integrin.

~~49~~22. The inhibitor or use according to any one of previous claims wherein said inhibitor i) reduces or inhibits extracellular matrix production and/or ii) reduces or inhibits
15 extracellular matrix deposition and/or iii) reduces or inhibits collagen and/or fibronectin production in primary lung fibroblasts and/or iv) reduces or inhibits collagen and/or fibronectin deposition in primary lung fibroblasts.

~~20~~23. An isolated polynucleotide comprising at least one sequence that encodes the inhibitor according to any one of claims ~~4~~5 to ~~48~~22, preferably said polynucleotide being a cDNA or a vector comprising said isolated polynucleotide, preferably said vector being selected from the group consisting of a plasmid, a viral vector, a non-episomal mammalian vector, an expression vector and a recombinant expression vector or an isolated cell comprising said isolated polynucleotide or said vector, preferably said isolated cell being a hybridoma or a Chinese Hamster Ovary (CHO) cell or a Human Embryonic Kidney cells (HEK293).
25

~~24~~24. The inhibitor or use according to any one of claims 1 to ~~48~~22 or the polynucleotide or the vector or the cell according to claim ~~49~~23 for use as a medicament, preferably for use in the treatment and/or prevention of fibrosis or of a fibrotic condition, preferably scleroderma or pulmonary fibrosis, preferably morphea, fibrosis as a result of Graft-Versus-Host Disease (GVHD), keloid and hypertrophic scar, subepithelial fibrosis, endomyocardial fibrosis, uterine fibrosis, myelofibrosis, retroperitoneal fibrosis, nephrogenic systemic fibrosis, scarring after surgery, asthma, aberrant wound healing, multifocal fibrosclerosis, cryptogenic fibrosing alveolitis (CFA), and idiopathic pulmonary fibrosis (IPF).
30

25. Use of the inhibitor according to any one of claims 1 to 22 or the polynucleotide or the vector or the cell according to claim 23 in the preparation of a medicament for use in the treatment and/or prevention of fibrosis or of a fibrotic condition.
- 5 26. Use of the inhibitor according to any one of claims 1 to 22 or the polynucleotide or the vector or the cell according to claim 23 in the preparation of a medicament for use in the treatment and/or prevention of fibrosis or of a fibrotic condition, wherein said fibrosis or fibrotic condition is scleroderma, pulmonary fibrosis, morphea, fibrosis as a result of Graft-Versus-Host Disease (GVHD), keloid and hypertrophic scar, subepithelial fibrosis, endomyocardial fibrosis, uterine fibrosis,
- 10 myelofibrosis, retroperitoneal fibrosis, nephrogenic systemic fibrosis, scarring after surgery, asthma, aberrant wound healing, multifocal fibrosclerosis, cryptogenic fibrosing alveolitis (CFA), or idiopathic pulmonary fibrosis (IPF).
- 15 ~~2227. A pharmaceutical composition comprising the inhibitor according to any one of claims 1 to 2249 or the polynucleotide or the vector or the cell according to claim 23 and pharmaceutically acceptable carrier, preferably for use in the treatment of fibrosis or of a fibrotic condition, preferably said composition further comprises a therapeutic agent.~~
28. Use of the pharmaceutical composition of claim 27 in the preparation of a medicament for use in the treatment of fibrosis or of a fibrotic condition.
- 20 29. The pharmaceutical composition of claim 27 further comprising a therapeutic agent.