

synthesized and transiently upregulated in the infarcted myocardium. Fibronectin-EDA can activate the immune system and other cells involved in matrix turnover, thereby inducing the migration and differentiation of cells involved in cardiac repair (e.g. leukocytes, lymphocytes and fibroblasts). Subsequently, cells activated by fibronectin-

5 EDA induce detrimental inflammatory reactions in the healing heart.

Cellular fibronectin is a multifunctional adhesive glycoprotein present in the ECM and is produced by cells in response to tissue injury as occurs with MI. It contains an alternatively spliced exon encoding type III repeat extra domain A (EIIIA; EDA), that acts as an endogenous ligand for both TLR2 and TLR4 and integrin $\alpha 4\beta 1$, $\alpha 4\beta 7$ and $\alpha 9\beta 1$.

10 *In vitro*, fibronectin-EDA induces pro-inflammatory gene expression and activates monocytes. *In vivo* injection of fibronectin-EDA in murine joints results in enhanced inflammation. Fibronectin-EDA is not normally expressed in healthy human tissue, but is highly upregulated in newly developing vasculature during embryogenesis and in several (pathological) conditions such as (cardiac) ischemic tissue, atherosclerotic lesions, fibrotic tissue, tumors, transplant rejection and wounds. Overexpression of EDA results in enhanced inflammation and injury after brain ischemia. Thus, fibronectin-EDA is capable of activating leukocytes and causes an upregulation of cytokines and chemokines. It was recently shown that fibronectin-EDA knockout mice exhibited reduced fibrosis, preserved cardiac function and reduced ventricular dilatation compared to wild-type mice

20 after myocardial infarction (Arslan F. et al. Circ. Res., Mar 2011; 108: 582 – 592).

WO2012/057613 describes that treatment of mice with antibodies directed to the EDA domain of fibronectin-EDA prevents left ventricular dilatation in said mice and improves survival after myocardial infarction.

There remains a need in the art for antibodies that are capable of treating, preventing, or

25 preventing the progression of myocardial infarction-related conditions in a subject and that increase the chance of survival of a subject after myocardial infarction. It is an object of the present invention to provide for such antibodies.

Summary of the invention

30 In one aspect, the present invention provides use of an antibody that binds fibronectin-EDA or an antigen-binding fragment thereof for the preparation of a medicament for use in improving angiogenesis, preferably after tissue injury.

The disclosure provides an antibody that binds fibronectin-EDA or an antigen-binding fragment thereof for use in improving angiogenesis, preferably after tissue injury.

35 Preferably wherein angiogenesis is improved in a subject suffering from ischemic disease, preferably in ischemic tissue of said subject. The disclosure further

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provides a method for stimulating angiogenesis in a subject in need thereof comprising administering to said subject a therapeutically effective amount of an antibody that binds fibronectin-EDA or an antigen-binding fragment thereof. Preferably wherein said subject is suffering from

ischemic disease, and preferably wherein angiogenesis is improved in ischemic tissue of said subject. The disclosure also provides an antibody that binds fibronectin-EDA or an antigen-binding fragment thereof for use in the treatment of a condition associated with pressure-overload. Preferably wherein said condition is cardiac remodelling. The

- 5 disclosure also provides a method for the treatment of a condition associated with pressure-overload in a subject comprising administering to the subject in need thereof a therapeutically effective amount of an antibody that binds fibronectin-EDA or an antigen-binding fragment thereof. Preferably wherein said condition is cardiac-remodelling.
- 10 The antibody that binds fibronectin-EDA or an antigen-binding fragment thereof is preferably a fibronectin-EDA or an antigen-binding fragment thereof as described herein.

The present disclosure provides an isolated immunoglobulin (Ig)-like molecule or antigen-binding fragment thereof specifically binding to an amino acid sequence GIXXXF (SEQ ID NO:1), wherein X may be any amino acid.

In an example , the amino acid at position 3 of SEQ ID NO:1 is selected from histidine, arginine, lysine and alanine, and preferably is histidine.

In an example, the amino acid at position 4 of SEQ ID NO: 1 is selected from glutamic acid and alanine, and preferably is glutamic acid.

- 20 In an example, the amino acid at position 5 of SEQ ID NO:1 is selected from leucine and alanine, and preferably is leucine.

In an example, the Ig-like molecule or fragment thereof specifically binds to an amino acid sequence GIHELF (SEQ ID NO:2).

- The present disclosure further provides an isolated immunoglobulin (Ig)-like molecule or antigen-binding fragment thereof specifically binding to an amino acid sequence LFPAP (SEQ ID NO:28).

- The Ig-like molecule or antigen-binding fragment thereof may be an antibody or an antigen-binding fragment thereof, e.g., a monoclonal antibody or an antigen-binding fragment thereof. The Ig-like molecule or antigen-binding fragment thereof may be of murine origin, e.g., may be derived from a mouse. The Ig-like molecule or antigen-binding fragment thereof may be chimeric, humanized or human.

- The disclosure also pertains to an Ig-like molecule or antigen-binding fragment thereof comprising a heavy chain variable region comprising a complementarity determining region (CDR)1 having the amino acid sequence shown in SEQ ID NO:3 or an amino acid sequence as shown in SEQ ID NO:3, wherein at most 2, preferably at most 1 amino acid is substituted, a CDR2 having the amino acid sequence shown in SEQ ID NO:4 or an

amino acid sequence as shown in SEQ ID NO:4, wherein at most 2, preferably at most 1 amino acid is substituted, and a CDR3 having the amino acid sequence shown in SEQ ID NO:5 or an amino acid sequence as shown in SEQ ID NO:5, wherein at most 3, preferably at most 2, more preferably at most 1 amino acid is substituted.

5 In an example, the present disclosure relates to an Ig-like molecule or antigen-binding fragment thereof comprising a heavy chain variable region comprising:

- a CDR1 having the amino acid sequence GYSIX₁SGYSWH, wherein X₁ is selected from T and A;

- a CDR2 having the amino acid sequence YIHX₂SGX₃ANYNPSLKS, wherein X₂ is
10 selected from Y and F, and wherein X₃ is selected from S and I;

- a CDR3 having the amino acid sequence EX₄X₅GX₆FDY, wherein X₄ is selected from K and A, X₅ is selected from T and R, and X₆ is selected from F and Y.

The present disclosure also relates to an Ig-like molecule or antigen-binding fragment thereof comprising a light chain variable region comprising a CDR1 having the amino acid sequence
15 shown in SEQ ID NO:6 or an amino acid sequence as shown in SEQ ID NO:6, wherein at most 3, preferably at most 2, more preferably at most 1 amino acid is substituted, a CDR2 having the amino acid sequence shown in SEQ ID NO:7 or an amino acid sequence as shown in SEQ ID NO:7, wherein at most 2, preferably at most 1 amino acid is substituted, and a CDR3 having the amino acid sequence shown in SEQ ID NO:8 or an amino acid sequence as
20 shown in SEQ ID NO:8, wherein at most 3, preferably at most 2, more preferably at most 1 amino acid is substituted.

In an example, the present disclosure provides an Ig-like molecule or antigen-binding fragment thereof comprising a light chain variable region comprising:

- a CDR1 having the amino acid sequence RSSQSX₇VX₈SNGNTYLX₉, wherein X₇ is
25 selected from L and I, X₈ is selected from H and R, and X₉ is selected from H and T;

- a CDR2 having the amino acid sequence KVSNRFS;

- a CDR3 having the amino acid sequence X₁₀QX₁₁X₁₂HVPPT, wherein X₁₀ is
selected from S and F, X₁₁ is selected from S and G, and X₁₂ is selected from A and S.

The present disclosure further relates to an Ig-like molecule or antigen-binding fragment
30 thereof comprising a heavy chain variable region comprising a CDR1 having the amino acid sequence shown in SEQ ID NO:3 or an amino acid sequence as shown in SEQ ID NO:3, wherein at most 2, preferably at most 1 amino acid is substituted, a CDR2 having the amino acid sequence shown in SEQ ID NO:4 or an amino acid sequence as shown in SEQ ID NO:4, wherein at most 2, preferably at most 1 amino acid is substituted, and a CDR3 having the
35 amino acid sequence shown in SEQ ID NO:5 or an amino acid sequence as shown in SEQ ID NO:5, wherein at most 3, preferably at most 2, more

preferably at most 1 amino acid is substituted; and a light chain variable region comprising a CDR1 having the amino acid sequence shown in SEQ ID NO:6 or an amino acid sequence as shown in SEQ ID NO:6, wherein at most 3, preferably at most 2, more preferably at most 1 amino acid is substituted, a CDR2 having the amino acid sequence shown in SEQ ID NO:7 or an amino acid sequence as shown in SEQ ID NO:7, wherein at most 2, preferably at most 1 amino acid is substituted, and a CDR3 having the amino acid sequence shown in SEQ ID NO:8 or an amino acid sequence as shown in SEQ ID NO:8, wherein at most 3, preferably at most 2, more preferably at most 1 amino acid is substituted.

In an example, such Ig-like molecule or antigen-binding fragment comprises a heavy

chain variable region comprising

- a CDR1 having the amino acid sequence GYSIX₁SGYSWH, wherein X₁ is selected from T and A;
 - a CDR2 having the amino acid sequence YIHX₂SGX₃ANYNPSLKS, wherein X₂ is selected from Y and F, and wherein X₃ is selected from S and I;
 - 15 - a CDR3 having the amino acid sequence EX₄X₅GX₆FDY, wherein X₄ is selected from K and A, X₅ is selected from T and R, and X₆ is selected from F and Y;
- and a light chain variable region comprising:
- a CDR1 having the amino acid sequence RSSQSX₇VX₈SNGNTYLX₉, wherein X₇ is selected from L and I, X₈ is selected from H and R, and X₉ is selected from H and T;
 - 20 - a CDR2 having the amino acid sequence KVSNRFS;
 - a CDR3 having the amino acid sequence X₁₀QX₁₁X₁₂HVPPT, wherein X₁₀ is selected from S and F, X₁₁ is selected from S and G, and X₁₂ is selected from A and S.

In one example, the Ig-like molecule, antibody or antigen-binding fragment thereof comprises a heavy chain variable region comprising:

- 25 - a CDR1 having the amino acid sequence shown in SEQ ID NO:9;
 - a CDR2 having the amino acid sequence shown in SEQ ID NO:10; and
 - a CDR3 having the amino acid sequence shown in SEQ ID NO:11;
- and a light chain variable region comprising:
- a CDR1 having the amino acid sequence shown in SEQ ID NO:12;
 - 30 - a CDR2 having the amino acid sequence shown in SEQ ID NO:13; and
 - a CDR3 having the amino acid sequence shown in SEQ ID NO:14.

Preferably, said Ig-like molecule, antibody or antigen-binding fragment thereof comprises a humanized heavy chain variable region of the heavy chain variable region having the amino acid sequence of SEQ ID NO:40 and a humanized light chain variable region of the light chain variable region having the amino acid sequence of SEQ ID NO:41.

In another example, the Ig-like molecule, antibody or antigen-binding fragment thereof comprises a heavy chain variable region comprising:

- a CDR1 having the amino acid sequence shown in SEQ ID NO:3;
- a CDR2 having the amino acid sequence shown in SEQ ID NO:4; and
- 5 - a CDR3 having the amino acid sequence shown in SEQ ID NO:5;

and a light chain variable region comprising:

- a CDR1 having the amino acid sequence shown in SEQ ID NO:6;
- a CDR2 having the amino acid sequence shown in SEQ ID NO:7; and
- a CDR3 having the amino acid sequence shown in SEQ ID NO:8.

- 10 Preferably, said Ig-like molecule, antibody or antigen-binding fragment thereof comprises a humanized heavy chain variable region of the heavy chain variable region having the amino acid sequence of SEQ ID NO:38 and a humanized light chain variable region of the light chain variable region having the amino acid sequence of SEQ ID NO:39.

In yet another example, the Ig-like molecule, antibody or antigen-binding fragment

- 15 thereof comprises a heavy chain variable region comprising:

- a CDR1 having the amino acid sequence shown in SEQ ID NO:15;
- a CDR2 having the amino acid sequence shown in SEQ ID NO:16; and
- a CDR3 having the amino acid sequence shown in SEQ ID NO:17;

and a light chain variable region comprising:

- 20 - a CDR1 having the amino acid sequence shown in SEQ ID NO:18;
- a CDR2 having the amino acid sequence shown in SEQ ID NO:19; and
 - a CDR3 having the amino acid sequence shown in SEQ ID NO:20.

Preferably, said Ig-like molecule, antibody or antigen-binding fragment thereof comprises

- 25 a humanized heavy chain variable region of the heavy chain variable region having the amino acid sequence of SEQ ID NO:42 and a humanized light chain variable region of the light chain variable region having the amino acid sequence of SEQ ID NO:43.

The present disclosure further provides an Ig-like molecule or antigen-binding fragment thereof comprising a heavy chain variable region comprising a complementarity

- 30 determining region (CDR)1 having the amino acid sequence shown in SEQ ID NO:29 or an amino acid sequence as shown in SEQ ID NO:29 wherein at most 2, preferably at most 1 amino acid is substituted, a CDR2 having the amino acid sequence shown in SEQ ID NO:30 or an amino acid sequence as shown in SEQ ID NO:30, wherein at most 2, preferably at most 1 amino acid is substituted, and a CDR3 having the amino acid
- 35 sequence SHY.

The disclosure also provides an Ig-like molecule or antigen-binding fragment thereof comprising a light chain variable region comprising a CDR1 having the amino acid sequence shown in SEQ ID NO:31 or an amino acid sequence as shown in SEQ ID NO:31, wherein at most 2, preferably at most 1 amino acid is substituted, a CDR2 having the amino acid sequence shown in SEQ ID NO:32 or an amino acid sequence as shown in SEQ ID NO:32, wherein at most 2, preferably at most 1 amino acid is substituted, and a CDR3 having the amino acid sequence shown in SEQ ID NO:33 or an amino acid sequence as shown in SEQ ID NO:33, wherein at most 2, preferably at most 1 amino acid is substituted.

- 10 In an example, Ig-like molecule or antigen-binding fragment thereof comprises a heavy chain variable region comprising a CDR1 having the amino acid sequence shown in SEQ ID NO:29 or an amino acid sequence as shown in SEQ ID NO:29, wherein at most 2, preferably at most 1 amino acid is substituted, a CDR2 having the amino acid sequence shown in SEQ ID NO:30 or an amino acid sequence as shown in SEQ ID NO:30, wherein at most 2, preferably at most 1 amino acid is substituted, and a CDR3 having the amino acid sequence SHY, and further comprising a light chain variable region comprising a CDR1 having the amino acid sequence shown in SEQ ID NO:31 or an amino acid sequence as shown in SEQ ID NO:31, wherein at most 2, preferably at most 1 amino acid is substituted, a CDR2 having the amino acid sequence shown in SEQ ID NO:32 or an amino acid sequence as shown in SEQ ID NO:32, wherein at most 2, preferably at most 1 amino acid is substituted, and a CDR3 having the amino acid sequence shown in SEQ ID NO:33 or an amino acid sequence as shown in SEQ ID NO:33, wherein at most 2, preferably at most 1 amino acid is substituted. In one example, the Ig-like molecule, antibody or antigen-binding fragment thereof comprises a heavy chain variable region comprising:

- a CDR1 having the amino acid sequence shown in SEQ ID NO:29;
- a CDR2 having the amino acid sequence shown in SEQ ID NO:30; and
- a CDR3 having the amino acid sequence SHY;

and a light chain variable region comprising:

- a CDR1 having the amino acid sequence shown in SEQ ID NO:31;
- a CDR2 having the amino acid sequence shown in SEQ ID NO:32; and
- a CDR3 having the amino acid sequence shown in SEQ ID NO:33.

Preferably, said Ig-like molecule, antibody or antigen-binding fragment thereof comprises a humanized heavy chain variable region of the heavy chain variable region having the amino acid sequence of SEQ ID NO:44 and a humanized light chain variable region of the light chain variable region having the amino acid sequence of SEQ ID NO:45.

In an example, the CDRs of the light chain and/or the heavy chain are integrated into human-derived framework regions.

The Ig-like molecule or antigen-binding fragment thereof may be an antibody, e.g., a chimeric antibody or a humanized antibody or antigen-binding fragment thereof.

- 5 The disclosure also provides a nucleic acid molecule encoding the Ig-like molecule or antigen-binding fragment thereof taught herein, and a vector comprising such nucleic acid molecule. Such vector may be a gene therapy vector.

Additionally, the disclosure provides a host cell comprising the nucleic acid molecule taught herein or the vector taught herein. The host cell may be a mammalian host cell.

- 10 The host cell may be a hybridoma.

The disclosure also provides a pharmaceutical composition comprising an agent selected from the group consisting of (a) the Ig-like molecule or antigen-binding fragment thereof as taught herein, (b) a nucleic acid molecule encoding the Ig-like molecule or antigen-binding fragment thereof, (c) a vector comprising such nucleic acid molecule and (d) a

- 15 host cell comprising such nucleic acid molecule or such vector, and a pharmaceutically acceptable carrier.

The disclosure further provides an Ig-like molecule or antigen-binding fragment thereof or pharmaceutical composition as taught herein for use as a medicament, particularly for
20 use in the treatment, prevention or prevention of the progression of adverse cardiac remodelling and conditions resulting from or relating to myocardial infarction and/or pressure overload, or for use in the treatment, prevention or prevention of the progression of adverse tissue remodelling, in particular fibronectin-EDA mediated adverse tissue remodelling.

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The present disclosure further provides a method of treating, preventing or preventing progression of adverse cardiac remodelling and conditions resulting from or relating to myocardial infarction and/or pressure overload, which comprises administering to a subject in need thereof, a therapeutically effective amount of an agent selected from the group

- 30 consisting of (a) the Ig-like molecule or antigen-binding fragment thereof as taught herein, a nucleic acid molecule encoding the Ig-like molecule or antigen-binding fragment thereof, (c) a vector comprising such nucleic acid molecule and (d) a host cell comprising such nucleic acid molecule or such vector. The subject may be human.

- 35 The present disclosure further provides an antibody that binds fibronectin-EDA or an antigen-binding fragment thereof for use in improving angiogenesis and a method for

Claims

1. Use of an antibody that binds fibronectin-EDA or an antigen-binding fragment thereof for the preparation of a medicament for use in improving angiogenesis, preferably
5 after tissue injury.
2. The use according to claim 1, wherein angiogenesis is improved in a subject suffering from ischemic disease, preferably in ischemic tissue of said subject.
- 10 3. The use according to claim 1 or 2, wherein the antibody or antigen-binding fragment thereof binds an amino acid sequence as set forth in SEQ ID NO:1 or SEQ ID NO:28.
4. The use according to claim 3 wherein the amino acid at position 3 of SEQ ID NO:1
15 is selected from histidine, arginine, lysine and alanine, preferably wherein the amino acid at position 3 of SEQ ID NO:1 is histidine, and/or wherein the amino acid at position 4 of SEQ ID NO: 1 is selected from glutamic acid and alanine, preferably wherein the amino acid at position 4 of SEQ ID NO:1 is glutamic acid, and/or wherein the amino acid at position 5 of SEQ ID NO:1 is selected from leucine and alanine, preferably wherein the
20 amino acid at position 5 of SEQ ID NO:1 is leucine.
5. The use according to claim 3 or 4, wherein the antibody or antigen-binding fragment thereof binds to an amino acid sequence as set forth in SEQ ID NO:2.
- 25 6 The use according to any one of claims 3-5 wherein the antibody or antigen-binding fragment thereof comprising a heavy chain variable region comprising a complementarity determining region (CDR)1 having the amino acid sequence shown in SEQ ID NO:3 or an amino acid sequence as shown in SEQ ID NO:3, wherein at most 2, preferably at most 1 amino acid is substituted, a CDR2 having the amino acid sequence
30 shown in SEQ ID NO:4 or an amino acid sequence as shown in SEQ ID NO:4, wherein at most 2, preferably at most 1 amino acid is substituted, and a CDR3 having the amino acid sequence shown in SEQ ID NO:5 or an amino acid sequence as shown in SEQ ID NO:5, wherein at most 3, preferably at most 2, more preferably at most 1 amino acid is substituted.

7 The use according to claim 6 wherein the antibody comprising a heavy chain variable region comprising:

- a CDR1 having the amino acid sequence GYSIX₁SGYSWH, wherein X₁ is selected from T and A;
- 5 – a CDR2 having the amino acid sequence YIHX₂SGX₃ANYNP₃SLKS, wherein X₂ is selected from Y and F, and wherein X₃ is selected from S and I;
- a CDR3 having the amino acid sequence EX₄X₅GX₆FDY, wherein X₄ is selected from K and A, X₅ is selected from T and R, and X₆ is selected from F and Y.

10 8. The use according to any one of claims 3-7 wherein the antibody comprises a light chain variable region comprising a CDR1 having the amino acid sequence shown in SEQ ID NO:6 or an amino acid sequence as shown in SEQ ID NO:6, wherein at most 3, preferably at most 2, more preferably at most 1 amino acid is substituted, a CDR2 having the amino acid sequence shown in SEQ ID NO:7 or an amino acid sequence as shown in
15 SEQ ID NO:7, wherein at most 2, preferably at most 1 amino acid is substituted, and a CDR3 having the amino acid sequence shown in SEQ ID NO:8 or an amino acid sequence as shown in SEQ ID NO:8, wherein at most 3, preferably at most 2, more preferably at most 1 amino acid is substituted.

20 9. The use according to claim 8 wherein the antibody comprising a light chain variable region comprising:

- a CDR1 having the amino acid sequence RSSQSX₇VX₈SNGNTYLX₉, wherein X₇ is selected from L and I, X₈ is selected from H and R, and X₉ is selected from H and T;
- 25 – a CDR2 having the amino acid sequence KVSNRFS;
- a CDR3 having the amino acid sequence X₁₀QX₁₁X₁₂HVPPT, wherein X₁₀ is selected from S and F, X₁₁ is selected from S and G, and X₁₂ is selected from A and S.

30 10. The use according to any one of claims 3-4 wherein the antibody comprises a heavy chain variable region comprising a CDR1 having the amino acid sequence shown in SEQ ID NO:3 or an amino acid sequence as shown in SEQ ID NO:3, wherein at most 2, preferably at most 1 amino acid is substituted, a CDR2 having the amino acid sequence shown in SEQ ID NO:4 or an amino acid sequence as shown in SEQ ID NO:4, wherein at
35 most 2, preferably at most 1 amino acid is substituted, and a CDR3 having the amino acid sequence shown in SEQ ID NO:5 or an amino acid sequence as shown in SEQ ID

NO:5, wherein at most 3, preferably at most 2, more preferably at most 1 amino acid is substituted; and a light chain variable region comprising a CDR1 having the amino acid sequence shown in SEQ ID NO:6 or an amino acid sequence as shown in SEQ ID NO:6, wherein at most 3, preferably at most 2, more preferably at most 1 amino acid is substituted, a CDR2 having the amino acid sequence shown in SEQ ID NO:7 or an amino acid sequence as shown in SEQ ID NO:7, wherein at most 2, preferably at most 1 amino acid is substituted, and a CDR3 having the amino acid sequence shown in SEQ ID NO:8 or an amino acid sequence as shown in SEQ ID NO:8, wherein at most 3, preferably at most 2, more preferably at most 1 amino acid is substituted.

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11. The use according to claim 10 wherein the antibody comprises

a heavy chain variable region comprising

- a CDR1 having the amino acid sequence GYSIX₁SGYSWH, wherein X₁ is selected from T and A;

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- a CDR2 having the amino acid sequence YIHX₂SGX₃ANYNPSLKS, wherein X₂ is selected from Y and F, and wherein X₃ is selected from S and I; and

- a CDR3 having the amino acid sequence EX₄X₅GX₆FDY, wherein X₄ is selected from K and A, X₅ is selected from T and R, and X₆ is selected from F and Y;

and a light chain variable region comprising:

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- a CDR1 having the amino acid sequence RSSQSX₇VX₈SNGNTYLX₉, wherein X₇ is selected from L and I, X₈ is selected from H and R, and X₉ is selected from H and T;

- a CDR2 having the amino acid sequence KVSNRFS; and

- a CDR3 having the amino acid sequence X₁₀QX₁₁X₁₂HVPPT, wherein X₁₀ is

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- selected from S and F, X₁₁ is selected from S and G, and X₁₂ is selected from A and S.

12. The use according to any one of claims 3-4 wherein the antibody comprises a heavy chain variable region comprising:

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- a CDR1 having the amino acid sequence shown in SEQ ID NO:9;

- a CDR2 having the amino acid sequence shown in SEQ ID NO:10; and

- a CDR3 having the amino acid sequence shown in SEQ ID NO:11;

and a light chain variable region comprising:

- a CDR1 having the amino acid sequence shown in SEQ ID NO:12;

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- a CDR2 having the amino acid sequence shown in SEQ ID NO:13; and

- a CDR3 having the amino acid sequence shown in SEQ ID NO:14.

13. The use according to any one of claims 3-4 wherein the antibody comprises a heavy chain variable region comprising:

- a CDR1 having the amino acid sequence shown in SEQ ID NO:3;
- a CDR2 having the amino acid sequence shown in SEQ ID NO:4; and
- a CDR3 having the amino acid sequence shown in SEQ ID NO:5;

and a light chain variable region comprising:

- a CDR1 having the amino acid sequence shown in SEQ ID NO:6;
- a CDR2 having the amino acid sequence shown in SEQ ID NO:7; and
- a CDR3 having the amino acid sequence shown in SEQ ID NO:8.

14. The use according to any one of claims 3-4 wherein the antibody comprises a heavy chain variable region comprising:

- a CDR1 having the amino acid sequence shown in SEQ ID NO:15;
- a CDR2 having the amino acid sequence shown in SEQ ID NO:16; and
- a CDR3 having the amino acid sequence shown in SEQ ID NO:17;

and a light chain variable region comprising:

- a CDR1 having the amino acid sequence shown in SEQ ID NO:18;
- a CDR2 having the amino acid sequence shown in SEQ ID NO:19; and
- a CDR3 having the amino acid sequence shown in SEQ ID NO:20.

15. The use according to any one of claims 3-4 wherein the antibody comprises a heavy chain variable region comprising a complementarity determining region (CDR)1 having the amino acid sequence shown in SEQ ID NO:29 or an amino acid sequence as shown in SEQ ID NO:29 wherein at most 2, preferably at most 1 amino acid is substituted, a CDR2 having the amino acid sequence shown in SEQ ID NO:30 or an amino acid sequence as shown in SEQ ID NO:30, wherein at most 2, preferably at most 1 amino acid is substituted, and a CDR3 having the amino acid sequence SHY.

16. The use according to any one of claims 3-4 wherein the antibody comprises a light chain variable region comprising a CDR1 having the amino acid sequence shown in SEQ ID NO:31 or an amino acid sequence as shown in SEQ ID NO:31, wherein at most 2, preferably at most 1 amino acid is substituted, a CDR2 having the amino acid sequence shown in SEQ ID NO:32 or an amino acid sequence as shown in SEQ ID NO:32, wherein at most 2, preferably at most 1 amino acid is substituted, and a CDR3 having the amino

acid sequence shown in SEQ ID NO:33 or an amino acid sequence as shown in SEQ ID NO:33, wherein at most 2, preferably at most 1 amino acid is substituted.

17. The use according to any one of claims 3-4 wherein the antibody comprises a heavy chain variable region comprising a CDR1 having the amino acid sequence shown in SEQ ID NO:29 or an amino acid sequence as shown in SEQ ID NO:29, wherein at most 2, preferably at most 1 amino acid is substituted, a CDR2 having the amino acid sequence shown in SEQ ID NO:30 or an amino acid sequence as shown in SEQ ID NO:30, wherein at most 2, preferably at most 1 amino acid is substituted, and a CDR3 having the amino acid sequence SHY, and further comprising a light chain variable region comprising a CDR1 having the amino acid sequence shown in SEQ ID NO:31 or an amino acid sequence as shown in SEQ ID NO:31, wherein at most 2, preferably at most 1 amino acid is substituted, a CDR2 having the amino acid sequence shown in SEQ ID NO:32 or an amino acid sequence as shown in SEQ ID NO:32, wherein at most 2, preferably at most 1 amino acid is substituted, and a CDR3 having the amino acid sequence shown in SEQ ID NO:33 or an amino acid sequence as shown in SEQ ID NO:33, wherein at most 2, preferably at most 1 amino acid is substituted.

18. The use according to claim 17 wherein the antibody comprises a heavy chain variable region comprising:

- a CDR1 having the amino acid sequence shown in SEQ ID NO:29;
- a CDR2 having the amino acid sequence shown in SEQ ID NO:30; and
- a CDR3 having the amino acid sequence SHY;

and/or a light chain variable region comprising:

- a CDR1 having the amino acid sequence shown in SEQ ID NO:31;
- a CDR2 having the amino acid sequence shown in SEQ ID NO:32; and
- a CDR3 having the amino acid sequence shown in SEQ ID NO:33.

19. The use according to any one of claims 3-4, wherein the CDRs of the light chain and/or the heavy chain are integrated into human-derived framework regions.

20. The use according to any one of claims 3-4 wherein the antibody comprises a heavy chain and a light chain, wherein said heavy chain has an amino acid sequence as shown in SEQ ID NO:34 and said light chain has an amino acid sequence as shown in SEQ ID NO:35 or wherein said heavy chain has an amino acid sequence as shown in SEQ ID NO:36 and said light chain has an amino acid sequence as shown in SEQ ID NO:37.

21. The use according to any one of claims 3-4 wherein the antibody comprises a heavy chain and a light chain, wherein said heavy chain comprises a constant region of an IgG4 heavy chain as set forth in SEQ ID NO:34 and said light chain comprises a constant region of an IgG4 light chain as set forth in SEQ ID NO:35 or wherein said heavy chain comprises a constant region of an IgG4 heavy chain as set forth in SEQ ID NO:36 and said light chain comprises a constant region of an IgG4 light chain as set forth in SEQ ID NO:37.

22. The use according to claim 21, wherein said heavy chain and/or light chain further comprise a variable region comprising one or more, preferably all, framework regions of an IgG4 heavy chain as set forth in SEQ ID NO:34 and/or of an IgG4 light chain as set forth in SEQ ID NO:35 or wherein said heavy chain and/or light chain further comprise a variable region comprising one or more, preferably all, framework regions of an IgG4 heavy chain as set forth in SEQ ID NO:36 and/or of an IgG4 light chain as set forth in SEQ ID NO:37.