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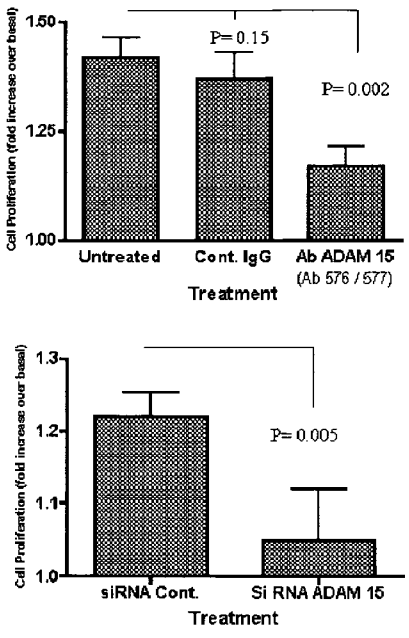
[Continued on next page]

(54) Title: ADAM-15 ANTIBODIES AND IMMUNOGENIC PEPTIDES

Fig. 3 A



(57) Abstract: The present invention relates to antibodies and antigen-binding fragments thereof, immunogenic peptide(s), and siRNA molecules which are capable of inhibiting neovascularization and/or angiogenesis and endothelial cell proliferation. The invention relates to antibodies and antigen-binding fragments thereof with specificity towards the metalloprotease domain of ADAM 15 and to immunogenic peptide(s) that elicits such antibodies. The invention also relates to compositions and kits comprising the antibodies and immunogenic peptide(s) of the invention, as well as methods and uses of the antibodies and antigen-binding fragments thereof and immunogenic peptide(s), as well as siRNA molecules.

WO 2009/118660 A4

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AMENDED CLAIMS
(received by the International Bureau on 22 February 2010 (22.02.10))

1. A method of inhibiting or preventing angiogenesis or of inhibiting or preventing pathological neovascularization comprising administering to a patient a therapeutically effective amount of an antibody or antigen-binding fragment thereof which specifically recognises the ADAM 15 catalytic cleft peptide comprising or consisting of the amino acid sequence:

IAHELGHSLGLDHD (SEQ ID NO: 3)

or a peptide with at least 70% sequence identity to SEQ ID NO: 3.

2. A method as claimed in claim 1, wherein the antibody or antigen-binding fragment thereof specifically binds to an epitope on human ADAM 15 polypeptide defined by amino acids 346-359 of SEQ ID NO: 1.

3. A method as claimed in claim 1, wherein the antibody or antigen-binding fragment thereof specifically binds to an epitope on human ADAM 15 polypeptide defined by the topographic region His^{352}, Ser^{353}, Leu^{354}, Gly^{355}, Leu^{356}, Asp^{357} and Asp^{359}, or by the topographic region Leu^{354}, Gly^{355}, Leu^{356}, Asp^{357}, His^{358} and Asp^{359}.

4. A method as claimed in claim 1, wherein the antibody or antigen-binding fragment thereof is a mouse, humanised, human, recombinant or synthetic antibody or antigen-binding fragment thereof.

5. A method as claimed in claim 1, wherein a therapeutically effective amount of an antisense nucleic and/or a short interfering nucleic acid (siNA) generated from the ADAM 15 specific oligonucleotides 5'AACTCCATCTGTTCTCCTGACTTCCTGTCTC 3' (SEQ ID NO: 4) as a sense template and 5' AAAAGTCAGGAGAACAGATGGAGCCTGTTCTC 3' (SEQ ID NO: 5) as an antisense template, wherein the nucleic knocksdown ADAM 15 expression.

6. A method of treating cancer in a patient comprising administering to said patient a therapeutically effective amount of an antibody or antigen-binding fragment thereof which

specifically recognises the catalytic cleft peptide comprising or consisting of the amino acid sequence:

IAHELGHSLGLDHD (SEQ ID NO: 3)

or a peptide with at least 70% sequence identity to SEQ ID NO: 3.

7. A method as claimed in claim 6, wherein the antibody or antigen-binding fragment thereof specifically binds to an epitope on human ADAM 15 polypeptide defined by amino acids 346-359 of SEQ ID NO: 1.

8. A method as claimed in claim 6, wherein the antibody or antigen-binding fragment thereof specifically binds to an epitope on human ADAM 15 polypeptide defined by the topographic region His^{352}, Ser^{353}, Leu^{354}, Gly^{355}, Leu^{356}, Asp^{357} and Asp^{359}, or by the topographic region Leu^{354}, Gly^{355}, Leu^{356}, Asp^{357}, His^{358} and Asp^{359}.

9. A method as claimed in claim 6, wherein a therapeutically effective amount of an antisense nucleic and/or a short interfering nucleic acid (siNA) generated from the ADAM 15 specific oligonucleotides 5'AACTCCATCTGTTCTCCTGACTTCCTGTCTC 3' (SEQ ID NO: 4) as a sense template and 5' AAAAGTCAGGAGAACAGATGGAGCCTGTTCTC 3' (SEQ ID NO: 5) as an antisense template, wherein the nucleic knocksdown ADAM 15 expression.

10. A method as claimed in claim 6, wherein the cancer is selected from the group consisting of cervical cancer, uterine cancer, ovarian cancer, pancreatic cancer, kidney cancer, gallbladder cancer, liver cancer, head and neck cancer, squamous cell carcinoma, gastrointestinal cancer, breast cancer (such as carcinoma, ductal, lobular, and nipple), prostate cancer, testicular cancer, lung cancer, non-small cell lung cancer, non-Hodgkin's lymphoma, multiple myeloma, leukemia (such as acute lymphocytic leukemia, chronic lymphocytic leukemia, acute myelogenous leukemia, and chronic myelogenous leukemia), brain cancer (e.g. astrocytoma, glioblastoma, medulloblastoma), neuroblastoma, sarcomas, colon cancer, rectum cancer, stomach cancer, anal cancer, bladder cancer, pancreatic cancer, endometrial cancer, plasmacytoma, lymphomas, retinoblastoma, Wilm's tumour, Ewing sarcoma, melanoma and other skin cancers.

11. A method as claimed in claim 6, where the cancer is metastatic carcinoma of the colon or rectum.

12. A method as claimed in claim 11, wherein the antibody or antigen-binding fragment thereof is administered simultaneously, separately or sequentially with 5-fluorouracil and/or bevacuzimab (anti-VEGF monoclonal antibody).

13. A method as claimed in claim 11, wherein the ADAM 15 specific siNA is administered simultaneously, separately or sequentially with 5-fluorouracil and/or bevacuzimab (anti-VEGF monoclonal antibody).

14. A method as claimed in claim 6, wherein the cancer is recurrent or metastatic non-squamous, non-small cell lung cancer.

15. A method as claimed in claim 14, wherein the antibody or antigen-binding fragment thereof is administered simultaneously, separately or sequentially with carboplatin and/or paclitaxel and/or bevacuzimab (anti-VEGF monoclonal antibody).

16. A method as claimed in claim 14, wherein the ADAM 15 specific siNA is administered simultaneously, separately or sequentially with carboplatin and/or paclitaxel and/or bevacuzimab (anti-VEGF monoclonal antibody).

17. A method as claimed in claim 6, wherein the antibody or antigen-binding fragment thereof is a mouse, humanised, human, recombinant or synthetic antibody or antigen-binding fragment thereof.

18. A method of inhibiting endothelial cell proliferation and/or smooth muscle cell proliferation comprising administering to a patient a therapeutically effective amount of an antibody or antigen-binding fragment thereof which specifically recognises the metalloprotease domain of the human ADAM 15 polypeptide.

19. A method as claimed in claim 18, wherein the antibody or antigen-binding fragment thereof specifically binds to a peptide comprising or consisting of the amino acid sequence:

IAHELGHSLGLDHD (SEQ ID NO: 3)

or a peptide with at least 70% sequence identity to SEQ ID NO: 3.

20. A method as claimed in claim 18, wherein the antibody or antigen-binding fragment thereof specifically binds to an epitope on human ADAM 15 polypeptide defined by amino acids 346-359 of SEQ ID NO: 1.

21. A method as claimed in claim 18, wherein the antibody or antigen-binding fragment thereof specifically binds to an epitope on human ADAM 15 polypeptide defined by the topographic region His^{352}, Ser^{353}, Leu^{354}, Gly^{355}, Leu^{356}, Asp^{357} and Asp^{359}, or by the topographic region Leu^{354}, Gly^{355}, Leu^{356}, Asp^{357}, His^{358} and Asp^{359}.

22. A method as claimed in claim 18, wherein the antibody or antigen-binding fragment thereof is a mouse, humanised, human, recombinant or synthetic antibody or antigen-binding fragment thereof.

23. A method as claimed in claim 18, wherein a therapeutically effective amount of an antisense nucleic and/or a short interfering nucleic acid (siNA) generated from the ADAM 15 specific oligonucleotides 5'AACTCCATCTGTTCTCCTGACTTCCTGTCTC 3' (SEQ ID NO: 4) as a sense template and 5' AAAAGTCAGGAGAACAGATGGAGCCTGTTCTC 3' (SEQ ID NO: 5) as an antisense template, wherein the nucleic acid knocksdown ADAM 15 expression.

24. An isolated antibody or antigen-binding fragment thereof which specifically recognizes human ADAM 15 catalytic cleft polypeptide comprising or consisting of the amino acid sequence:

IAHELGHSLGLDHD (SEQ ID NO: 3)

or a peptide with at least 70% sequence identity to SEQ ID NO: 3, wherein the antibody is a non rabbit-polyclonal antibody, and wherein the antibody or antigen-binding fragment is capable of inhibiting angiogenesis or pathological neovascularisation.

25. A isolated nucleic acid generated from the ADAM 15 specific oligonucleotides 5'AACTCCATCTGTTCTCCTGACTTCCTGTCTC 3' (SEQ ID NO: 4) for the sense template and 5' AAAAGTCAGGAGAACAGATGGAGCCTGTTCTC 3' (SEQ ID NO: 5) for the antisense template, wherein the nucleic acid is an antisense nucleic acid and/or a short interfering nucleic acid (siNA) that knocksdown ADAM 15 expression and which is capable of inhibiting angiogenesis.

26. An isolated antibody or antigen-binding fragment thereof which specifically recognizes human ADAM 15 polypeptide, wherein the antibody is a non rabbit-polyclonal antibody, and wherein the antibody or antigen-binding fragment is capable of inhibiting the proliferation of endothelial cells and/or smooth muscle cells.

27. A isolated nucleic acid generated from the ADAM 15 specific oligonucleotides 5'AACTCCATCTGTTCTCCTGACTTCCTGTCTC 3' (SEQ ID NO: 4) for the sense template and 5' AAAAGTCAGGAGAACAGATGGAGCCTGTTCTC 3' (SEQ ID NO: 5) for the antisense template, wherein the nucleic acid is an antisense nucleic acid and/or a short interfering nucleic acid (siNA) that knocksdown ADAM 15 expression and which is capable of inhibiting the proliferation of endothelial cells and/or smooth muscle cells.

28. An isolated antibody or antigen-binding fragment thereof which specifically recognizes human ADAM 15 polypeptide, wherein the antibody is a non rabbit-polyclonal antibody, and wherein the antibody is capable of preventing proteolytic cleavage of the urokinase receptor (uPAR) by ADAM 15.

29. A isolated nucleic acid generated from the ADAM 15 specific oligonucleotides 5'AACTCCATCTGTTCTCCTGACTTCCTGTCTC 3' (SEQ ID NO: 4) for the sense template and 5' AAAAGTCAGGAGAACAGATGGAGCCTGTTCTC 3' (SEQ ID NO: 5) for the antisense template, wherein the nucleic acid is an antisense nucleic acid and/or a short interfering nucleic acid (siNA) that knocksdown ADAM 15 expression and which is capable of inhibiting the cleavage of the urokinase receptor (uPAR) by ADAM 15.

30. An isolated antibody or antigen-binding fragment thereof which specifically recognizes human ADAM 15 polypeptide, wherein the antibody is a non rabbit-polyclonal

antibody, and wherein the antibody is capable of inhibiting the activation of the phosphoinositol 3 kinase (PI3 kinase) pathway including the Akt kinase (protein kinase B).

31. A isolated nucleic acid generated from the ADAM 15 specific oligonucleotides 5'AACTCCATCTGTTCTCCTGACTTCCTGTCTC 3' (SEQ ID NO: 4) for the sense template and 5' AAAAGTCAGGAGAACAGATGGAGCCTGTTCTC 3' (SEQ ID NO: 5) for the antisense template, wherein the nucleic acid is an antisense nucleic acid and/or a short interfering nucleic acid (siNA) that knocksdown ADAM 15 expression and which is capable of inhibiting the activation of the phosphoinositol 3 kinase (PI3 kinase) pathway including the Akt kinase (protein kinase B).

32. An isolated antibody or antigen-binding fragment thereof which specifically recognizes human ADAM 15, wherein the antibody is a non rabbit-polyclonal antibody, and wherein the antibody is capable of inhibiting the inactivation of glycogen synthase kinase 3 (GSK 3).

33. A isolated nucleic acid generated from the ADAM 15 specific oligonucleotides 5'AACTCCATCTGTTCTCCTGACTTCCTGTCTC 3' (SEQ ID NO: 4) for the sense template and 5' AAAAGTCAGGAGAACAGATGGAGCCTGTTCTC 3' (SEQ ID NO: 5) for the antisense template, wherein the nucleic acid is an antisense nucleic acid and/or a short interfering nucleic acid (siNA) that knocksdown ADAM 15 expression and which is capable of inhibiting the inactivation of glycogen synthase kinase 3 (GSK 3).

34. An isolated antibody or antigen-binding fragment thereof which specifically recognizes human ADAM 15, wherein the antibody is a non-rabbit polyclonal antibody, and wherein the antibody is capable of inhibiting cell survival.

35. A isolated nucleic acid generated from the ADAM 15 specific oligonucleotides 5'AACTCCATCTGTTCTCCTGACTTCCTGTCTC 3' (SEQ ID NO: 4) for the sense template and 5' AAAAGTCAGGAGAACAGATGGAGCCTGTTCTC 3' (SEQ ID NO: 5) for the antisense template, wherein the nucleic acid is an antisense nucleic acid and/or a short interfering nucleic acid (siNA) that knocksdown ADAM 15 expression and which is capable of inhibiting cell survival.

36. An isolated antibody or antigen-binding fragment thereof which specifically recognizes the ADAM 15 metalloprotease domain catalytic cleft peptide comprising or consisting of the amino acid sequence:

IAHELGHSLGLDHD (SEQ ID NO: 3)

or a peptide with at least 70% sequence identity to SEQ ID NO: 3, wherein the antibody is a non rabbit-polyclonal antibody.

37. An isolated antibody or antigen-binding fragment thereof as claimed in claim 36, wherein the antibody or antigen-binding fragment thereof specifically binds to an epitope on human ADAM 15 polypeptide defined by amino acids 346-359 of SEQ ID NO: 1, wherein the antibody is a non rabbit-polyclonal antibody.

38. An isolated antibody or antigen-binding fragment thereof as claimed in claim 36, wherein the antibody or antigen-binding fragment thereof specifically binds to human ADAM 15 polypeptide, wherein the antibody is a non rabbit-polyclonal antibody, and wherein the antibody or antigen-binding fragment thereof binds to the ADAM 15 epitope defined by amino acids 346-359 of SEQ ID NO: 1 such that the antibody prevents proteolytic cleavage of the urokinase receptor uPAR by ADAM 15.

39. An isolated antibody or antigen-binding fragment thereof as claimed in claim 36, wherein the antibody or antigen-binding fragment thereof specifically binds to human ADAM 15 polypeptide, wherein the antibody is a non rabbit-polyclonal antibody, and wherein the antibody or antigen-binding fragment thereof binds to the ADAM 15 epitope defined by amino acids 346-359 of SEQ ID NO: 1 such that the antibody inhibits activation of the Akt kinase (protein kinase B).

40. An isolated antibody or antigen-binding fragment thereof as claimed in claim 36, wherein the antibody or antigen-binding fragment thereof specifically binds to human ADAM 15 polypeptide, wherein the antibody is a non rabbit-polyclonal antibody, and

wherein the antibody or antigen-binding fragment thereof binds to the ADAM 15 epitope defined by amino acids 346-359 of SEQ ID NO: 1 such that the antibody prevents the inactivation of glycogen synthase kinase 3 (GSK 3).

41. An isolated antibody or antigen-binding fragment thereof as claimed in claim 36, wherein the antibody or antigen-binding fragment thereof specifically binds to human ADAM 15 polypeptide, wherein the antibody is a non rabbit-polyclonal antibody, and wherein the antibody or antigen-binding fragment thereof binds to the ADAM 15 epitope defined by amino acids 346-359 of SEQ ID NO: 1 such that the antibody inhibits cell survival.

42. An isolated antibody or antigen-binding fragment thereof as claimed in claim 36, wherein the antibody or antigen-binding fragment thereof specifically binds to an epitope on human ADAM 15 polypeptide defined by the topographic region His^{352}, Ser^{353}, Leu^{354}, Gly^{355}, Leu^{356}, Asp^{357} and Asp^{359}, or by the topographic region Leu^{354}, Gly^{355}, Leu^{356}, Asp^{357}, His^{358} and Asp^{359}, wherein the antibody is non rabbit-polyclonal antibody.

43. An antibody as claimed in claim 36, wherein the antibody or antigen-binding fragment thereof is a mouse, humanised, human, recombinant or synthetic antibody or antigen-binding fragment thereof.

44. A nucleic acid molecule which encodes an antibody as claimed in claim 22.

45. An expression vector comprising a nucleic acid as claimed in claim 44.

46. A host cell comprising an expression vector as claimed in claim 45.

47. A method of treating an inflammatory condition, preferably Inflammatory Bowel Disease, Crohn's Disease, rheumatoid arthritis or osteoarthritis, comprising administering to a patient a therapeutically effective amount of an antibody or antigen-binding fragment thereof which specifically recognises the ADAM 15 catalytic cleft peptide comprising or consisting of the amino acid sequence:

IAHELGHSLGLDHD (SEQ ID NO: 3)

or a peptide with at least 70% sequence identity to SEQ ID NO: 3.

48. A method as claimed in claim 47, wherein the antibody or antigen-binding fragment thereof specifically binds to an epitope on human ADAM 15 polypeptide defined by amino acids 346-359 of SEQ ID NO: 1.

49. A method as claimed in claim 47, wherein the antibody or antigen-binding fragment thereof specifically binds to an epitope on human ADAM 15 polypeptide defined by the topographic region His^{352}, Ser^{353}, Leu^{354}, Gly^{355}, Leu^{356}, Asp^{357} and Asp^{359}, or by the topographic region Leu^{354}, Gly^{355}, Leu^{356}, Asp^{357}, His^{358} and Asp^{359}.

50. A method as claimed in claim 47, wherein the antibody or antigen-binding fragment thereof is a mouse, humanised, human, recombinant or synthetic antibody or antigen-binding fragment thereof.

51. A method as claimed in claim 47, wherein a therapeutically effective amount of an antisense nucleic and/or a short interfering nucleic acid (siNA) generated from the ADAM 15 specific oligonucleotides 5'AACTCCATCTGTTCTCCTGACTTCCTGTCTC 3' (SEQ ID NO: 4) as a sense template and 5' AAAAGTCAGGAGAACAGATGGAGCCTGTTCTC 3' (SEQ ID NO: 5) as an antisense template, wherein the nucleic acid knocksdown ADAM 15 expression.

52. A method of treating an inflammatory vascular disorder, preferably restenosis or atherosclerosis, comprising administering to a patient a therapeutically effective amount of an antibody or antigen-binding fragment thereof which specifically recognises the metalloprotease domain of the human ADAM 15 polypeptide.

53. A method as claimed in claim 52, wherein the antibody or antigen-binding fragment thereof specifically binds to a peptide comprising or consisting of the amino acid sequence:

IAHELGHSLGLDHD (SEQ ID NO: 3)

or a peptide with at least 70% sequence identity to SEQ ID NO: 3.

54. A method as claimed in claim 52, wherein the antibody or antigen-binding fragment thereof specifically binds to an epitope on human ADAM 15 polypeptide defined by amino acids 346-359 of SEQ ID NO: 1.

55. A method as claimed in claim 52, wherein the antibody or antigen-binding fragment thereof specifically binds to an epitope on human ADAM 15 polypeptide defined by the topographic region His^{352}, Ser^{353}, Leu^{354}, Gly^{355}, Leu^{356}, Asp^{357} and Asp^{359}, or by the topographic region Leu^{354}, Gly^{355}, Leu^{356}, Asp^{357}, His^{358} and Asp^{359}.

56. A method as claimed in claim 52, wherein the antibody or antigen-binding fragment thereof is a mouse, humanised, human, recombinant or synthetic antibody, or antigen-binding fragment thereof.

57. A method as claimed in claim 52, wherein a therapeutically effective amount of an antisense nucleic and/or a short interfering nucleic acid (siNA) generated from the ADAM 15 specific oligonucleotides 5'AACTCCATCTGTTCTCCTGACTTCCTGTCTC 3' (SEQ ID NO: 4) as a sense template and 5' AAAAGTCAGGAGAACAGATGGAGCCTGTTCTC 3' (SEQ ID NO: 5) as an antisense template, wherein the nucleic acid knocksdown ADAM 15 expression.

58. A method of treating acute macular degeneration, comprising administering to a patient a therapeutically effective amount of an antibody or antigen-binding fragment thereof which specifically recognises the ADAM 15 catalytic cleft peptide comprising or consisting of the amino acid sequence:

IAHELGHSLGLDHD (SEQ ID NO: 3)

or a peptide with at least 70% sequence identity to SEQ ID NO: 3.

59. A method as claimed in claim 58, wherein the antibody or antigen-binding fragment thereof specifically binds to an epitope on human ADAM 15 polypeptide defined by amino acids 346-359 of SEQ ID NO: 1.

60. A method as claimed in claim 58, wherein the antibody or antigen-binding fragment thereof specifically binds to an epitope on human ADAM 15 polypeptide defined by the topographic region His^{352}, Ser^{353}, Leu^{354}, Gly^{355}, Leu^{356}, Asp^{357} and Asp^{359}, or by the topographic region Leu^{354}, Gly^{355}, Leu^{356}, Asp^{357}, His^{358} and Asp^{359}.

61. A method as claimed in claim 58, wherein the antibody or antigen-binding fragment thereof is a mouse, humanised, human, recombinant or synthetic antibody, or antigen-binding fragment thereof.

62. A method as claimed in claim 58, wherein a therapeutically effective amount of an antisense nucleic and/or a short interfering nucleic acid (siNA) generated from the ADAM 15 specific oligonucleotides 5'AACTCCATCTGTTCTCCTGACTTCCTGTCTC 3' (SEQ ID NO: 4) as a sense template and 5' AAAAGTCAGGAGAACAGATGGAGCCTGTTCTC 3' (SEQ ID NO: 5) as an antisense template, wherein the nucleic acid knocksdown ADAM 15 expression.

63. A method of treating diabetic retinopathy or a proliferative retinopathy, comprising administering to a patient a therapeutically effective amount of an antibody or antigen-binding fragment thereof which specifically recognises the ADAM 15 catalytic cleft peptide comprising or consisting of the amino acid sequence:

IAHELGHSLGLDHD (SEQ ID NO: 3)

or a peptide with at least 70% sequence identity to SEQ ID NO: 3.

64. A method as claimed in claim 63, wherein the antibody or antigen-binding fragment thereof specifically binds to an epitope on human ADAM 15 polypeptide defined by amino acids 346-359 of SEQ ID NO: 1.

65. A method as claimed in claim 63, wherein the antibody or antigen-binding fragment thereof specifically binds to an epitope on human ADAM 15 polypeptide defined by the topographic region His^{352}, Ser^{353}, Leu^{354}, Gly^{355}, Leu^{356}, Asp^{357} and Asp^{359}, or by the topographic region Leu^{354}, Gly^{355}, Leu^{356}, Asp^{357}, His^{358} and Asp^{359}.

66. A method as claimed in claim 63, wherein the antibody or antigen-binding fragment thereof is a mouse, humanised, human, recombinant or synthetic antibody, or antigen-binding fragment thereof.

67. A method as claimed in claim 63, wherein a therapeutically effective amount of an antisense nucleic and/or a short interfering nucleic acid (siNA) generated from the ADAM 15 specific oligonucleotides 5'AACTCCATCTGTTCTCCTGACTTCCTGTCTC 3' (SEQ ID NO: 4) as a sense template and 5' AAAAGTCAGGAGAACAGATGGAGCCTGTTCTC 3' (SEQ ID NO: 5) as an antisense template, wherein the nucleic acid knocksdown ADAM 15 expression.

68. A method for therapeutically enhancing plasmin activity in patients with several disorders, including cancer or vascular disorders, by inhibiting ADAM 15 cleavage of the urokinase receptor (uPAR) by administering to a patient a therapeutically effective amount of an antibody or antigen binding fragment thereof that inhibits ADAM 15 catalytic activity.

69. A method as claimed in claim 68, wherein a therapeutically effective amount of an antisense nucleic and/or a short interfering nucleic acid (siNA) generated from the ADAM 15 specific oligonucleotides 5'AACTCCATCTGTTCTCCTGACTTCCTGTCTC 3' (SEQ ID NO: 4) as a sense template and 5' AAAAGTCAGGAGAACAGATGGAGCCTGTTCTC 3' (SEQ ID NO: 5) as an antisense template, wherein the nucleic acid knocksdown ADAM 15 expression.

70. A method of producing therapeutic anti-ADAM15 antibodies in human patients, the method comprising administering to said patient a suitable dosage of peptide comprising or consisting of the amino acid sequence:

X1 - IAHELGHSLGLDHD - X2 (SEQ ID NO: 8)

wherein X1 is an N-terminal protecting group, optionally absent,
X2 is a C-terminal protecting group, optionally absent,
or a peptide with at least 70%, sequence identity to SEQ ID NO: 8,
wherein the peptide is optionally bound to a carrier,
optionally in admixture with one or more adjuvants, diluents and/or excipients.

71. A method of producing therapeutic anti-ADAM 15 antibodies in human patients as claimed in claim 68 with properties described in claims 18, 24, 26, 28, 30 & 32 and for the treatment of pathologies described in claims 1, 6, 10, 11, 14, 47, 52, 58, 63 & 68.

72. A method for generating antibodies with specific catalytic inhibitory activity directed towards the metalloproteases of the metzincin superfamily using an antigen consisting of a peptide incorporating the consensus sequence outlined in SEQ ID NO: 2 in part or entirety, or corresponding to the equivalent region encompassed by amino acids 346-359 of ADAM 15 SEQ ID NO: 1 in part or entirety as observed in the amino acid sequences of individual members of the metzincin superfamily.

73. A method for the development of diagnostic procedures and assays targeting ADAM 15 expression or measuring ADAM 15 activity, both *in vitro* and *in vivo*, incorporating the antibodies and/or siNA described herein

STATEMENT UNDER ARTICLE 19(1)

Amendments have been made to the claims section as filed involving replacement of several claims with amended claims that provide both additional novelty and inventiveness. Furthermore, several new claims have been added to obtain protection against highly novel aspects of the invention relating to the role of ADAM 15 in positively regulating the activation of the PI3 kinase/Akt pathway (Fig. 4 as filed) and cell survival (Fig.3 as filed). In addition, new claims are introduced towards the use of interfering nucleic acids to knockdown ADAM 15 expression, as opposed to antibodies targeting catalytic activity, as well as claims towards the inhibition of ADAM 15 as a method to therapeutically enhance plasmin generation (Fig. 6 as filed). New claims are introduced towards the use of ADAM 15 antibodies in diagnostic and prognostic procedures and assays as well as a method of generating specific antibodies to individual members of the metzincin superfamily that inhibit their catalytic activity.

Respectfully submitted on behalf of applicants/inventors.

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