CLAIMS

1. A human antibody which binds human Tissue Factor.

2. The antibody of claim 1, wherein the antibody binds to the extracellular domain of Tissue Factor with an apparent affinity (EC_{50}) of one of 3 nM or less, 0.50 nM or less, 0.35 nM or less, 0.20 nM or less, or 0.1 nM or less.

3. The antibody of any one of the preceding claims, wherein the antibody binds to mammalian cells expressing Tissue Factor, with an apparent affinity (EC_{50}) of one of 10 nM or less, 8 nM or less, 5 nM or less, 2 nM or less, 1 nM or less, 0.5 nM or less, or 0.3 nM or less.

4. The antibody according to claim 3, wherein the mammalian cells expressing Tissue Factor are A431 cells transfected with a construct encoding Tissue Factor.

5. The antibody of any one of the preceding claims, wherein the antibody is capable of inducing antibody-dependent cellular cytotoxicity in A431 cells with an EC_{50} value of one of 2 nM or less, 1 nM or less, 0.7 nM or less, 0.3 nM or less, 0.2 nM or less, or 0.1 nM or less, or 0.05 nM or less.

6. The antibody of any one of the preceding claims, wherein the antibody is effective in inhibiting growth of established MDA-MB-231 tumorsand/or in inhibiting growth of established BxPC3 tumors.

7. The antibody of any one of the preceding claims, wherein the antibody inhibits tissue factor induced blood coagulation, with a median inhibition concentration of one of less than 10 nM, less than 5 nM, less than 2 nM, or less than 1 nM.

8. The antibody of any one of the preceding claims, wherein the antibody inhibits FVIIa binding to Tissue Factor with a maximum inhibition value of inhibition of one of more than 80% or more than 90%.

9. The antibody of any one of the preceding claims, wherein the antibody inhibits FVIIa-induced IL-8 release by MDA-MB-231 cells with a maximum inhibition value of inhibition of one of more than 40%, more than 50%, or more than 60%.

10. The antibody of any one of the preceding claims, wherein the antibody inhibits conversion of FX into FXa by the TF/FVIIa complex by one of less than 50%, less than 40%, or in the range of 1-30%.

11. The antibody of any one of the preceding claims, wherein said antibody competes for Tissue Factor binding with an antibody comprising a VH region comprising the sequence of SEQ ID NO:9 and a VL region comprising the sequence of SEQ ID NO:65.

12. The antibody of any one of the preceding claims, wherein binding to Tissue Factor does not involve any one of the amino acids W in position 45, K in position 46 or Y in position 94 of Tissue Factor.

13. The antibody of any one of the preceding claims, wherein said antibody competes for Tissue Factor binding with an antibody comprising a VH region comprising the sequence of SEQ ID NO:37 and a VL region comprising the sequence of SEQ ID NO:93.

14. The antibody of any one of the preceding claims, wherein said antibody inhibits FVIIa induced ERK phosphorylation with a median inhibition concentration of one of less than 10 nM, less than 5 nM, or less than 2 nM

15. The antibody of any of the claims 1-8, and 10-14, wherein the antibody inhibits ERK phosphorylation with a median inhibition concentration of one of less than 10 nM, less than 5 nM, or less than 2 nM and do not inhibit FVII induced IL-8 release by more than maximum 10%.

16. The antibody of any one of the preceding claims, wherein the antibody is capable of inducing C3c and C4c deposition..

17. The antibody of any of the preceding claims, wherein the antibody Fab fragments binds to the extracellular domain of tissue factor with an EC50 value of one of below 0.1 µg/mL, below 0.05 µg/mL, or below 0.04 µg/mL measured by ELISA.

18. The antibody of any of the claims 1-16, wherein the antibody Fab fragments binds to the extracellular domain of tissue factor with an EC50 value of above 1.0 µg/mL as measured by ELISA.

19. The antibody of any of the claims 1-16 wherein the antibody Fab fragments binds to the extracellular domain of tissue factor with an EC50 value of one of below 10µg/mL, below 1 µg/mL, below 0.5 µg/mL, or below 0.2 µg/mL.

20. The antibody of any of the claims above, wherein the antibody binds to human tissue factor and not murine tissue factor and shows reduced binding as compared to binding to human TF to the shuffle construct 42-84 mm, containing the human sequence for TF except for amino acid 42-84, which has been replaced with mouse sequence.

21. The antibody of claims 1-19, wherein the antibody binds to human tissue factor and not murine tissue factor and shows reduced binding as compared to binding to human TF to the shuffle construct 85-122 mm, containing the human sequence for TF except for amino acid 85-122, which has been replaced with mouse sequence.

22. The antibody of claims 1-19, wherein the antibody binds to human tissue factor and not murine tissue factor and shows reduced binding as compared to binding to human TF to the shuffle construct 123-137 mm containing the human sequence for TF except for amino acid 123-137, which has been replaced with mouse sequence.

23. The antibody of claims 1-19, wherein the antibody binds to human tissue factor and not murine tissue factor and shows reduced binding as compared to binding to human TF to the shuffle construct 185-225 mm containing the human sequence for TF except for amino acid 185-225, which has been replaced with mouse sequence.

24.The antibody of claims 1-19, wherein the antibody binds to human tissue factor and not murine tissue factor and shows reduced binding as compared to binding to

human TF to both the shuffle construct 226-250 mm containing the human sequence for TF except for amino acid 226-250, which has been replaced with mouse sequence.

25. The antibody according to any of the claims 20-24, which shows reduced binding as compared to binding to human TF to more than one shuffle construct, such as reduced binding

- to the shuffle construct 42-84 mm as defined in claim 20 and to the shuffle construct 85-122 mm as defined in claim 21

or

- to the shuffle construct 123-137 mm as defined in claim 22, and the shuffle construct 185-225 mm as defined in claim 23, and the shuffle construct 226-250 mm, as defined in claim 24.

26. The antibody of any one of the preceding claims, wherein said antibody
- competes for Tissue Factor binding with an antibody comprising a VH region comprising the sequence of SEQ ID NO:9 and a VL region comprising the sequence of SEQ ID NO:65, and
- does not compete for Tissue Factor binding with an antibody comprising a VH region comprising the sequence of SEQ ID NO:37 and a VL region comprising the sequence of SEQ ID NO:93.

27.The antibody of claim 26, wherein said antibody comprises a VH CDR3 region having

a) the sequence as set forth in
   - SEQ ID No: 12,
   - SEQ ID No: 16,
   - SEQ ID No: 20,
   - SEQ ID No: 24,
   - SEQ ID No: 28,

or

b) a variant of any of said sequences, such as a variant having at most 1, 2, 3, 4 or 5 amino-acid modifications, preferably substitutions, such as conservative substitutions.

28. The antibody of claim 27, wherein the antibody comprises a VH CDR3 region having the sequence as set forth in SEQ ID NO: 12 or a variant thereof, wherein the variant comprises modification in one or more of the positions 2, 3, 6, 9 and 11,

29. The antibody according to claim 28, wherein the modification is a substitution selected from the group consisting of:

R is substituted with K when in position 2,

S is substituted with A or T when in position 3,

G is substituted with T when in position 6,

L is substituted with F when in position 9, and

S is substituted with Y when in position 11.

30. The antibody of claim 1 or 27, wherein the antibody comprises:

a) a VH region comprising the CDR1, 2 and 3 sequences of SEQ ID NO:10, 11 and 12 and a VL region comprising the CDR1, 2 and 3 sequences of SEQ ID NO:66, 67 and 68,

b) a VH region comprising the CDR1, 2 and 3 sequences of SEQ ID NO:14, 15 and 16 and a VL region comprising the CDR1, 2 and 3 sequences of SEQ ID NO:70, 71 and 72,

c) a VH region comprising the CDR1, 2 and 3 sequences of SEQ ID NO:18, 19, 20 and a VL region comprising the CDR1, 2 and 3 sequences of SEQ ID NO:74, 75 and 76,

d) a VH region comprising the CDR1, 2 and 3 sequences of SEQ ID NO:22, 23 and 24 and a VL region comprising the CDR1, 2 and 3 sequences of SEQ ID NO:78, 79 and 80,

e) a VH region comprising the CDR1, 2 and 3 sequences of SEQ ID NO: 26, 27 and 28 and a VL region comprising the CDR1, 2 and 3 sequences of SEQ ID NO: 82, 83 and 84, or

f) a variant of any of said antibodies, wherein said variant has at most 1, 2 or 3 conservative amino-acid substitutions in said sequences.

31. The antibody of claim 27, comprising a VH having

a) one of at least 80% identity, at least 90%, at least 95%, or at least 98% or 100% identity to a VH region sequence selected from the group consisting of: SEQ ID NO:9, 13, 17, 21 and 25, or

b) one of at most 20, 15, 10, 5, 4, 3, 2 or 1 conservative amino-acid substitutions as compared to a VH region sequence selected from the group consisting of: SEQ ID NO:9, 13, 17, 21, 21 and 25.

32.The antibody of claim 27 comprising a VL having

a) one of at least 80% identity, at least 90%, at least 95%, at least 98% or 100% identity to a VL region sequence selected from the group consisting of: SEQ ID NO:65, 69, 73, 77 and 81, or

b) one of at most 20, 15, 10, 5, 4, 3, 2 or 1 conservative amino-acid substitutions as compared to a VH region sequence selected from the group consisting of: SEQ ID NO:65, 69, 73, 77 and 81.

33. The antibody of claim 27 comprising:

a) a VH region comprising the sequence of SEQ ID NO:9 and a VL region comprising the sequence of SEQ ID NO: 65,

b) a VH region comprising the sequence of SEQ ID NO:13 and a VL region comprising the sequence of SEQ ID NO:69,

c) a VH region comprising the sequence of SEQ ID NO:17 and a VL region comprising the sequence of SEQ ID NO:73,

d) a VH region comprising the sequence of SEQ ID NO:21 and a VL region comprising the sequence of SEQ ID NO:77,

e) a VH region comprising the sequence of SEQ ID NO:25 and a VL region comprising the sequence of SEQ ID NO:81, or

f) a variant of any of said antibodies, wherein said variant has at most 1,2 or 3 conservative amino-acid substitutions in said sequences.

34. The antibody of any one of claims 1 to 25, wherein said antibody

- competes for Tissue Factor binding with an antibody comprising a VH region comprising the sequence of SEQ ID NO:9 and a VL region comprising the sequence of SEQ ID NO:65, and

- competes for Tissue Factor binding with an antibody comprising a VH region comprising the sequence of SEQ ID NO:37 and a VL region comprising the sequence of SEQ ID NO:93.

35. The antibody of claim 34, wherein said antibody comprises a VH CDR3 region having

a) the sequence as set forth in
   - SEQ ID No: 8,
   - SEQ ID No: 52,

   or

a variant of any of said sequences, such as a variant having at most 1,2 or 3 conservative amino-acid

36.The antibody of claim 1 or 34, wherein the antibody comprises:

a) a VH region comprising the CDR1, 2 and 3 sequences of SEQ ID NO:6, 7 and 8 and a VL region comprising the CDR1, 2 and 3 sequences of SEQ ID NO:62, 63 and 64,
b) a VH region comprising the CDR1, 2 and 3 sequences of SEQ ID NO:50, 51 and 52 and a VL region comprising the CDR1, 2 and 3 sequences of SEQ ID NO:106, 107 and 108, or
c) a variant of any of said antibodies, wherein said variant has at most 1, 2 or 3 conservative amino-acid substitutions in said sequences.

37.The antibody of claim 34 comprising a VH having

a) one of at least 80% identity, at least 90%, at least 95%, at least 98% or 100% identity to a VH region sequence selected from the group consisting of: SEQ ID NO:5 and 49, or
b) one of at most 20, 15, 10, or 5, 4, 3, 2 or 1 conservative amino-acid substitutions as compared to a VH region sequence selected from the group consisting of: SEQ ID NO:5 and 49.

38 The antibody of claim 34 comprising a VL having

a) one of at least 80% identity, at least 90%, at least 95%, at least 98% or 100% identity to a VL region sequence selected from the group consisting of: SEQ ID NO: 61 and 105, or
b) one of at most 20, 15, or 10, 5, 4, 3, 2 or 1 conservative amino-acid substitutions as compared to a VH region sequence selected from the group consisting of: SEQ ID NO:61 and 105.

39. The antibody of claim 34 comprising:

a) a VH region comprising the sequence of SEQ ID NO:5 and a VL region comprising the sequence of SEQ ID NO:61,

b) a VH region comprising the sequence of SEQ ID NO:49 and a VL region comprising the sequence of SEQ ID NO:105, or

c) a variant of any of said antibodies, wherein said variant has at most 1,2 or 3 amino-acid conservative amino-acid substitutions in said sequences.

40. The antibody of any one of the claims 1 to 25, wherein said antibody

- does not compete for Tissue Factor binding with an antibody comprising a VH region comprising the sequence of SEQ ID NO:9 and a VL region comprising the sequence of SEQ ID NO:65, and

- competes for Tissue Factor binding with an antibody comprising a VH region comprising the sequence of SEQ ID NO:37 and a VL region comprising the sequence of SEQ ID NO:93.

41. The antibody of claim 40, wherein said antibody comprises a VH CDR3 region having

a) the sequence as set forth in

- SEQ ID No: 32,
- SEQ ID No: 36,
- SEQ ID No: 40,
- SEQ ID No: 56,

or

b) a variant of any of said sequences, such as a variant having at most 1,2 or 3 amino-acid conservative substitutions .

42. The antibody of claim 1 or 40, wherein the antibody comprises:

a) a VH region comprising the CDR1, 2 and 3 sequences of SEQ ID NO: 30, 31 and 32 and a VL region comprising the CDR1, 2 and 3 sequences of SEQ ID NO: 86, 87 and 88,

b) a VH region comprising the CDR1, 2 and 3 sequences of SEQ ID NO:34, 35 and 36 and a VL region comprising the CDR1, 2 and 3 sequences of SEQ ID NO:90, 91 and 92,

c) a VH region comprising the CDR1, 2 and 3 sequences of SEQ ID NO:38, 39 and 40 and a VL region comprising the CDR1, 2 and 3 sequences of SEQ ID NO:94, 95 and 96,
d) a VH region comprising the CDR1, 2 and 3 sequences of SEQ ID NO:54, 55 and 56 and a VL region comprising the CDR1, 2 and 3 sequences of SEQ ID NO:110, 11 and 112, or
e) a variant of any of said antibodies, wherein said variant has at most 1, 2 or 3 conservative amino-acid substitutions in said sequences.

43. The antibody of claim 40 comprising a VH having
a) one of at least 80% identity, at least 90%, at least 95%, at least 98% or 100% identity to a VH region sequence selected from the group consisting of: SEQ ID NO:29, 33, 37 and 53, or
b) one of at most 20, 15, or 10, 5, 4, 3, 2 or 1 conservative amino-acid substitutions as compared to a VH region sequence selected from the group consisting of: SEQ ID NO:29, 33, 37 and 53.

44.The antibody of claim 40 comprising a VL having
a) one of at least 80% identity, at least 90%, at least 95%, at least 98% or 100% identity to a VL region sequence selected from the group consisting of: SEQ ID NO:85, 89, 93 and 109, or
b) one of at most 20, 15, or 10, 5, 4, 3, 2 or 1 conservative amino-acid substitutions such as as compared to a VH region sequence selected from the group consisting of: SEQ ID NO:85, 89, 93 and 109.

45. The antibody of claim 40 comprising:
a) a VH region comprising the sequence of SEQ ID NO:29 and a VL region comprising the sequence of SEQ ID NO:85,
b) a VH region comprising the sequence of SEQ ID NO:33 and a VL region comprising the sequence of SEQ ID NO:89,
c) a VH region comprising the sequence of SEQ ID NO:37 and a VL region comprising the sequence of SEQ ID NO:93,
d) a VH region comprising the sequence of SEQ ID NO:53 and a VL region comprising the sequence of SEQ ID NO:109, or

e) a variant of any of said antibodies, wherein said variant has at most 1,2 or 3 conservative amino-acid substitutions in said sequences.

46. The antibody of any one of the preceding claims 1 to 25, wherein said antibody competes for Tissue Factor binding with an antibody comprising a VH region comprising the sequence of SEQ ID NO:41 and a VL region comprising the sequence of SEQ ID NO:97.

47. The antibody of claim 46, wherein said antibody comprises a VH CDR3 region having

a) the sequence as set forth in
   - SEQ ID No: 4,
   - SEQ ID No: 44,
   - SEQ ID No: 48,

or

b) a variant of any of said sequences, such as a variant having at most 1,2 or 3 amino-acid conservative substitutions.

48. The antibody of claim 1 or 46, wherein the antibody comprises:

a) a VH region comprising the CDR1, 2 and 3 sequences of SEQ ID NO:2, 3 and 4 and a VL region comprising the CDR1, 2 and 3 sequences of SEQ ID NO:58, 59 and 60,
b) a VH region comprising the CDR1, 2 and 3 sequences of SEQ ID NO:42, 43 and 44 and a VL region comprising the CDR1, 2 and 3 sequences of SEQ ID NO:98, 99 and 100,
c) a VH region comprising the CDR1, 2 and 3 sequences of SEQ ID NO:46, 47 and 48 and a VL region comprising the CDR1, 2 and 3 sequences of SEQ ID NO:102, 103 and 104, or
d) a variant of any of said antibodies, wherein said variant has at most 1, 2 or 3 conservative amino-acid modifications in said sequences.

49. The antibody of claim 46 comprising a VH having

a) one of at least 80% identity, at least 90%, at least 95%, at least 98% or 100% identity to a VH region sequence selected from the group consisting of: SEQ ID NO:1, 41 and 45, or

b) one of at most 20, 15, 10, or 5, 4, 3, 2 or 1 conservative amino-acid modifications as compared to a VH region sequence selected from the group consisting of: SEQ ID NO:1, 41 and 45.

50. The antibody of claim 46 comprising a VL having

a) one of at least 80% identity, at least 90%, at least 95%, at least 98% or 100% identity to a VL region sequence selected from the group consisting of: SEQ ID NO:57, 97 and 101, or

b) one of at most 20, 15, 10, 5, 4, 3, 2 or 1 conservative amino-acid modifications as compared to a VH region sequence selected from the group consisting of: SEQ ID NO:57, 97 and 101.

51.The antibody of claim 46 comprising:

a) a VH region comprising the sequence of SEQ ID NO:1 and a VL region comprising the sequence of SEQ ID NO:57,

b) a VH region comprising the sequence of SEQ ID NO:41 and a VL region comprising the sequence of SEQ ID NO: 97,

c) a VH region comprising the sequence of SEQ ID NO:45 and a VL region comprising the sequence of SEQ ID NO:101, or

d) a variant of any of said antibodies, wherein said variant preferably has at most 1,2 or 3 conservative amino-acid modifications in said sequences.

52.The antibody of any one of the claims 1 to 6wherein the antibody has an affinity to tissue factor which is less than 5 nM, such as less than 3.5 nM, e.g. less than 2 nM.

53.The antibody of any one of the claims 1 to 6 wherein the antibody has a kd of more than 10^{-3} sec^{-1}, and/or a ka of more than $5x10^{4}$,mol^{-1} sec^{-1}

54. The antibody of any one of the claims 1 to 6 wherein the antibody has a kd of more than 10^{-3} sec^{-1} , and an avidity of less than 5 nM, such as less than 1 nM, e.g. less than 0.2 nM.

55. The antibody of any one of the claims 1 to 6, or 53 or 54 wherein the antibody exhibits no binding to healthy tissue, in particular no binding to human glomeruli, but does exhibit binding to pancreatic tumors.

56. The antibody of any one of the claims 1 to 6 or 53 to 55, wherein the antibody is effective in inhibiting growth of established BX-PC3 tumors

57. The antibody of any one of the preceding claims, wherein the antibody further has one or more of the following properties: inhibition of proliferation, inhibition of tumor angiogenesis, induction of apoptosis of tumor cells, binding to alternatively spliced Tissue Factor.

58. The antibody of any one of the claims 1 to 6 which competes for Tissue Factor binding with an antibody comprising

a) a VH region comprising the sequence of SEQ ID NO:9 and a VL region comprising the sequence of SEQ ID NO:65,
b) a VH region comprising the sequence of SEQ ID NO:1 and a VL region comprising the sequence of SEQ ID NO:57,
c) a VH region comprising the sequence of SEQ ID NO:5 and a VL region comprising the sequence of SEQ ID NO:61,
d) a VH region comprising the sequence of SEQ ID NO:13 and a VL region comprising the sequence of SEQ ID NO:69,
e) a VH region comprising the sequence of SEQ ID NO:17 and a VL region comprising the sequence of SEQ ID NO:73,
f) a VH region comprising the sequence of SEQ ID NO:21 and a VL region comprising the sequence of SEQ ID NO:77,
g) a VH region comprising the sequence of SEQ ID NO:25 and a VL region comprising the sequence of SEQ ID NO:81,
h) a VH region comprising the sequence of SEQ ID NO:29 and a VL region comprising the sequence of SEQ ID NO:85,
i) a VH region comprising the sequence of SEQ ID NO:33 and a VL region comprising the sequence of SEQ ID NO:89,
j) a VH region comprising the sequence of SEQ ID NO:37 and a VL region comprising the sequence of SEQ ID NO:93,

k) a VH region comprising the sequence of SEQ ID NO:41 and a VL region comprising the sequence of SEQ ID NO: 97,
l) a VH region comprising the sequence of SEQ ID NO:45 and a VL region comprising the sequence of SEQ ID NO:101,
m) a VH region comprising the sequence of SEQ ID NO:49 and a VL region comprising the sequence of SEQ ID NO:105, or
n) a VH region comprising the sequence of SEQ ID NO:53 and a VL region comprising the sequence of SEQ ID NO:109

59. The antibody of any one of the claims 1 to 6 which binds to the same epitope on Tissue Factor as an antibody having:

a) a VH region comprising the sequence of SEQ ID NO:9 and a VL region comprising the sequence of SEQ ID NO: 65,
b) a VH region comprising the sequence of SEQ ID NO:1 and a VL region comprising the sequence of SEQ ID NO:57,
c) a VH region comprising the sequence of SEQ ID NO:5 and a VL region comprising the sequence of SEQ ID NO:61,
d) a VH region comprising the sequence of SEQ ID NO:13 and a VL region comprising the sequence of SEQ ID NO:69,
e) a VH region comprising the sequence of SEQ ID NO:17 and a VL region comprising the sequence of SEQ ID NO:73,
f) a VH region comprising the sequence of SEQ ID NO:21 and a VL region comprising the sequence of SEQ ID NO:77,
g) a VH region comprising the sequence of SEQ ID NO:25 and a VL region comprising the sequence of SEQ ID NO:81,
h) a VH region comprising the sequence of SEQ ID NO:29 and a VL region comprising the sequence of SEQ ID NO:85,
i) a VH region comprising the sequence of SEQ ID NO:33 and a VL region comprising the sequence of SEQ ID NO:89,
j) a VH region comprising the sequence of SEQ ID NO:37 and a VL region comprising the sequence of SEQ ID NO:93,
k) a VH region comprising the sequence of SEQ ID NO:41 and a VL region comprising the sequence of SEQ ID NO: 97,
l) a VH region comprising the sequence of SEQ ID NO:45 and a VL region comprising the sequence of SEQ ID NO:101,

m) a VH region comprising the sequence of SEQ ID NO:49 and a VL region comprising the sequence of SEQ ID NO:105, or

n) a VH region comprising the sequence of SEQ ID NO:53 and a VL region comprising the sequence of SEQ ID NO:109.

60. The antibody of any one of the preceding claims, wherein the antibody comprises:

- a heavy chain variable region derived from a human germline V_H sequence selected from the group consisting of: IGHV1-18*01, IGHV3-23*01, IGHV3-30*01, IGHV3-33*01, IGHV3-33*03, IGHV1-69*02, IGHV1-69*04 and IGHV5-51*01

and/or

- a light chain variable region derived from a human germline Vκ sequence selected from the group consisting of: IGKV3-20*01, IGKV1-13*02, IGKV3-11*01, and IGKV1D-16*01.

61. The antibody of any one of the preceding claims, wherein the antibody is a full-length antibody, preferably an IgG1 antibody, in particular an IgG1,κ antibody.

62. The antibody of any one of the preceding claims, wherein the antibody is conjugated to another moiety.

63. The antibody of any one of the claims 1 to 3 or 16 to 51, wherein the antibody is an effector-function-deficient antibody.

64.The antibody of claim 63, wherein the effector-function-deficient anti-Tissue-Factor antibody is a stabilized human IgG4 antibody.

65.The antibody of any one of the claims 1 to 3 or 16 to 51, wherein the antibody is a monovalent antibody.

66. The antibody of claim 65, wherein said monovalent antibody is constructed by a method comprising:

i) providing a nucleic acid construct encoding the light chain of said monovalent antibody, said construct comprising a nucleotide sequence encoding the VL region of a selected antigen specific antibody and a nucleotide sequence encoding the constant

CL region of an Ig, wherein said nucleotide sequence encoding the VL region of a selected antigen specific antibody and said nucleotide sequence encoding the CL region of an Ig are operably linked together, and wherein, in case of an IgG1 subtype, the nucleotide sequence encoding the CL region has been modified such that the CL region does not contain any amino acids capable of forming disulfide bonds or covalent bonds with other peptides comprising an identical amino acid sequence of the CL region in the presence of polyclonal human IgG or when administered to an animal or human being;

ii) providing a nucleic acid construct encoding the heavy chain of said monovalent antibody, said construct comprising a nucleotide sequence encoding the VH region of a selected antigen specific antibody and a nucleotide sequence encoding a constant CH region of a human Ig, wherein the nucleotide sequence encoding the CH region has been modified such that the region corresponding to the hinge region and, as required by the Ig subtype, other regions of the CH region, such as the CH3 region, does not comprise any amino acid residues which participate in the formation of disulphide bonds or covalent or stable non-covalent inter-heavy chain bonds with other peptides comprising an identical amino acid sequence of the CH region of the human Ig in the presence of polyclonal human IgG or when administered to an animal human being, wherein said nucleotide sequence encoding the VH region of a selected antigen specific antibody and said nucleotide sequence encoding the CH region of said Ig are operably linked together;

iii) providing a cell expression system for producing said monovalent antibody;

iv) producing said monovalent antibody by co-expressing the nucleic acid constructs of (i) and (ii) in cells of the cell expression system of (iii).

67 The antibody of claim 65, wherein the monovalent antibody comprises

(i) a variable region of an antibody of claims 1 to 27 or an antigen binding part of the said region, and

(ii) a C_H region of an immunoglobulin or a fragment thereof comprising the C_H2 and C_H3 regions, wherein the C_H region or fragment thereof has been modified such that the region corresponding to the hinge region and, if the immunoglobulin is not an IgG4 subtype, other regions of the C_H region, such as the C_H3 region, do not comprise any amino acid residues, which are capable of forming disulfide bonds with an identical C_H region or other covalent or stable non-covalent inter-heavy chain bonds with an identical C_H region in the presence of polyclonal human IgG.

68.The antibody of any of the claims 65 to 67, wherein the heavy chain has been modified such that the entire hinge has been deleted.

69. A bispecific molecule comprising an antibody of any of claims 1 to 64 and a second binding specificity.

70.An expression vector comprising a nucleotide sequence encoding one or more of the amino acid sequences selected from the group consisting of SEQ ID NO:1 – SEQ ID NO: 112.

71. An expression vector according to claim 70, further comprising a nucleotide sequence encoding the constant region of a light chain, a heavy chain or both light and heavy chains of a human antibody.

72.A recombinant eukaryotic or prokaryotic host cell which produces an antibody as defined in any of claims 1 to 61 or 63 to 69.

73. A pharmaceutical composition comprising an antibody as defined in any of claims 1 to 56 or a bispecific molecule as defined in claim 69, and a pharmaceutically acceptable carrier.

74.The antibody as defined in any of claims 1 to 68 or a bispecific molecule as defined in claim 68 for use as a medicament.

75.The antibody or the bispecific molecule of claim 74, wherein the use is for the treatment of cancer.

76. The antibody or the bispecific molecule of claim 75, wherein the cancer is selected from the group consisting of: tumors of the central nervous system, head and neck cancer, lung cancer. breast cancer, esophageal cancer, stomach cancer, liver and biliary cancer, pancreatic cancer, colorectal cancer, bladder cancer, kidney cancer, prostate cancer, endometrial cancer, ovarian cancer, malignant melanoma, sarcoma, tumors of unknown primary origin, bone marrow cancer, acute

lymphoblastic leukemia, chronic lymphoblastic leukemia and non-Hodgkin lymphoma, skin cancer, glioma, cancer of the brain, uterus, and rectum.

77. The antibody or the bispecific molecule of claim 74, wherein the use is for the treatment of pancreatic cancer.

78.The antibody or the bispecific molecule of claim 74, wherein the use is for the treatment of colorectal cancer.

79.The antibody or the bispecific molecule of claim 74, wherein the use is for the treatment of ovarian cancer.

80.The antibody or the bispecific molecule of claim 74, wherein the use is for the treatment of breast cancer.

81.The antibody or the bispecific molecule of claim 74, wherein the use is for the treatment of prostate cancer.

82.The antibody or the bispecific molecule of claim 74, wherein the use is for the treatment of bladder cancer.

83. The antibody or the bispecific molecule of claim 74, wherein the medicament is for the treatment of cancer in combination with one or more further therapeutic agent, such as a chemotherapeutic agent.

84. Use of the antibody of any one of the claims 1-68 or the bispecific molecule of claim 697 for the manufacture of a medicament for treatment of cancer.

85. The use of claim 84, comprising the further features of any of claims 76 to 83.

86. A method for producing an antibody of any of claims 1 to 61 or 63 to 68, said method comprising the steps of
a) culturing a host cell of claim 72, and
b) purifying the antibody from the culture media.

87. A diagnostic composition comprising an antibody as defined in any of claims 1 to 69.

88. A method for detecting the presence of Tissue Factor in a sample, comprising:
- contacting the sample with an antibody of any of claims 1 to 68 or a bispecific molecule of claim 69 under conditions that allow for formation of a complex between the antibody or bispecific molecules and Tissue Factor; and
- analyzing whether a complex has been formed.

89. A kit for detecting the presence of Tissue Factor in a sample comprising
- an antibody of any of claims 1 to 68 or a bispecific molecule of claim 69; and
- instructions for use of the kit.

CLAIMS

1. A human antibody which binds human Tissue Factor, wherein said antibody comprises a VH region comprising the CDR1, 2 and 3 sequences of SEQ ID NO:10, 11 and 12 and a VL region comprising the CDR1, 2 and 3 sequences of SEQ ID NO:66, 67 and 68.

2. The antibody of claim 1, wherein the antibody binds to the extracellular domain of Tissue Factor with an apparent affinity (EC_{50}) of one of 3 nM or less, 0.50 nM or less, 0.35 nM or less, 0.20 nM or less.

3. The antibody of any one of the preceding claims, wherein the antibody binds to mammalian cells expressing Tissue Factor, with an apparent affinity (EC_{50}) of one of 10 nM or less, 8 nM or less, 5 nM or less, 2 nM or less, 1 nM or less, 0.5 nM or less, or 0.3 nM or less.

4. The antibody according to claim 3, wherein the mammalian cells expressing Tissue Factor are A431 cells transfected with a construct encoding Tissue Factor.

5. The antibody of any one of the preceding claims, wherein the antibody is capable of inducing antibody-dependent cellular cytotoxicity in A431 cells with an EC_{50} value of one of 2 nM or less, 1 nM or less, 0.7 nM or less, 0.3 nM or less, 0.2 nM or less, or 0.1 nM or less.

6. The antibody of any one of the preceding claims, wherein the antibody is effective in inhibiting growth of established MDA-MB-231 tumors and/or in inhibiting growth of established BxPC3 tumors.

7. The antibody of any one of the preceding claims, wherein the antibody inhibits tissue factor induced blood coagulation, with a median inhibition concentration of one of less than 10 nM, less than 5 nM, less than 2 nM.

8. The antibody of any one of the preceding claims, wherein the antibody inhibits FVIIa binding to Tissue Factor with a maximum inhibition value of inhibition of one of more than 80% or more than 90%.

9. The antibody of any one of the preceding claims, wherein the antibody inhibits FVIIa-induced IL-8 release by MDA-MB-231 cells with a maximum inhibition value of inhibition of one of more than 40%, more than 50%, or more than 60%.

10. The antibody of any one of the preceding claims, wherein the antibody inhibits conversion of FX into FXa by the TF/FVIIa complex by one of less than 50%, less than 40%, or in the range of 1-30%.

11. The antibody of any one of the preceding claims, wherein said antibody competes for Tissue Factor binding with an antibody comprising a VH region comprising the sequence of SEQ ID NO:9 and a VL region comprising the sequence of SEQ ID NO:65.

12. The antibody of any one of the preceding claims, wherein said antibody inhibits FVIIa induced ERK phosphorylation with a median inhibition concentration of one of less than 10 nM, less than 5 nM, or less than 2 nM

13. The antibody of any one of the preceding claims, wherein the antibody is capable of inducing C3c and C4c deposition.

14. The antibody of any of the preceding claims, wherein the antibody Fab fragments binds to the extracellular domain of tissue factor with an EC50 value of one of below 0.1 µg/mL, below 0.05 µg/mL, or below 0.04 µg/mL measured by ELISA.

15. The antibody of any of the claims 1-13 wherein the antibody Fab fragments binds to the extracellular domain of tissue factor with an EC50 value of one of below 10µg/mL, below 1 µg/mL, below 0.5 µg/mL, or below 0.2 µg/mL.

16. The antibody of any of the claims above, wherein the antibody binds to human tissue factor and not murine tissue factor and shows reduced binding as compared to binding to human TF to the shuffle construct 42-84 mm, containing the human sequence for TF except for amino acid 42-84, which has been replaced with mouse sequence.

17. The antibody of any one of claims 1-12, wherein said antibody
- competes for Tissue Factor binding with an antibody comprising a VH region comprising the sequence of SEQ ID NO:9 and a VL region comprising the sequence of SEQ ID NO:65, and
- does not compete for Tissue Factor binding with an antibody comprising a VH region comprising the sequence of SEQ ID NO:37 and a VL region comprising the sequence of SEQ ID NO:93.

18. The antibody of claim 1, comprising a VH having
a) one of at least 80% identity, at least 90%, at least 95%, or at least 98% or 100% identity to a VH region sequence selected from the group consisting of: SEQ ID NO:9, or
b) one of at most 20, 15, 10, 5, 4, 3, 2 or 1 conservative amino-acid substitutions as compared to a VH region sequence selected from the group consisting of: SEQ ID NO:9.

19. The antibody of claim 1 comprising a VL having
a) one of at least 80% identity, at least 90%, at least 95%, at least 98% or 100% identity to a VL region sequence selected from the group consisting of: SEQ ID NO:65, or
b) one of at most 20, 15, 10, 5, 4, 3, 2 or 1 conservative amino-acid substitutions as compared to a VH region sequence selected from the group consisting of: SEQ ID NO:65.

20. The antibody of claim 1 comprising:
a) a VH region comprising the sequence of SEQ ID NO:9 and a VL region comprising the sequence of SEQ ID NO: 65, or
b) a variant of any of said antibodies, wherein said variant has at most 1,2 or 3 conservative amino-acid substitutions in said sequences.

21. The antibody of any one of the claims 1 to 5 wherein the antibody has an affinity to tissue factor which is less than 5 nM, such as less than 3.5 nM.

22. The antibody of any one of the claims 1 to 5 wherein the antibody has a kd of more than 10^{-3} sec^{-1}, and/or a ka of more than $5x10^{4}$,mol^{-1} sec^{-1}

23. The antibody of any one of the claims 1 to 5 wherein the antibody has a kd of more than 10^{-3} sec^{-1}, and an avidity of less than 5 nM.

24. The antibody of any one of the claims 1 to 5 or 22 to 23, wherein the antibody is effective in inhibiting growth of established BX-PC3 tumors

25. The antibody of any one of the preceding claims, wherein the antibody further has one or more of the following properties: inhibition of proliferation, inhibition of tumor angiogenesis, induction of apoptosis of tumor cells, binding to alternatively spliced Tissue Factor.

26. The antibody of any one of the claims 1 to 5 which competes for Tissue Factor binding with an antibody comprising

a) a VH region comprising the sequence of SEQ ID NO:9 and a VL region comprising the sequence of SEQ ID NO: 65

27. The antibody of any one of the claims 1 to 5 which binds to the same epitope on Tissue Factor as an antibody having:

a) a VH region comprising the sequence of SEQ ID NO:9 and a VL region comprising the sequence of SEQ ID NO: 65

28. The antibody of any one of the preceding claims, wherein the antibody is a full-length antibody, preferably an IgG1 antibody, in particular an IgG1,κ antibody.

29. The antibody of any one of the preceding claims, wherein the antibody is conjugated to another moiety.

30. The antibody of any one of the claims 1 to 3 or 14 to 20, wherein the antibody is an effector-function-deficient antibody.

31. The antibody of claim 30, wherein the effector-function-deficient anti-Tissue-Factor antibody is a stabilized human IgG4 antibody.

32. The antibody of any one of the claims 1 to 3 or 14 to 20, wherein the antibody is a monovalent antibody.

33. The antibody of claim 32, wherein the monovalent antibody comprises
(i) a variable region of an antibody of claims 1 to 26 or an antigen binding part of the said region, and
(ii) a C_H region of an immunoglobulin or a fragment thereof comprising the C_H2 and C_H3 regions, wherein the C_H region or fragment thereof has been modified such that the region corresponding to the hinge region and, if the immunoglobulin is not an IgG4 subtype, other regions of the C_H region, such as the C_H3 region, do not comprise any amino acid residues, which are capable of forming disulfide bonds with an identical C_H region or other covalent or stable non-covalent inter-heavy chain bonds with an identical C_H region in the presence of polyclonal human IgG.

34. The antibody of any of the claims 32 to 33, wherein the heavy chain has been modified such that the entire hinge has been deleted.

35. A bispecific molecule comprising an antibody of any of claims 1 to 31 and a second binding specificity.

36. An expression vector comprising a nucleotide sequence encoding one or more of the amino acid sequences selected from the group consisting of SEQ ID NO:9 to SEQ ID NO:12 and SEQ ID NO:65 to SEQ ID NO:68 .

37. An expression vector according to claim 36, further comprising a nucleotide sequence encoding the constant region of a light chain, a heavy chain or both light and heavy chains of a human antibody.

38. A recombinant eukaryotic or prokaryotic host cell which produces an antibody as defined in any of claims 1 to 28 or 30 to 34.

39. A pharmaceutical composition comprising an antibody as defined in any of claims 1 to 24 or a bispecific molecule as defined in claim 35, and a pharmaceutically acceptable carrier.

40. The antibody as defined in any of claims 1 to 34 or a bispecific molecule as defined in claim 35 for use as a medicament.

41. The antibody or the bispecific molecule of claim 40, wherein the use is for the treatment of cancer.

42. The antibody or the bispecific molecule of claim 41, wherein the cancer is selected from the group consisting of: tumors of the central nervous system, head and neck cancer, lung cancer, breast cancer, esophageal cancer, stomach cancer, liver and biliary cancer, pancreatic cancer, colorectal cancer, bladder cancer, kidney cancer, prostate cancer, endometrial cancer, ovarian cancer, malignant melanoma, sarcoma, tumors of unknown primary origin, bone marrow cancer, acute lymphoblastic leukemia, chronic lymphoblastic leukemia and non-Hodgkin lymphoma, skin cancer, glioma, cancer of the brain, uterus, and rectum.

43. The antibody or the bispecific molecule of claim 40, wherein the use is for the treatment of pancreatic cancer.

44. The antibody or the bispecific molecule of claim 40, wherein the use is for the treatment of colorectal cancer.

45. The antibody or the bispecific molecule of claim 40, wherein the use is for the treatment of ovarian cancer.

46. The antibody or the bispecific molecule of claim 40, wherein the use is for the treatment of breast cancer.

47. The antibody or the bispecific molecule of claim 40, wherein the use is for the treatment of prostate cancer.

48. The antibody or the bispecific molecule of claim 40, wherein the use is for the treatment of bladder cancer.

49. The antibody or the bispecific molecule of claim 40, wherein the medicament is for the treatment of cancer in combination with one or more further therapeutic agent, such as a chemotherapeutic agent.

50. Use of the antibody of any one of the claims 1-34 or the bispecific molecule of claim 35 for the manufacture of a medicament for treatment of cancer.

51. The use of claim 50, comprising the further features of any of claims 42 to 49.

52. A method for producing an antibody of any of claims 1 to 28 or 30 to 34, said method comprising the steps of
a) culturing a host cell of claim 38, and
b) purifying the antibody from the culture media.

53. A diagnostic composition comprising an antibody as defined in any of claims 1 to 35.

54. A method for detecting the presence of Tissue Factor in a sample, comprising:
- contacting the sample with an antibody of any of claims 1 to 25 or a bispecific molecule of claim 35 under conditions that allow for formation of a complex between the antibody or bispecific molecules and Tissue Factor; and
- analyzing whether a complex has been formed.

55. A kit for detecting the presence of Tissue Factor in a sample comprising
- an antibody of any of claims 1 to 34 or a bispecific molecule of claim 35; and
- instructions for use of the kit.