Claims

1. An isolated antibody molecule that specifically binds to the exosite 1 region of thrombin.

2. An antibody molecule according to claim 1 that inhibits thrombin activity.

3. An antibody molecule according to claim 2 which causes minimal inhibition of haemostasis and/or bleeding.

4. An antibody molecule according to claim 2 or claim 3 which does not inhibit haemostasis and/or cause bleeding.

5. An antibody molecule according to any one of the preceding claims wherein the antibody molecule comprises an HCDR3 having the amino acid sequence of SEQ ID NO: 5 or the amino acid sequence of SEQ ID NO: 5 with one or more amino acid substitutions, deletions or insertions.

6. An antibody molecule according to claim 5 wherein the antibody molecule comprises an HCDR2 having the amino acid sequence of SEQ ID NO: 4 or the amino acid sequence of SEQ ID NO: 4 with one or more amino acid substitutions, deletions or insertions.

7. An antibody molecule according to claim 5 or claim 6 wherein the antibody molecule comprises an HCDR1 having the amino acid sequence of SEQ ID NO: 3 or the amino acid sequence of SEQ ID NO: 3 with one or more amino acid substitutions, deletions or insertions.

8. An antibody molecule according to any one of claims 1 to 7 wherein the antibody molecule comprises a VH domain having the amino acid sequence of SEQ ID NO: 2 or the amino acid sequence of SEQ ID NO: 2 with one or more amino acid substitutions, deletions or insertions.

9. An antibody molecule according to any one of claims 1 to 8 wherein antibody molecule comprises LCDR1, LCDR2 and LCDR3 having the sequences of SEQ ID NOs 7, 8 and 9 respectively, or the

sequences of SEQ ID NOs 7, 8 and 9 respectively, with one or more amino acid substitutions, deletions or insertions.

10. An antibody molecule according to any one of claims 1 to 9 wherein the antibody molecule comprises a VL domain having the amino acid sequence of SEQ ID NO: 6 or the amino acid sequence of SEQ ID NO: 6 with one or more amino acid substitutions, deletions or insertions.

11. An antibody molecule according to any one of claims 1 to 10 comprising a VH domain comprising a HCDR1, HCDR2 and HCDR3 having the sequences of SEQ ID NOs 3, 4 and 5, respectively, and a VL domain comprising a LCDR1, LCDR2 and LCDR3 having the sequences of SEQ ID NOs 7, 8 and 9, respectively.

12. An antibody molecule according to claim 11 comprising a VH domain having the amino acid sequence of SEQ ID NO: 2 and a VL domain having the amino acid sequence of SEQ ID NO: 6.

13. An antibody molecule which competes with an antibody molecule according to any one of claims 5 to 12 for binding to exosite 1.

14. An antibody molecule according to any one of claims 1 to 13 which is a whole antibody.

15. An antibody molecule according to claim 14 which is an IgA or IgG.

16. An antibody molecule according to any one of claims 1 to 13 which is an antibody fragment.

17. A pharmaceutical composition comprising an antibody molecule according to any one of claims 1 to 16 and a pharmaceutically acceptable excipient.

18. An antibody molecule according to any one of claims 1 to 16 for use in a method of treatment of the human or animal body.

19. An antibody molecule according to any one of claims 1 to 16 for use in a method of treatment of a thrombin-mediated condition.

20. Use of an antibody molecule according to any one of claims 1 to 16 in the manufacture of a medicament for use in treating a thrombin-mediated condition.

21. A method of treatment of a thrombin-mediated condition comprising administering an antibody molecule according to any one of claims 1 to 16 to an individual in need thereof.

22. An antibody molecule according to claim 19, use according to claim 20 or method according to claim 21, wherein the thrombin-mediated condition is a thrombotic condition.

23. An antibody molecule, use or method according to claim 22 wherein the thrombotic condition is thrombosis or embolism.

24. An antibody molecule according to claim 19, use according to claim 20 or method according to claim 21 wherein the thrombin-mediated condition is inflammation, infection, tumour growth, tumour metastasis or dementia.

25. A method for producing an antibody antigen-binding domain for the exosite 1 epitope of thrombin, the method comprising;

(i) providing, by way of addition, deletion, substitution or insertion of one or more amino acids in the amino acid sequence of a parent VH domain comprising HCDR1, HCDR2 and HCDR3,

wherein the parent VH domain HCDR1, HCDR2 and HCDR3 have the amino acid sequences of SEQ ID NOS: 3, 4 and 5 respectively, a VH domain which is an amino acid sequence variant of the parent VH domain,

(ii) optionally combining the VH domain thus provided with one or more VL domains to provide one or more VH/VL combinations; and

(iii) testing said VH domain which is an amino acid sequence variant of the parent VH domain or the VH/VL combination or combinations to identify an antibody antigen binding domain for the exosite 1 epitope of thrombin.

26. A method for producing an antibody molecule that specifically binds to the exosite 1 epitope of thrombin, which method comprises:

providing starting nucleic acid encoding a VH domain or a starting repertoire of nucleic acids each encoding a VH domain, wherein the VH domain or VH domains either comprise a HCDR1, HCDR2 and/or HCDR3 to be replaced or lack a HCDR1, HCDR2 and/or HCDR3 encoding region;

combining said starting nucleic acid or starting repertoire with donor nucleic acid or donor nucleic acids encoding or produced by mutation of the amino acid sequence of an HCDR1, HCDR2, and/or HCDR3 having the amino acid sequences of SEQ ID NOS: 3, 4 and 5 respectively, such that said donor nucleic acid is or donor nucleic acids are inserted into the CDR1, CDR2 and/or CDR3 region in the starting nucleic acid or starting repertoire, so as to provide a product repertoire of nucleic acids encoding VH domains;

expressing the nucleic acids of said product repertoire to produce product VH domains;

optionally combining said product VH domains with one or more VL domains;

selecting an antibody molecule that binds exosite 1 of thrombin, which antibody molecule comprises a product VH domain and optionally a VL domain; and

recovering said antibody molecule or nucleic acid encoding it.

CLAIMS

1. An isolated antibody molecule that specifically binds to the exosite 1 region of thrombin.

2. An antibody molecule according to Claim 1 that inhibits thrombin activity.

3. An antibody molecule according to Claim 2 which causes minimal inhibition of haemostasis and/or bleeding.

4. An antibody molecule according to Claim 2 or 3 which does not inhibit haemostasis and/or cause bleeding.

5. An antibody molecule according to any preceding claim in which the antibody molecule comprises an HCDR3 having the amino acid sequence of SEQ ID NO: 5 or the amino acid sequence of SEQ ID NO: 5 with one or more amino acid substitutions, deletions or insertions.

6. An antibody molecule according to Claim 5, in which the antibody molecule comprises an HCDR2 having the amino acid sequence of SEQ ID NO: 4 or the amino acid sequence of SEQ ID NO: 4 with one or more amino acid substitutions, deletions or insertions.

7. An antibody molecule according to Claim 5 or 6, in which the antibody molecule comprises an HCDR1 having the amino acid sequence of SEQ ID NO: 3 or the amino acid sequence of SEQ ID NO: 3 with one or more amino acid substitutions, deletions or insertions.

8. An antibody molecule according to any of Claims 1 to 7, in which the antibody molecule comprises a VH domain having the amino acid sequence of SEQ ID NO: 2 or the amino acid sequence of SEQ ID NO: 2 with one or more amino acid substitutions, deletions or insertions.

9. An antibody molecule according to any of Claims 1 to 8, in which antibody molecule comprises LCDR1, LCDR2 and LCDR3 having the sequences of SEQ ID NOs 7, 8 and 9 respectively, or the sequences of SEQ ID NOs 7, 8 and 9 respectively, with one or more amino acid substitutions, deletions or insertions.

10. An antibody molecule according to any of Claims 1 to 9, in which the antibody molecule comprises a VL domain having the amino acid sequence of SEQ ID NO: 6 or the

amino acid sequence of SEQ ID NO: 6 with one or more amino acid substitutions, deletions or insertions.

11. An antibody molecule according to any of Claims 1 to 10 comprising a VH domain comprising a HCDR1, HCDR2 and HCDR3 having the sequences of SEQ ID NOs 3, 4 and 5, respectively, and a VL domain comprising a LCDR1, LCDR2 and LCDR3 having the sequences of SEQ ID NOs 7, 8 and 9, respectively.

12. An antibody molecule according to Claim 11 comprising a VH domain having the amino acid sequence of SEQ ID NO: 2 and a VL domain having the amino acid sequence of SEQ ID NO: 6.

13. An antibody molecule according to any of Claims 1 to 12 comprising one or more substitutions, deletions or insertions which remove a glycosylation site.

14. An antibody molecule according to Claim 13 comprising a VL domain having the amino acid sequence of SEQ ID NO: 6 in which the glycosylation site is mutated out by introducing a substitution at N28 or S30.

15. An antibody molecule which competes with an antibody molecule according to any of Claims 5 to 12 for binding to exosite 1.

16. An antibody molecule according to any of Claims 1 to 15 which is a whole antibody.

17. An antibody molecule according to Claim 16 which is an IgA or IgG.

18. An antibody molecule according to any of Claims 1 to 15 which is an antibody fragment.

19. A pharmaceutical composition comprising an antibody molecule according to any of Claims 1 to 18 and a pharmaceutically acceptable excipient.

20. An antibody molecule according to any of Claims 1 to 18 for use in a method of treatment of the human or animal body.

21. An antibody molecule according to any of Claims 1 to 18 for use in a method of treatment of a thrombin-mediated condition.

22. Use of an antibody molecule according to any of Claims 1 to 18 in the manufacture of a medicament for use in treating a thrombin-mediated condition.

23. An antibody molecule according to Claim 21 for a use as specified therein or a use according to Claim 22, in which the thrombin-mediated condition is a thrombotic condition.

24. An antibody molecule for a use or a use according to Claim 23, in which the thrombotic condition is thrombosis or embolism.

25. An antibody molecule according to Claim 21 for a use as specified therein or a use according to Claim 22, in which the thrombin-mediated condition is inflammation, infection, tumour growth, tumour metastasis or dementia.

26. A method for producing an antibody antigen-binding domain for the exosite 1 epitope of thrombin, the method comprising;

(i) providing, by way of addition, deletion, substitution or insertion of one or more amino acids in the amino acid sequence of a parent VH domain comprising HCDR1, HCDR2 and HCDR3,

in which the parent VH domain HCDR1, HCDR2 and HCDR3 have the amino acid sequences of SEQ ID NOS: 3, 4 and 5 respectively, a VH domain which is an amino acid sequence variant of the parent VH domain,

(ii) optionally combining the VH domain thus provided with one or more VL domains to provide one or more VH/VL combinations; and

(iii) testing said VH domain which is an amino acid sequence variant of the parent VH domain or the VH/VL combination or combinations to identify an antibody antigen binding domain for the exosite 1 epitope of thrombin.

27. A method for producing an antibody molecule that specifically binds to the exosite 1 epitope of thrombin, which method comprises:

providing starting nucleic acid encoding a VH domain or a starting repertoire of nucleic acids each encoding a VH domain, in which the VH domain or VH domains either comprise a HCDR1, HCDR2 and/or HCDR3 to be replaced or lack a HCDR1, HCDR2 and/or HCDR3 encoding region;

combining said starting nucleic acid or starting repertoire with donor nucleic acid or donor nucleic acids encoding or produced by mutation of the amino acid sequence of an HCDR1, HCDR2, and/or HCDR3 having the amino acid sequences of SEQ ID NOS: 3, 4 and 5 respectively, such that said donor nucleic acid is or donor nucleic acids are inserted into the CDR1, CDR2 and/or CDR3 region in the starting nucleic acid or starting repertoire, so as to provide a product repertoire of nucleic acids encoding VH domains;

expressing the nucleic acids of said product repertoire to produce product VH domains;

optionally combining said product VH domains with one or more VL domains;

selecting an antibody molecule that binds exosite 1 of thrombin, which antibody molecule comprises a product VH domain and optionally a VL domain; and

recovering said antibody molecule or nucleic acid encoding it.