Claims

1. An agent which comprises a fibrinogen binding precursor bound to an insoluble carrier, the fibrinogen binding precursor not being fibrinogen, wherein the fibrinogen binding precursor comprises a peptide or peptide analogue that can be cleaved by a wound site specific serine protease to expose a fibrinogen binding peptide or peptide analogue bound to the carrier, the fibrinogen binding peptide or peptide analogue having increased ability, compared to the fibrinogen binding precursor, to bind fibrinogen such that bound fibrinogen can bind to platelets thereby causing platelet aggregation but platelet aggregation caused by the agent is minimised unless the fibrinogen binding precursor is converted by the wound site specific serine protease.

2. An agent according to claim 1, wherein the fibrinogen binding peptide comprises the amino acid sequence NH_2-GPRP- (SEQ ID NO: 17) at its amino terminal end.

3. An agent according to claim 1, wherein the fibrinogen binding precursor comprises a fibrinogen binding peptide joined at its amino terminal end to a blocking component that blocks or inhibits binding of fibrinogen to the fibrinogen binding peptide, such that cleavage of the fibrinogen binding precursor by the wound site specific agent exposes the fibrinogen binding peptide to allow increased binding of fibrinogen to the fibrinogen binding peptide.

4. An agent according to claim 3, wherein the wound site specific serine protease is thrombin, and the fibrinogen binding precursor includes a thrombin cleavage site.

5. An agent according to claim 4, wherein the fibrinogen binding precursor comprises a peptide which includes the amino acid sequence NH_2-ZYXR/GPRP (SEQ ID NO: 18) at its amino terminal end, where "/" represents the thrombin cleavage site, and X is any amino acid, Y is any amino acid, and Z is at least one amino acid.

6. An agent according to claim 5, wherein X is proline, Y is aspartic acid, or Z is leucine or proline.

7. An agent according to claim 5, wherein the peptide comprises one of the following amino acid sequences at its amino terminal end: NH_2-LVPR/GPRP (SEQ ID NO: 19), NH_2-ADPR/GPRP (SEQ ID NO: 20), NH_2-LDPR/GPRP (SEQ ID NO: 21), or NH_2-LVPR/GPRV (SEQ ID NO: 22), where "/" represents the thrombin cleavage site.

8. An agent according to any of claims 4 to 7, which further comprises a thrombin binding site.

9. An agent according to claim 8, wherein the fibrinogen binding precursor and the thrombin binding site are bound separately to the insoluble carrier.

10. An agent according to claim 8, wherein the thrombin binding site is a peptide sequence which is part of the fibrinogen binding precursor.

11. An agent according to claim 10, wherein the peptide sequence is a sequence to which a thrombin exocite I or II domain can bind.

12. An agent according to claim 10 or 11, wherein the peptide sequence corresponds to peptide sequence of the PAR-1 receptor, fibrinogen, or Factor VIII to which a thrombin exocite I or II domain can bind, or to the thrombin binding peptide hirudin.

13. An agent according to claim 12, wherein the peptide sequence is WEDEEKNES (SEQ ID NO: 24), VRPEHPAETEYDSLYPEDDL (SEQ ID NO: 25), EEEDWD (SEQ ID NO: 26) or EDSYED (SEQ ID NO: 27).

14. An agent according to any preceding claim, wherein the fibrinogen binding precursor comprises a peptide with a carboxy-terminal residue, or a modified carboxy-terminal residue, which is covalently bound to the insoluble carrier.

15. An agent according to claim 14, wherein the carboxy-terminal residue is a cysteine residue, or wherein the modified carboxy-terminal residue is a maleimide-modified lysine residue.

16. An agent according to claim 14 or 15, wherein the fibrinogen binding precursor comprises a spacer sequence between the carboxy-terminal residue, or the modified carboxy-terminal residue, and the fibrinogen binding component.

17. An agent according to claim 16, wherein the spacer sequence is GGGGGG (SEQ ID NO: 29) or GGGGG (SEQ ID NO: 30).

18. An agent according to any preceding claim which further comprises a wound site targeting component that can bind to a cell surface protein tissue factor.

19. An agent according to claim 18, wherein the wound site targeting component is immobilised to the insoluble carrier.

20. An agent according to claim 18, wherein the wound site targeting component is part of the fibrinogen binding precursor.

21. An agent according to claim 20, wherein the fibrinogen binding precursor is a peptide comprising a fibrinogen binding peptide, and the wound site targeting component is bound to the amino terminal end of the fibrinogen binding peptide such that cleavage of the fibrinogen binding precursor by the wound site specific agent releases the wound site targeting component to expose the fibrinogen binding peptide.

22. An agent according to claim 18, wherein the wound site targeting component comprises Factor VII or a fragment or derivative thereof capable of binding cell surface protein tissue factor, or Factor VIIa or a fragment or derivative thereof capable of binding cell surface protein tissue factor.

23. A pharmaceutical composition comprising an agent as defined in any of claims 1 to 22, and a pharmaceutically acceptable carrier, excipient, or diluent.

24. An agent as defined in any of claims 1 to 22 for use as a medicament.

25. Use of an agent as defined in any of claims 1 to 22 in the manufacture of a medicament for preventing, treating, or ameliorating thrombocytopenia or thrombasthenia.

26. An agent as defined in any of claims 1 to 22 for preventing, treating, or ameliorating thrombocytopenia or thrombasthenia.

~~27. A fibrinogen binding precursor peptide for use as part of an agent according to claim 1 wherein the fibrinogen binding precursor peptide can be cleaved by a wound site specific serine protease to a fibrinogen binding peptide, the fibrinogen binding peptide having increased ability to bind fibrinogen compared to the fibrinogen binding precursor peptide and the fibrinogen binding precursor peptide not being fibrinogen.~~

~~28. A peptide according to claim 27 which comprises an amino acid sequence of any of SEQ ID NOs: 32-36, or 38-41.~~

~~29. A method of identifying a fibrinogen binding precursor peptide or peptide analogue for use as part of an agent according to claim 1 which comprises:~~

i) incubating a wound site specific serine protease with a labeled candidate fibrinogen binding precursor peptide or peptide analogue bound to an insoluble carrier under conditions that permit cleavage of known fibrinogen binding precursor peptides or peptide analogues to fibrinogen binding peptides or peptide analogues by the wound site specific serine protease;

ii) determining the amount of label on the insoluble carrier before and after incubation with the wound site specific serine protease; and

iii) identifying the candidate fibrinogen binding precursor peptide or peptide analogue as a fibrinogen binding precursor peptide or peptide analogue if the amount of label on the insoluble carrier after incubation with the wound site specific serine protease is less than the amount of label on the insoluble carrier before incubation with the wound site specific serine protease.

30. A method according to claim 29, which further comprises determining binding of fibrinogen to the insoluble carrier before and after incubation with the wound site specific serine protease, and in step (iii) identifying the candidate fibrinogen binding precursor peptide or peptide analogue as a fibrinogen binding precursor peptide or peptide analogue if the amount of label on the insoluble carrier after incubation with the wound site specific serine protease is less than the amount of label on the insoluble carrier before incubation with the wound site specific serine protease, and the binding of fibrinogen to the insoluble carrier is increased after incubation with the wound site specific serine protease.

31. A method of identifying a fibrinogen binding precursor peptide or peptide analogue for use as part of an agent according to claim 1, which comprises:

i) contacting a wound site specific serine protease with a candidate fibrinogen binding precursor peptide or peptide analogue bound to an insoluble carrier under conditions that permit cleavage of fibrinogen binding precursor peptides or peptide analogues to fibrinogen binding peptides or peptide analogues by the wound site specific serine protease;

ii) determining whether the candidate fibrinogen binding precursor peptide or peptide analogue bound to the insoluble carrier promotes clot formation, or platelet aggregation after it has been contacted with the wound site specific serine protease; and

iii) identifying the candidate fibrinogen binding precursor peptide or peptide analogue as a fibrinogen binding precursor peptide or peptide analogue if clot formation or platelet aggregation is promoted after the candidate fibrinogen binding precursor has been contacted

with the wound site specific serine protease, but minimal clot formation or platelet aggregation is promoted prior to contact with the wound site specific serine protease.