Claims

1. A peptide dendrimer that comprises a branched core, and a plurality of fibrinogen-binding peptides separately covalently attached to the branched core, wherein the branched core comprises:

from two to ten multi-functional amino acid residues, wherein each fibrinogen-binding peptide is separately covalently attached to a multi-functional amino acid residue of the branched core;

a plurality of multi-functional amino acid residues, wherein one or more fibrinogen-binding peptides are separately covalently attached to each of at least two adjacent multi-functional amino acid residues of the branched core;

a plurality of multi-functional amino acid residues, wherein two or more fibrinogen-binding peptides are separately covalently attached to at least one of the multi-functional amino acid residues of the branched core;

a plurality of multi-functional amino acid residues, wherein two or more multi-functional amino acid residues are covalently linked through a side chain of an adjacent multi-functional amino acid residue; or

a single multi-functional amino acid residue, and a fibrinogen-binding peptide is separately covalently attached to each functional group of the multi-functional amino acid residue;

wherein the multi-functional amino acid residues comprise tri- or tetra-functional amino acid residues, or tri- and tetra-functional amino acid residues, or the single multi-functional amino acid residue is a tri- or tetra-functional amino acid residue.

2. A peptide dendrimer according to claim 1, wherein the branched core comprises a plurality of consecutive multi-functional amino acid residues and preferably up to ten multi-functional amino acid residues.

3. A peptide dendrimer according to claim 2, wherein the multi-functional amino acid residue, or the plurality of multi-functional amino acid residues, comprise a lysine, ornithine, arginine, aspartic acid, glutamic acid, asparagine, glutamine, or cysteine residue.

4. A peptide dendrimer according to any preceding claim, of the following general formula (I):

FBP-(linker)-X-(linker)-Y
|
Z

(I)

where:

FBP is a fibrinogen-binding peptide;

–(linker)- is an optional linker, preferably a non-peptide linker;

X is a tri-functional amino acid residue, preferably a lysine, ornithine, arginine, aspartic acid, glutamic acid, asparagine, glutamine, or cysteine residue;

Y is –FBP, or -NH_2;

Z is –(linker)-FBP when Y is -FBP, or -[-X_n-(linker)-FBP]$_a$-(linker)-FBP when Y is -NH_2, or -[-X_n-(linker)-FBP]$_a$-(linker)-FBP when Y is -FBP;

where:

X_n is a tri-functional amino acid residue, preferably a lysine, ornithine, arginine, aspartic acid, glutamic acid, asparagine, glutamine, or cysteine residue; and

a is 1-10, preferably 1-3.

5. A peptide dendrimer according to any preceding claim, of the following general formula (II):

FBP-(linker)-NH-CH-CO-(linker)-Y
|
Z

(II)

where:

FBP is a fibrinogen-binding peptide;

–(linker)- is an optional linker, preferably comprising –NH$(CH_2)_5$CO–;

Y is –FBP, or -NH_2;

Z is:

-R-(linker)-FBP, when Y is -FBP, or

-R-COCHNH-(linker)-FBP
|
R-(linker)-FBP, when Y is -NH_2; or

-R-COCHNH-(linker)-FBP
|
R-COCHNH-(linker)-FBP
|
R-(linker)-FBP, when Y is -NH_2; or

-R-COCHNH-(linker)-FBP
|
R-COCHNH-(linker)-FBP
|
R-COCHNH-(linker)-FBP
|
R-(linker)-FBP, when Y is -NH_2; or

-[-R-COCHNH-(linker)-FBP]$_a$
|
R-(linker)-FBP, when Y is –FBP and a is 1-10, preferably 1-3

where R is -$(CH_2)_4$NH-, -$(CH_2)_3$NH-, or -$(CH_2)_3$NHCNHNH.

6. A peptide dendrimer according to any preceding claim, of the following general formula (III):

FBP–(linker)-NH-CH-CO-(linker)-Y
|
Z

(III)

where:

FBP is a fibrinogen-binding peptide;

–(linker)- is an optional linker, preferably comprising –NH$(CH_2)_5$CO–;

Y is –FBP, or -NH_2;

Z is:

-$(CH_2)_4$NH-(linker)-FBP, when Y is -FBP; or

$-(CH_2)_4NHCOCHNH-(linker)-FBP$
$|$
$(CH_2)_4NH-(linker)-FBP$, when Y is $-NH_2$; or

$-(CH_2)_4NHCOCHNH-(linker)-FBP$
$|$
$(CH_2)_4NHCOCHNH-(linker)-FBP$
$|$
$(CH_2)_4NH-(linker)-FBP$, when Y is $-NH_2$; or

$-(CH_2)_4NHCOCHNH-(linker)-FBP$
$|$
$(CH_2)_4NHCOCHNH-(linker)-FBP$
$|$
$(CH_2)_4NHCOCHNH-(linker)-FBP$
$|$
$(CH_2)_4NH-(linker)-FBP$, when Y is $-NH_2$; or

$-[-(CH_2)_4NHCOCHNH-(linker)-FBP]_a$
$|$
$(CH_2)_4NH-(linker)-FBP$, when Y is –FBP and a is 1-10, preferably 1-3.

7. A peptide dendrimer according to any preceding claim, wherein the fibrinogen-binding peptides bind preferentially to hole 'a' of fibrinogen over hole 'b' of fibrinogen.

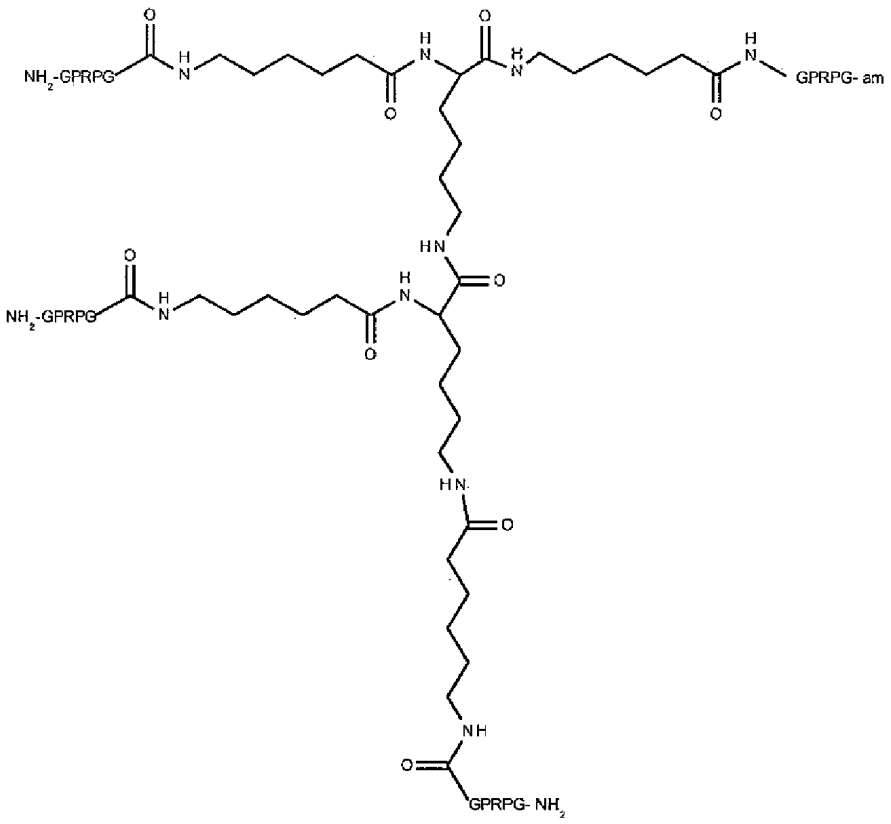
8. A peptide dendrimer according to any of claims 1 to 6, wherein the fibrinogen-binding peptides bind preferentially to hole 'b' of fibrinogen over hole 'a' of fibrinogen.

9. A peptide dendrimer according to any preceding claim, wherein each fibrinogen-binding peptide is attached to the branched core by a non-peptide linker.

10. A peptide dendrimer according to claim 9, wherein the linker comprises a straight-chain linker, preferably a straight-chain alkyl group, and more preferably:

$–NH(CH_2)_nCO–$, where n is 1-10.

11. A peptide dendrimer according to any preceding claim, which does not comprise the following:



12. A peptide dendrimer according to any preceding claim comprising fibrinogen-binding peptides of different sequence.

13. A peptide dendrimer according to claim 12, wherein the fibrinogen-binding peptides of different sequence have different selectivity of binding to hole 'a' over hole 'b' of fibrinogen.

14. A peptide dendrimer according to claim 12 or 13, wherein the fibrinogen-binding peptides of different sequence comprise a first fibrinogen-binding peptide that binds preferentially to hole 'a' of fibrinogen over hole 'b' of fibrinogen, and a second fibrinogen-binding peptide that binds with higher selectivity of binding to hole 'a' of fibrinogen over hole 'b' of fibrinogen than the first fibrinogen-binding peptide.

15. A peptide dendrimer according to claim 14, wherein the first fibrinogen-binding peptide comprises an amino acid sequence GPRP- (SEQ ID NO: 1) at its amino-terminal end.

16. A peptide dendrimer according to claim 14 or 15, wherein the second fibrinogen-binding peptide comprises an amino acid sequence -APFPRPG (SEQ ID NO: 14) at its carboxy-terminal end.

17. A peptide dendrimer according to claim 12 or 13, wherein the fibrinogen-binding peptides of different sequence comprise a first fibrinogen-binding peptide that binds preferentially to hole 'a' of fibrinogen over hole 'b' of fibrinogen, and a second fibrinogen-binding peptide that binds preferentially to hole 'b' of fibrinogen over hole 'a' of fibrinogen.

18. A peptide dendrimer according to claim 17, wherein the first fibrinogen-binding peptide comprises an amino acid sequence GPRP- (SEQ ID NO: 1) at its amino-terminal end.

19. A peptide dendrimer according to claim 17 or 18, wherein the second fibrinogen-binding peptide comprises an amino acid sequence GHRP- (SEQ ID NO: 10), preferably an amino acid sequence GHRPY- (SEQ ID NO: 11), at its amino terminal end.

20. A composition comprising a peptide dendrimer according to any preceding claim, and a peptide conjugate comprising two or more fibrinogen-binding peptides.

21. A composition according to claim 20, wherein the peptide conjugate is a peptide dendrimer according to any of claims 1 to 19.

22. A composition according to claim 20 or 21, wherein the fibrinogen-binding peptides of the peptide dendrimer bind preferentially to hole 'a' of fibrinogen over hole 'b' of fibrinogen, and the fibrinogen-binding peptides of the peptide conjugate bind preferentially to hole 'b' of fibrinogen over hole 'a' of fibrinogen.

23. A composition according to claim 20 or 21, wherein the fibrinogen-binding peptides of the peptide dendrimer bind preferentially to hole 'b' of fibrinogen over hole 'a' of fibrinogen, and the fibrinogen-binding peptides of the peptide conjugate bind preferentially to hole 'a' of fibrinogen over hole 'b' of fibrinogen.

24. A pharmaceutical composition, which comprises a peptide dendrimer according to any of claims 1 to 19, or a composition according to any of claims 20 to 23, and a pharmaceutically acceptable carrier, excipient, or diluent.

25. A pharmaceutical composition according to claim 24, which is a ready-to-use haemostatic formulation in which the pharmaceutically acceptable carrier, excipient, or diluent comprises hydrated gelatin.

26. A peptide dendrimer according to any of claims 1 to 19, or a composition according to any of claims 20 to 25, which is sterile.

27. A method of sterilising a peptide dendrimer according to any of claims 1 to 19, or a composition according to any of claims 20 to 25, which comprises exposing the peptide dendrimer or composition to gamma irradiation, preferably up to 30 kGy.

28. A method of polymerising fibrinogen, which comprises contacting fibrinogen with a peptide dendrimer according to any of claims 1 to 19, or with a composition according to any of claims 20 to 25.

29. A kit for formation of a hydrogel, which comprises a peptide dendrimer according to any of claims 1 to 19, or a composition according to any of claims 20 to 25, and, separately, fibrinogen.

30. A hydrogel comprising a copolymer of a peptide dendrimer according to any of claims 1 to 19, or of a composition according to any of claims 20 to 25, and fibrinogen.

31. Use of a peptide dendrimer according to any of claims 1 to 19, or a composition according to any of claims 20 to 25, in the manufacture of a medicament for the treatment of bleeding or for treating a wound.

32. A use according to claim 31, wherein the medicament is administered to the site of bleeding or to the wound.

33. A peptide dendrimer according to any of claims 1 to 19, or a composition according to any of claims 20 to 25, for use as a medicament.

34. A peptide dendrimer according to any of claims 1 to 19, or a composition according to any of claims 20 to 25, for use in the treatment of bleeding or for use in treating a wound.