

WHAT IS CLAIMED IS:

1. A linker unit comprising a first center core, a plurality of first linking arms, a plurality of first elements, and optionally a first coupling arm, wherein

the first center core comprises, (1) a first polypeptide comprising a plurality of lysine (K) residues, wherein each K residue and its next K residue are separated by a filler sequence comprising glycine (G) and serine (S) residues, and the number of K residues ranges from 2 to 15; or (2) a second polypeptide comprising the sequence of $(X_{aa}-K)_n$, where X_{aa} is a PEGylated amino acid having 2 to 12 repeats of ethylene glycol (EG) unit, and n is an integral from 2 to 15;

the plurality of first linking arms are respectively linked to the K residues of the first center core;

the plurality of first elements are respectively linked to the plurality of first linking arms via forming an amide bond therebetween, or via thiol–maleimide reaction, copper catalyzed azide-alkyne cycloaddition (CuAAC) reaction, strained-promoted azide-alkyne click chemistry (SPAAC) reaction, or inverse electron demand Diels–Alder (iEDDA) reaction, wherein each of the first elements is a tissue plasminogen activator, an inhibitor of Factor Xa or thrombin, or an single-chain variable fragment (scFv) specific for fibrin; and

the amino acid residue at the N- or C-terminus of the first center core has the azide or the alkyne group; or the amino acid residue at the N- or C-terminus of the first center core is a cysteine residue, and the thiol group of the cysteine residue is linked with the first coupling arm having the azide, the alkyne, the tetrazine, the cyclooctene, or the cyclooctyne group at the free terminus of the first coupling arm, wherein,

when the plurality of first elements are respectively linked to the plurality of first linking arms via CuAAC or SPAAC reaction, then the amino acid residue at the N-

or C-terminus of the first center core is a cysteine residue, and the free terminus of the first coupling arm is the tetrazine or the cyclooctene group; or

when the plurality of first elements are respectively linked to the plurality of first linking arms via iEDDA reaction, then the amino acid residue at the N- or C-terminus of the first center core has the azide or the alkyne group, or the amino acid residue at the N- or C-terminus of the first center core is a cysteine residue, and the free terminus of the first coupling arm is the azide, the alkyne, or the cyclooctyne group.

2. The linker unit of claim 1, wherein

each of the first linking arms is a PEG chain having 2-20 repeats of EG units; and the first coupling arm is a PEG chain having 2-12 repeats of EG units.

3. The linker unit of claim 1, wherein

the amino acid residue having the azide group is L-azidohomoalanine (AHA), 4-azido-L-phenylalanine, 4-azido-D-phenylalanine, 3-azido-L-alanine, 3-azido-D-alanine, 4-azido-L-homoalanine, 4-azido-D-homoalanine, 5-azido-L-ornithine, 5-azido-D-ornithine, 6-azido-L-lysine, or 6-azido-D-lysine;

the amino acid residue having the alkyne group is L-homopropargylglycine (L-HPG), D-homopropargylglycine (D-HPG), or beta-homopropargylglycine (β -HPG);

the cyclooctene group is trans-cyclooctene (TCO); and the cyclooctyne group is dibenzocyclooctyne (DBCO), difluorinated cyclooctyne (DIFO), or bicyclononyne (BCN); and

the tetrazine group is 1,2,3,4-tetrazine, 1,2,3,5-tetrazine, 1,2,4,5-tetrazine, or 6-methyl tetrazine.

4. The linker unit of claim 1, further comprising a second element that is linked to the first center core via any of the following reactions,

CuAAC reaction occurred between the azide or alkyne group and the second element;

SPAAC reaction occurred between the azide or cyclooctyne group and the second element; and

iEDDA reaction occurred between the cyclooctene group or tetrazine group and the second element.

5. The linker unit of claim 4, wherein

one of the first and second elements is an scFv specific for fibrin, and the other of the first and second elements is a tissue plasminogen activator or an inhibitor of Factor Xa or thrombin.

6. The linker unit of claim 5, wherein

the tissue plasminogen activator is alteplase, reteplase, tenecteplase, or lanoteplase;

the inhibitor of Factor Xa is apixaban, edoxaban, or rivaroxaban; and the inhibitor of thrombin is argatroban or melagatran.

7. Use of a linker unit for the manufacture of a medicament for preventing the formation of blood clot in a subject in need thereof, wherein the linker unit is the linker unit of claim 4, wherein one of the first and second elements is the scFv specific for fibrin, and the other of the first and second elements is the inhibitor of Factor Xa or thrombin.

8. Use of a linker unit for the manufacture of a medicament for treating thrombosis in a subject in need thereof, wherein the linker unit is the linker unit of claim 5, wherein one of the first and second elements is the scFv specific for fibrin, and the other of the first and second elements is the tissue plasminogen activator.

9. A molecular construct comprising a first linker unit and a second linker unit, wherein,

the first linker unit is the linker unit of claim 1;

the second linker unit comprises,

a second center core comprising a plurality of amine groups,

a plurality of second linking arms respectively linked to the plurality of amine groups of the second center core,

a plurality of second elements respectively linked to the plurality of second linking arms, and

optionally, a second coupling arm linked to the second center core;

one of the first and second elements is the scFv specific for fibrin, and the other of the first and second elements is the tissue plasminogen activator or the inhibitor of Factor Xa or thrombin; and

the first and second linker units are coupled to each other via CuAAC reaction, SPAAC reaction or iEDDA reaction occurred between any of the followings: the first and second center cores, the first coupling arm and the second center core, the first and second coupling arms, or the first center core and the second coupling arm.

10. The molecular construct of claim 9, wherein,
each of the plurality of second linking arms is a PEG chain having 2-20 repeats of ethylene glycol (EG) units; and
the second coupling arm is a PEG chain having 2-12 repeats of EG units.
11. The molecular construct of claim 9, wherein the second center core is a compound core, wherein the second coupling arm linked to said compound core is linked thereto via forming an amide bond with one of the plurality of amine groups of the compound core and has an azide, an alkyne, a cyclooctene, a cyclooctyne or a tetrazine group at the free-terminus thereof.
12. The molecular construct of claim 11, wherein the compound is selected from the group consisting of, benzene-1,3,5-triamine, 2-(aminomethyl)-2-methylpropane-1,3-diamine, tris(2-aminoethyl)amine, benzene-1,2,4, 5-tetraamine, 3,3',5,5'-tetraamine-1,1'-biphenyl, tetrakis(2-aminoethyl)methane, tetrakis- (ethylamine)hydrazine, N,N,N',N',-tetrakis(aminoethyl)ethylenediamine, benzene-1,2,3,4, 5,6-hexamine, 1-N,1-N,3-N,3-N,5-N,5-N-hexakis(methylamine)-benzene-1,3,5-triamine, 1-N,1-N,2-N,2-N,4-N,4-N,5-N,5-N,-octakis(methylamine)-benzene-1,2,4,5-triamine, and N,N-bis[(1-amino-3,3-diaminoethyl)pentyl] methanediamine.
13. The molecular construct of claim 9, wherein
the tissue plasminogen activator is alteplase, reteplase, tenecteplase, or lanoteplase;
the inhibitor of Factor Xa is apixaban, edoxaban, or rivaroxaban; and
the inhibitor of thrombin is argatroban or melagatran.

14. A molecular construct comprising,

- a pair of CH₂-CH₃ segments of an IgG.Fc;
- a pair of effector elements, wherein each effector element is a tissue plasminogen activator or a drug bundle;
- a pair of targeting elements, wherein each targeting element is a single-chain variable antibody (scFv) specific for fibrin;
- optionally, a peptide extension that has the sequence of (G₂₋₄S)₂₋₈C, and is linked to the C-terminus of one of the pair of CH₂-CH₃ segments; and
- optionally, a coupling arm that is linked to the C-terminus of the peptide extension via thiol-maleimide reaction occurred therebetween; wherein,
- when each effector element is the tissue plasminogen activator, then the pair of effector elements is linked to the N-termini of the pair of CH₂-CH₃ segments, and the pair of targeting elements is linked to the C-termini of the pair of CH₂-CH₃ segments, or vice versa, or
- when each effector element is the drug bundle, then the pair of effector elements is linked to the C-termini of the pair of CH₂-CH₃ segments, and the pair of targeting elements is linked to the N-termini of the pair of CH₂-CH₃ segments; wherein the drug bundle comprises,
- a center core that is a compound having a plurality of amine groups or is a polypeptide comprising a plurality of lysine (K) residues;
- a plurality of linking arms, each having one terminus linked to the center core by reacting with one of the amine groups or one of the K residues, and carrying, a maleimide, an N-hydroxysuccinimidyl (NHS), an azide, an alkyne, a tetrazine or a strained alkyne group at the free terminus thereof; and

a plurality of molecules of an inhibitor of Factor Xa or an inhibitor of thrombin, wherein each of the molecules is linked to the center core via connecting through the linking arm by reacting with the maleimide, the NHS, the azide, the alkyne, the tetrazine or the strained alkyne group, and the drug bundle is linked to the coupling arm via iEDDA reaction, SPAAC reaction, or CuAAC reaction occurred therebetween.

15. The molecular construct of claim 14, wherein the pair of CH₂-CH₃ segments is derived from human γ 1 or γ 4 immunoglobulin.

16. The molecular construct of claim 14, wherein

the inhibitor of Factor Xa is apixaban, edoxaban, or rivaroxaban;

the inhibitor of thrombin is argatroban or melagatran; and

the tissue plasminogen activator is alteplase, reteplase, tenecteplase, or lanoteplase.

17. The molecular construct of claim 9, wherein the second center core is a polypeptide.

18. The molecular construct of claim 17, wherein the polypeptide comprises, (1) a plurality of K residues, wherein the number of the K residues ranges from 2 to 15, and each K residue and its next K residue are separated by a filler sequence comprising G and S residues; or (2) the sequence of (X_{aa}-K)_n, wherein X_{aa} is a PEGylated amino acid having 2 to 12 repeats of EG unit, and n is an integral from 2 to 15.

19. The molecular construct of claim 18, wherein the amino acid residue at the N- or C-terminus of the second center core has the azide or the alkyne group; or the amino acid residue at the N- or C-terminus of the second center core is a cysteine residue, and the thiol group of the cysteine residue is linked with the second coupling arm having the azide, the alkyne, the tetrazine, the cyclooctene, or the cyclooctyne group at the free terminus of the second coupling arm.