

WHAT IS CLAIMED IS:

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

the 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 each 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 linking arms are respectively linked to the K residues of the center core; each of the plurality of linking arms has a N-hydroxysuccinimidyl (NHS), an azide, an alkyne, a tetrazine, a cyclooctene, or a cyclooctyne group at its free terminus; and

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

when the free terminus of the linking arm is the azide, the alkyne, or the cyclooctyne group, then the amino acid residue at the N- or C-terminus of the center core is a cysteine residue, and the free terminus of the coupling arm is the tetrazine or the cyclooctene group; or

when the free terminus of the linking arm is the tetrazine group or cyclooctene group, then the amino acid residue at the N- or C-terminus of the center core has the azide or the alkyne group, or the amino acid residue at the N- or C-terminus of the center core is a cysteine residue, and the free terminus of the coupling arm is the azide, the alkyne, or the cyclooctyne group.

2. The linker unit of claim 1, wherein the filler sequence has the sequence of GS, GGS, GSG, or SEQ ID NOs: 1-16.

3. The linker unit of claim 1, wherein each of the linking arms is a PEG chain having 2-20 repeats of EG units, and coupling arm is a PEG chain having 2-12 repeats of EG units, wherein the EG unit of the PEG chain of the linking arm has, optionally, a disulfide linkage at the free terminus thereof.

4. 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), bicyclononyne (BCN), or dibenzocyclooctyne (DICO); or

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

5. The linker unit of claim 1, further comprising

a plurality of first elements that are respectively linked to the plurality of linking arms via forming an amide bound therebetween, or via copper catalyzed azide-alkyne cycloaddition (CuAAC) reaction, strained-promoted azide-alkyne click chemistry (SPAAC) reaction, or inverse electron demand Diels-Alder (IEDDA) reaction; and

optionally, a second element that is linked to the center core via any of the following reactions,

CuAAC reaction occurred between the azide or the 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.

6. The linker unit of claim 5, wherein,

the plurality of first elements are respectively linked to the plurality of linking arms via forming an amide bound therebetween,

the second element is linked to the azide or alkyne group at the N- or C- terminus of the center core via CuAAC reaction, and the linker unit further comprising, optionally, a third element that is linked to the coupling arm via IEDDA reaction; or

the plurality of first elements are respectively linked to the plurality of linking arms via forming an amide bound therebetween, the second element is linked to the azide group at the N- or C- terminus of the center core via SPAAC reaction, and the linker unit further comprising, optionally, a third element that is linked to the coupling arm via iEDDA reaction.

7. The linker unit of claim 1 or 3, further comprising a plurality of connecting arms that are respectively linked to the plurality of linking arms via CuAAC reaction, SPAAC reaction, or iEDDA reaction, wherein each of the plurality of connecting arms has a maleimide or the NHS group at its free terminus.

8. The linker unit of claim 7, further comprising a plurality of first elements that are respectively linked to the plurality of linking arms via thiol-maleimide reaction or forming an amide bound therebetween; and

optionally, a second element that is linked to the center core via any of the following reactions:

CuAAC reaction occurred between the azide or the 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.

9. The linker unit of claim 5 or 8, wherein when the first element is the fingolimod, fingolimod phosphate, interferon- β , or the scFv specific for integrin- α 4 or β -amyloid, the second element is an scFv specific for transferrin receptor.

10. The linker unit of claim 5 or 8, wherein when the first element is the scFv specific for the viral protein or the bacterial protein, the second element is an scFv specific for CD32 or CD16b;

the viral protein is F protein of respiratory syncytia virus (RSV), gp120 protein of human deficiency virus type 1 (HIV-1), hemagglutinin A (HA) protein of influenza A virus, or glycoprotein of cytomegalovirus; and

the bacterial protein is endotoxin of Gram(-) bacteria, surface antigen of *Clostridium difficile*, lipoteichoic acid of *Staphylococcus aureus*, anthrax toxin of *Bacillus anthracis*, or Shiga-like toxin type I or II of *Escherichia coli*.

11. A linker unit comprising,

a center core that 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 each 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; wherein at least one of the N- and C-terminal amino acid residues of the center core is an amino acid having an azide or an alkyne group or is a cysteine residue, wherein when one of the N- and C-terminal amino acid residues is the cysteine residue, the linker unit further comprises, optionally, a coupling arm that is linked to the cysteine residue via the thiol group of the cysteine residue and has the azide, the alkyne, a tetrazine, a cyclooctene, or a cyclooctyne group at the free terminus thereof,

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

optionally, a plurality of connecting arms respectively linked to the plurality of the linking arms via CuAAC reaction, SPAAC reaction, or iEDDA reaction;

a plurality of first elements that are respectively linked to the plurality of linking arms via forming an amide bound therebetween, or via thiol-maleimide reaction, CuAAC reaction, SPAAC reaction, or iEDDA reaction; or respectively linked to the plurality of connecting arms via forming an amide bound therebetween, or via thiol-maleimide reaction, wherein,

each of the first elements is fingolimod, fingolimod phosphate, interferon- β , or a single-chain variable fragment (scFv) specific for integrin- $\alpha 4$, β -amyloid, a viral protein, a bacterial protein; and

when the plurality of linking arms are linked to the plurality of connecting arms or the plurality of first elements via CuAAC reaction or SPAAC reaction, then the amino acid residue at the N- or C-terminus of the center core is a cysteine residue, and the free terminus of the coupling arm is the tetrazine or the cyclooctene group; or

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

optionally, a second element that is linked to the 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 or tetrazine group and the second element.

12. The linker unit of claim 11, wherein the filler sequence has the sequence of GS, GGS, GSG, or SEQ ID NOs: 1-16.

13. The linker unit of claim, wherein each of the linking arms is a PEG chain having 2-20 repeats of EG units, and coupling arm is a PEG chain having 2-12 repeats of EG units, wherein the EG unit of the PEG chain of the linking arm has, optionally, a disulfide linkage at the free terminus thereof.

14. The linker unit of claim 11, 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), bicyclononyne (BCN), or dibenzocyclooctyne (DICO);

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

15. The linker unit of claim 11, wherein

when the first element is the scFv specific for the viral protein or the bacterial protein, the second element is an scFv specific for CD32 or CD16b;

the viral protein is F protein of respiratory syncytia virus (RSV), gp120 protein of human immunodeficiency virus type 1 (HIV-1), hemagglutinin A (HA) protein of influenza A virus, or glycoprotein of cytomegalovirus; and

the bacterial protein is endotoxin of Gram(-) bacteria, surface antigen of *Clostridium difficile*, lipoteichoic acid of *Staphylococcus aureus*, anthrax toxin of *Bacillus anthracis*, or Shiga-like toxin type I or II of *Escherichia coli*.

16. The linker unit of claim 11, wherein,

when the first element is the fingolimod, fingolimod phosphate, interferon- β , or the scFv specific for integrin- $\alpha\alpha$ or β -amyloid, the second element is an scFv specific for transferrin receptor.

17. The linker unit of claim 11, wherein,

when the plurality of first elements that are respectively linked to the plurality of linking arms via forming the amide bound therebetween or via thiol-maleimide reaction, and

the second element is linked to the azide or alkyne group of the N- or C-terminal amino acid residues of the center core via CuAAC reaction;

the linker unit further comprises optionally, a third element that is linked to the coupling arm via iEDDA reaction; or

when the plurality of first elements that are respectively linked to the plurality of linking arms via forming the amide bound therebetween or via thiol-maleimide reaction, and

the second element is linked to the azide group of the N- or C-terminal amino acid residues of the center core via SPAAC reaction.

the linker unit further comprises, optionally, a third element that is linked to the coupling arm via iEDDA reaction.

18. A pharmaceutical for the treatment of a central nervous system (CNS) disease, comprising administering the linker unit of claim 9 or 16.

19. The pharmaceutical of claim 18, wherein,

the CNS disease is multiple sclerosis, and the first element is the fingolimod, fingolimod phosphate, interferon- β , or the scFv specific for integrin- $\alpha 4$; or

the CNS disease is Alzheimer's disease, and the first element is the scFv specific for β -amyloid.

20. A pharmaceutical for the treatment of an infectious disease, comprising administering the linker unit of claim 10 or 15.