

WHAT IS CLAIMED IS:

1. A linker unit comprising,

a core, which comprises, 2-20 lysine (K) residues, one or more spacers, and a first conjugating moiety, wherein,

any two of the K residues are adjacent to each other or are separated by one of the spacers,

each of the spacers comprises, independently, (1) one or more non-K amino acid residues, or (2) a PEGylated amino acid having 2 to 12 repeats of ethylene glycol (EG) unit,

at least one of the spacers is linked to the N-terminus of the first K residue starting from the N-terminus or the C-terminus of the last K residue starting from the N-terminus, and

the first conjugating moiety has either a carboxyl group or an amine group, and a conjugating group selected from the group consisting of, azide, alkyne, tetrazine, cyclooctene and cyclooctyne groups, wherein,

when the spacer is linked to the N-terminus of the first K residue, the first conjugating moiety has the carboxyl group and is bonded to the spacer via forming an amide bond with the alpha-amine group of the spacer; or

when the spacer is linked to the C-terminus of the last K residue, the first conjugating moiety has the amine group and is bonded to the spacer via forming an amide bond with the carboxyl group of the spacer; and

a plurality of linking arms, wherein,

each of the linking arms is a peptide comprising 2-12 non-K amino acid residues; or a polyethylene glycol (PEG) chain having 2-24 repeats of EG units

each of the linking arms has a reactive group at one terminus thereof and a functional group at the other terminus thereof, and is linked to the K residues of the core via forming an amide bond between the reactive group of the linking arm and the amine group of the K residue of the core, and

the functional group is selected from the group consisting of amine, carboxyl, hydroxyl, *tert*-Butyldimethylsilyl (TBDMS), N-hydroxysuccinimidyl (NHS), maleimide, vinyl sulfone, mono-sulfone, methylsulfonyl benzothiazole, iodo, iodoacetamide, azide, alkyne, cyclooctyne, tetrazine, and cyclooctene groups, with the proviso that when the conjugating group is the azide, alkyne, or cyclooctyne group, then the functional group is the tetrazine or cyclooctene group, and when the conjugating group is the tetrazine or the cyclooctene group, then the functional group is the azide, alkyne, or cyclooctyne group.

2. The linker unit of claim 1, wherein each of the spacers comprises one or more glycine (G) and/or serine (S) residues.

3. The linker unit of claim 1, wherein the reactive group is a succinimidyl ester (SE), tetrafluorophenyl (TFP) ester, or carboxyl group.

4. The linker unit of claim 1, wherein,

the core comprises two spacers respectively linked to the N-terminus of the first K residue and the C-terminus of the last K residue; and

the core further comprises a second conjugating moiety, which has either a carboxyl group or an amine group, and a conjugating group selected from the group consisting of, azide, alkyne, tetrazine, cyclooctene and cyclooctyne groups, wherein,

one of the first and second conjugating moieties is bonded to the N-terminus of the spacer linked to the N-terminus of the first K residue, and

the other of the first and second conjugating moieties is bonded to the C-terminus of the spacer linked to the C-terminus of the last K residue.

5. The linker unit of claim 4, wherein,

the functional group is the maleimide, vinyl sulfone, mono-sulfone, iodo or iodoacetamide group;

the conjugating group of one of the first and second conjugating moieties is the azide, alkyne, or cyclooctyne group; and

the conjugating group of the other of the first and second conjugating moieties is the tetrazine or cyclooctene group.

6. The linker unit of claim 1, wherein the peptide of the linking arm comprises 5-10 amino acid residues that are independently selected from the group consisting of, G, S, glutamic acid (E) and arginine (R) residues.

7. The linker unit of claim 1, wherein,

the cyclooctene group is norbornene or trans-cyclooctene (TCO);

the cyclooctyne group is dibenzocyclooctyne (DIBO), difluorinated cyclooctyne (DIFO), bicyclononyne (BCN), or dibenzazacyclooctyne (DIBAC); or

the tetrazine group is 1,2,3,4-tetrazine, 1,2,3,5-tetrazine or 1,2,4,5-tetrazine, or derivatives thereof.

8. The linker unit of claim 1, wherein the core further comprises a plurality of first elements respectively linked to the plurality of linking arms via forming an amide bond or an ester bond therebetween, or via thiol-maleimide reaction, SN2 reaction, copper catalyzed azide-alkyne cycloaddition (CuAAC) reaction, strained-promoted azide-alkyne click chemistry (SPAAC) reaction, or inverse electron demand Diels–Alder (iEDDA) reaction.
9. The linker unit of claim 8, wherein the core further comprises a second element linked to the conjugating group via CuAAC reaction, SPAAC reaction or iEDDA reaction.
10. The linker unit of claim 9, wherein,
each of the first element is a first antibody fragment specific for a first cell surface antigen; and
the second element is a cytotoxic drug or a second antibody fragment specific for a second cell surface antigen.
11. The linker unit of claim 10, wherein,
the first cell surface antigen is selected from the group consisting of, CD5, CD19, CD20, CD22, CD23, CD27, CD30, CD33, CD34, CD37, CD38, CD43, CD72a, CD78, CD79a, CD79b, CD86, CD134, CD137, CD138, and CD319; or
the second cell surface antigen is CD3 or CD16a.
12. The linker unit of claim 9, wherein,
each of the first elements is a peptide hormone, a first growth factor, or a first antibody fragment specific for a tumor-associated antigen; and
the second element is a cytotoxic drug, a toll-like receptor agonist, a chelator complexed with a radioactive nuclide, a cytokine, or a second antibody fragment specific for a second growth factor, a cell surface antigen, a hapten, or the cytokine.
13. The linker unit of claim 12, wherein,
the first growth factor is selected from the group consisting of epidermal growth factor (EGF), mutant EGF, epiregulin, heparin-binding epidermal growth factor (HB-EGF), vascular endothelial growth factor A (VEGF-A), basic fibroblast growth factor (bFGF), and hepatocyte growth factor (HGF);
the second growth factor is selected from the group consisting of, EGF, mutant EGF, VEGF-A, bFGF, and HGF;

the peptide hormone is selected from the group consisting of, secretin, cholecystokinin (CCK), somatostatin, octreotide, and thyroid-stimulating hormone (TSH);

the tumor-associated antigen is selected from the group consisting of, epidermal growth factor receptor (HER1), HER2, HER3, HER4, carbohydrate antigen 19-9 (CA 19-9), CA 125, carcinoembryonic antigen (CEA), mucin 1 (MUC 1), ganglioside GD2, melanoma-associated antigen (MAGE), prostate-specific membrane antigen (PSMA), prostate stem cell antigen (PSCA), mesothelin, mucine-related Tn, Sialyl Tn, Globo H, stage-specific embryonic antigen-4 (SSEA-4), and epithelial cell adhesion molecule (EpCAM); or

the cell surface antigen is selected from the group consisting of CD3, CD16a, CD28, CD134, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death 1 (PD-1), and programmed cell death 1 ligand 1 (PD-L1).

14. The linker unit of claim 5, wherein the core further comprises,

a plurality of first elements that are respectively linked to the plurality of linking arms via forming an amide bond or an ester bond therebetween, or via thiol-maleimide reaction or SN2 reaction; and

a second element and a third element, respectively linked to the conjugating groups of the first and second conjugating moieties, wherein one of the second and third elements is linked to one conjugating group via iEDDA reaction, and the other of the second and third elements is linked to the other conjugating group via SPAAC or CuAAC reaction.

15. A molecular construct, comprising a first linker unit and a second linker unit, independently according to any of claims 1 to 8, wherein the first and the second linker units are coupled by the reaction occurred between the conjugating groups of the first and the second linker units via CuAAC reaction, SPAAC reaction or iEDDA reaction.

16. The molecular construct of claim 15, further comprising a plurality of first elements and a plurality of second elements, respectively linked to the plurality of linking arms of the first linker unit and the second linker unit via forming an amide bond or an ester bond therebetween, or via thiol-maleimide reaction, SN2 reaction, CuAAC reaction, SPAAC reaction, or iEDDA reaction.

17. The molecular construct of claim 16, wherein,

each of the first element is a first antibody fragment specific for a first cell surface antigen; and

each of the second element is a cytotoxic drug or a second antibody fragment specific for a second cell surface antigen.

18. The molecular construct of claim 17, wherein,

the first cell surface antigen is selected from the group consisting of, CD5, CD19, CD20, CD22, CD23, CD27, CD30, CD33, CD34, CD37, CD38, CD43, CD72a, CD78, CD79a, CD79b, CD86, CD134, CD137, CD138, and CD319; or

the second cell surface antigen is CD3 or CD16a.

19. The molecular construct of claim 16, wherein,

each of the first elements is a peptide hormone, a first growth factor, or a first antibody fragment specific for a tumor-associated antigen; and

each of the second elements is a cytotoxic drug, a toll-like receptor agonist, a chelator complexed with a radioactive nuclide, a cytokine, or a second antibody fragment specific for a second growth factor, a cell surface antigen, a hapten, or the cytokine.

20. The molecular construct of claim 19, wherein,

the first growth factor is selected from the group consisting of EGF, mutant EGF, epiregulin, HB-EGF, VEGF-A, bFGF, and HGF;

the second growth factor is selected from the group consisting of, EGF, mutant EGF, VEGF-A, bFGF, and HGF;

the peptide hormone is selected from the group consisting of, secretin, CCK, somatostatin, octreotide, and TSH;

the tumor-associated antigen is selected from the group consisting of, HER1, HER2, HER3, HER4, CA 19-9, CA 125CEA, MUC 1, ganglioside GD2, MAGE, PSMA, PSCA, mesothelin, mucine-related Tn, Sialyl Tn, Globo H, SSEA-4, and EpCAM; or

the cell surface antigen is selected from the group consisting of CD3, CD16a, CD28, CD134, CTLA-4, PD-1, and PD-L1.