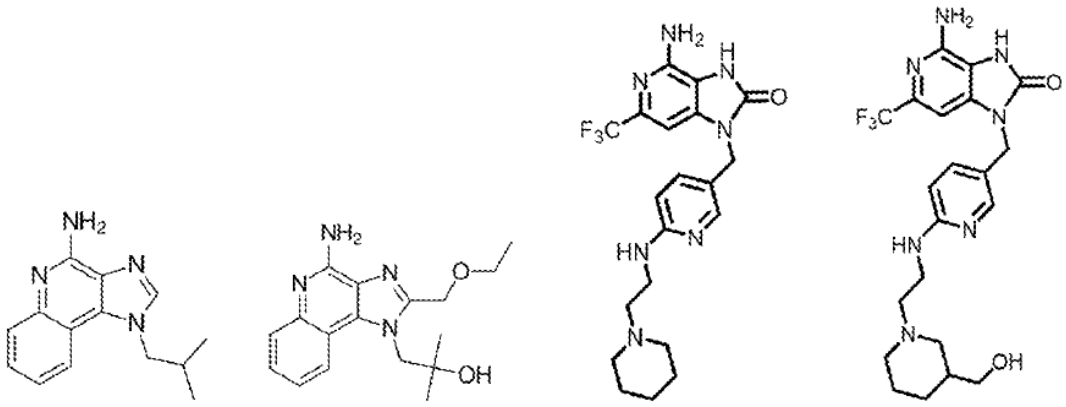
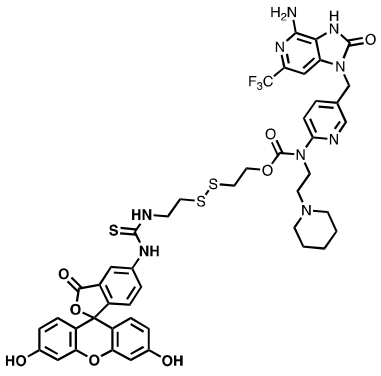
CLAIMS

1. A system to rejuvenate an exhausted classical CAR T cell, comprising at least two components: a first component is a conjugate comprising a targeting ligand covalently linked to a payload drug; and a second component is a targeting ligand binding module linked to a membrane-anchoring module, wherein the targeting ligand binding module of the second component recognizes the targeting ligand in the first component with high affinity to form a complex, the payload drug either blocks the inhibitory signaling of the exhausted classical CAR T, or re-activates said CAR T through an antigen independent pathway, and wherein the membrane-anchoring module mediates internalization of the two component complex into the exhausted CAR T cell.
2. The system according to claim 1, wherein the first component comprises a releasable linker between the targeting ligand and the payload drug.
3. The system according to claim 1, wherein the first component comprises a non-releasable linker between the targeting ligand and the payload drug.
4. The system according to any one of claims 1 to 3, wherein the binding affinity between the targeting ligand and the ligand-binding module is in sub-nanomolar range.
5. A method to rejuvenate an exhausted CAR T cell, comprising:
    a. providing said exhausted CAR T cell a first component comprising a conjugate, wherein the conjugate comprises a targeting ligand covalently linked to a payload of drug through a releasable or unreleasable linker;
    b. providing said exhausted CAR T cell a second component comprising a fusion receptor linked to the exhausted CAR construct, wherein the fusion receptor comprises a targeting ligand binding module and a membrane bound receptor module;
    c. letting the targeting ligand binding module of the second component bind to the targeting ligand in the first component to form a complex,
    d. letting the membrane bound CAR module mediate internalization of the complex into the exhausted CAR T cell;
    e. letting the payload drug either block the inhibitory signaling of the exhausted CAR T, or re-activate said CAR T through an antigen independent pathway.
6. The method according to claim 5, wherein the payload drug executes its function within the endosome of the exhausted CAR T, and the targeting ligand and the payload drug are linked by a nonreleasable linker.

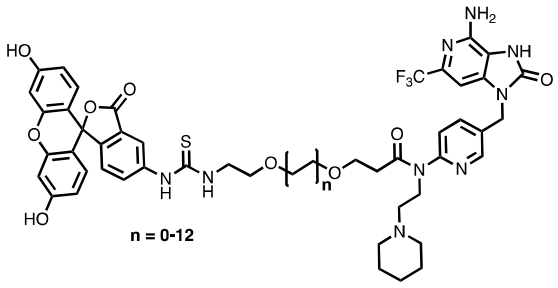
7. The method according to claim 5, wherein the payload drug executes its function as a free drug in the cytosol of the exhausted CAR T, and the targeting ligand and the payload drug are linked by a releasable linker.
8. The system according to any one of claims 1 to 4 or the method of any one of claims 5 to 7, wherein the targeting ligand of the first component is folate, FITC or FK506.
9. The system according to any one of claims 1 to 4 or 8 or the method of any one of claims 5 to 8, wherein the targeting ligand binding module of the second component comprises an anti-FITC antibody fragment or FKBP or folate receptor.
10. The system according to any one of claims 1 to 4 or 8 or 9 or the method of any one of claims 5 to 9, wherein the membrane anchoring module is a folate receptor.
11. The system according to any one of claims 1 to 4 or 8 to 10 or the method of any one of claims 5 to 10, wherein the payload of drug is a Toll Like Receptor 7 (TLR7) agonist or Simulator of interferon genes (STING) agonist.
12. The system according to any one of claims 1 to 4 or 8 to 10 or the method of any one of claims 5 to 10, wherein the payload of drug is an inhibitor to following proteins: SHP1/2, TC-PTP or DGKα.
13. The system or method according to claim 11, wherein the TLR7 agonist is selected from the group consisting of



14. The system according to any one of claims 1 to 4 or the method of any one of claims 5 to 7, wherein the first component is a Fluorescein-TLR7 agonist having the structure of

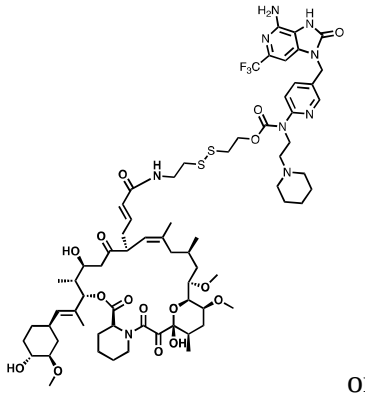


or

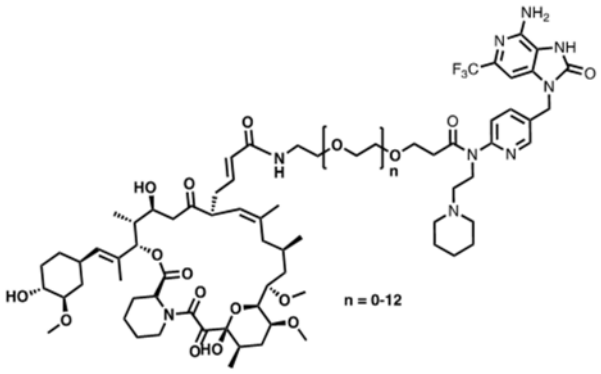


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15. The system according to any one of claims 1 to 4 or the method of any one of claims 5 to 7, wherein the first component is a FK506-TLR7 agonist having the structure of

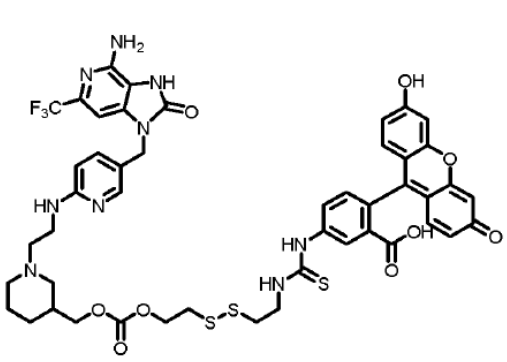


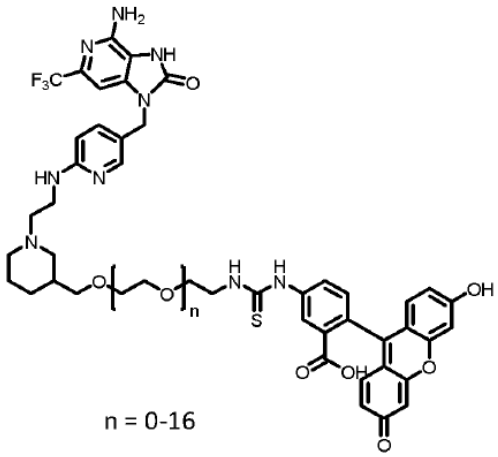
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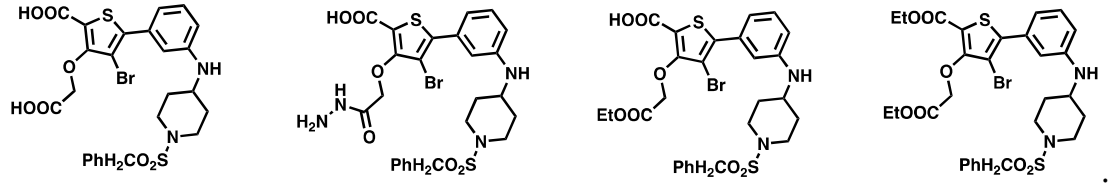
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16. The system according to any one of claims 1 to 4 or the method of any one of claims 5 to 7, wherein the first component is one of the following:

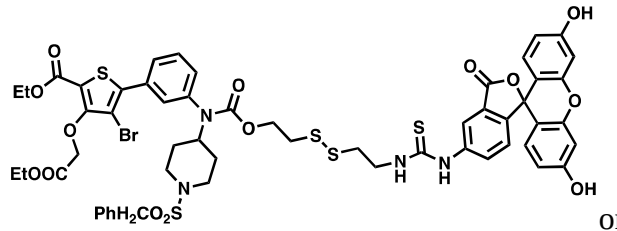




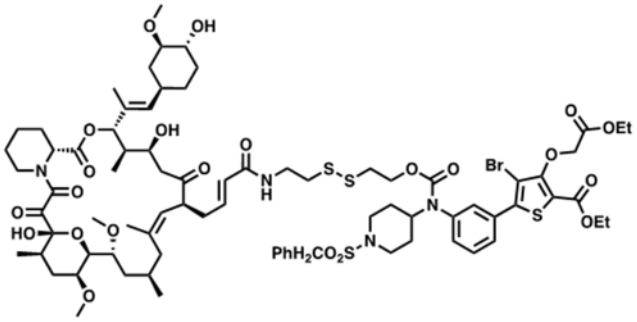
17. The system according to any one of claims 1 to 4 or the method of any one of claims 5 to 7, wherein the first component comprising the payload drug is selected from the group consisting of following TC-PTP phosphatase inhibitors:



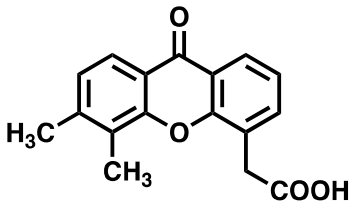
18. The system or method according to claim 17, wherein the phosphatase inhibitor is connected to the fluorescein or FK506 (tacrolimus) to form the following structures:



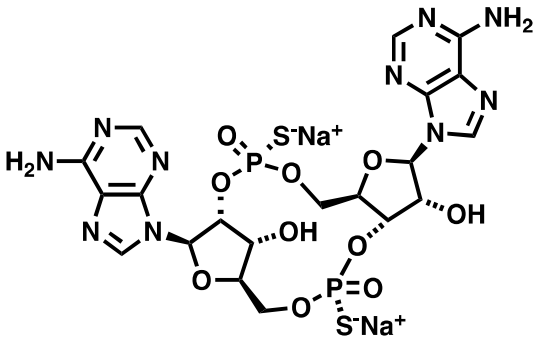
or



19. The system according to any one of claims 1 to 4 or the method of any one of claims 5 to 7, wherein the payload drug in the first component comprises a STING agonist of one of the following structures.

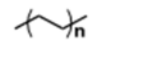


DMXAA

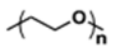


ADU-S100

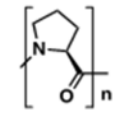
20. The system according to any one of claims 1 to 4 or 8 to 19 the method of any one of claims 5 to 19, wherein the first component comprises a spacer between the targeting ligand and the payload drug selected from the group consisting of the following structures:



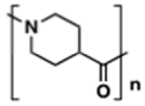
alkyl



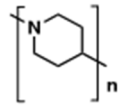
poly ethylene glycol (PEG)



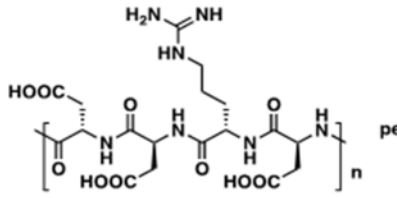
polyproline



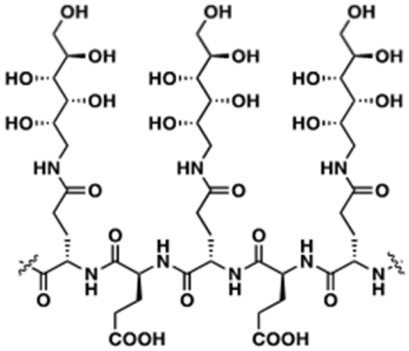
oligo-(4-piperidine carboxylic acid)



oligo piperidine



peptide



saccharo-peptide

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