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 cell, or re-activates the CAR T cell through an antigen independent pathway; and the membrane-anchoring module mediates internalization of the first component into the exhausted classical 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 targeting ligand-binding module is in sub-nanomolar range.

5. A first component for use in rejuvenating an exhausted CAR T cell, wherein:

a. the first component comprises a conjugate, the conjugate comprising a targeting ligand covalently linked to a payload drug through a releasable or nonreleasable linker;

b. the CAR T cell comprises a second component comprising a fusion receptor, the fusion receptor comprising a targeting ligand-binding module and a membrane-

anchoring module;

c. the targeting ligand-binding module of the second component binds to the targeting ligand in the first component to form a complex;

d. the membrane-anchoring module mediates internalization of the first component into the exhausted CAR T cell;

e. the payload drug either blocks the inhibitory signaling of the exhausted CAR T cell, or re-activates the exhausted CAR T cell through an antigen independent pathway.

6. The first component for use according to claim 5, wherein the payload drug executes its function within the endosome of the exhausted CAR T cell, and the targeting ligand and the payload drug are linked by a nonreleasable linker.

7. The first component for use according to claim 5, wherein the payload drug executes its function as a free drug in the cytosol of the exhausted CAR T cell, 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 first component for use according to any one of claims 5 to 7, wherein the targeting ligand of the first component is folate, FITC or FK506.

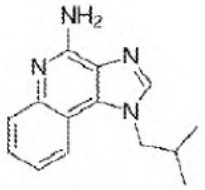
9. The system according to any one of claims 1 to 4 and 8 or the first component for use according to any one of claims 5 to 8, wherein the targeting ligand-binding module of the second component comprises an anti-FITC antibody fragment or FKBP or folate receptor.

10. The system according to any one of claims 1 to 4 or 8 and 9 or the first component for use according to any one of claims 5 to 9, wherein the membrane-anchoring module is a folate receptor.

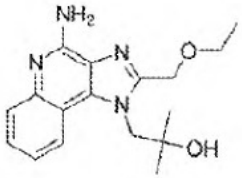
11. The system according to any one of claims 1 to 4 and 8 to 10 or the first component for use according to any one of claims 5 to 10, wherein the payload drug is a Toll Like Receptor 7 (TLR7) agonist or Simulator of interferon genes (STING) agonist.

12. The system according to any one of claims 1 to 4 and 8 to 10 or the first component for use according to any one of claims 5 to 10, wherein the payload drug is an inhibitor to the following proteins: SHP1/2, TC-PTP or DGKα.

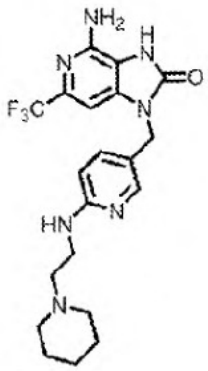
13. The system or the first component for use according to claim 11, wherein the TLR7 agonist is selected from the group consisting of



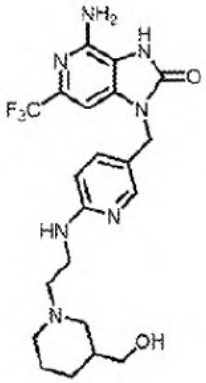
Imiquimod



Resiquimod

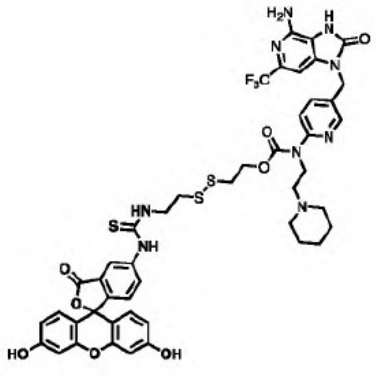


TLR7 agonist

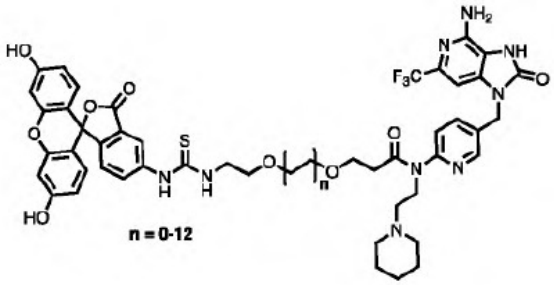


JTLR7.

14. The system according to any one of claims 1 to 4, 8 to 11 and 13 or the first component for use according to any one of claims 5 to 11 and 13, wherein the first component is a Fluorescein-TLR7 agonist having the structure of

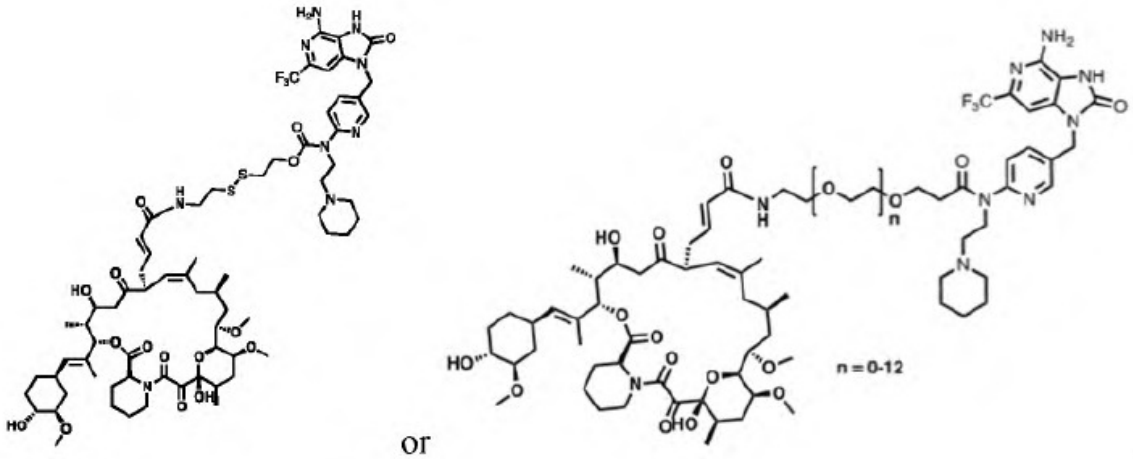


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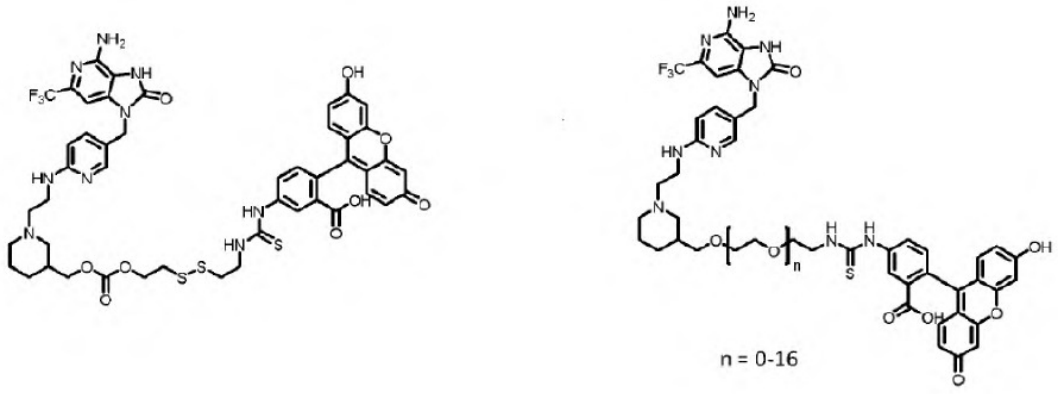
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15. The system according to any one of claims 1 to 4, 8 to 11 and 13 or the first component for use according to any one of claims 5 to 11 and 13, wherein the first component is a FK506-TLR7 agonist having the structure of



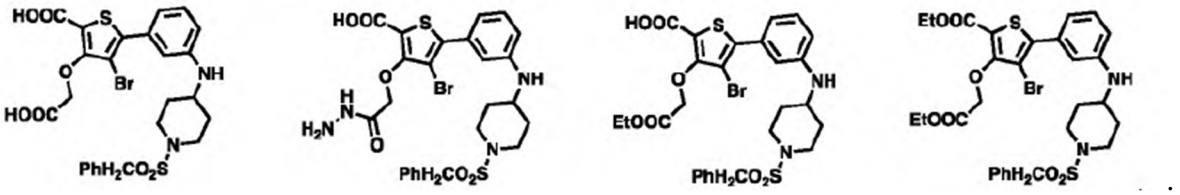
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16. The system according to any one of claims 1 to 4, 8 to 10 and 13 or the first component for use according to any one of claims 5 to 10 and 13, wherein the first component is one of the following:

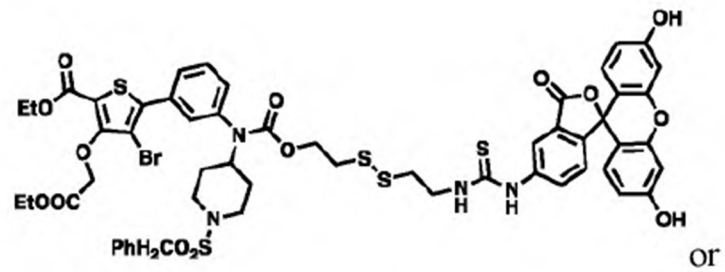


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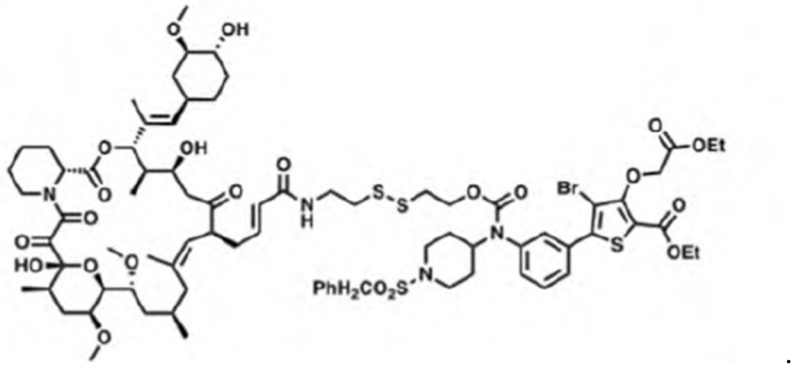
17. The system according to any one of claims 1 to 4, 8 to 10 and 12 or the first component for use according to any one of claims 5 to 10 and 12, wherein the first component comprising the payload drug is selected from the group consisting of following TC-PTP phosphatase inhibitors:



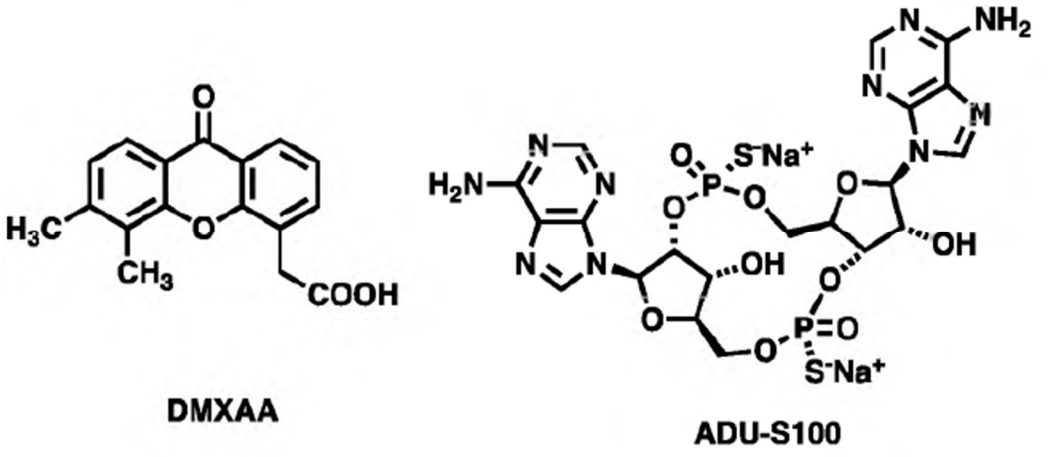
18. The system or the first component for use according to claim 17, wherein the phosphatase inhibitor is connected to fluorescein or FK506 (tacrolimus) to form the following structures:



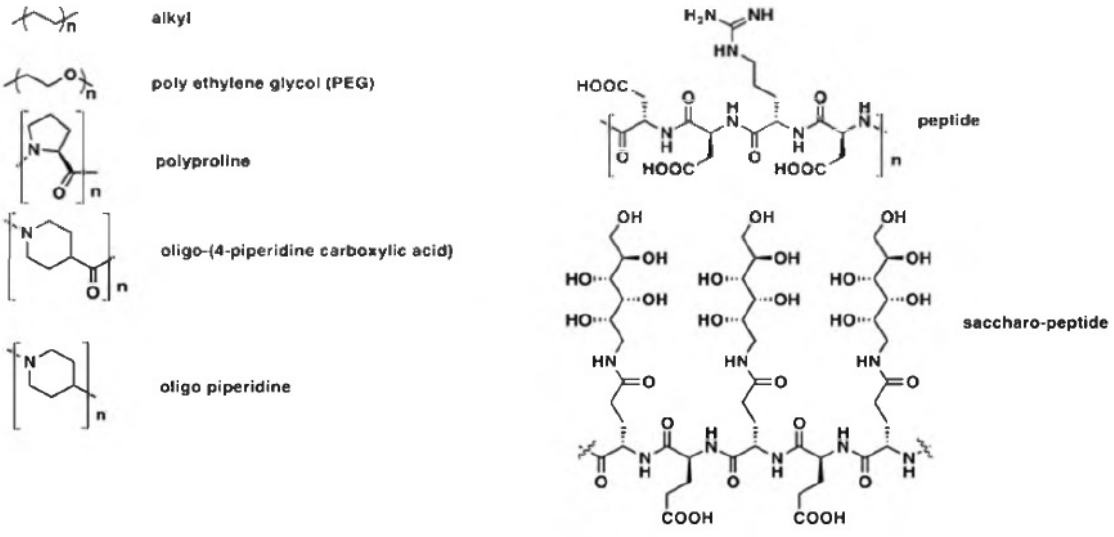
or



19. The system according to any one of claims 1 to 4 and 8 to 11 or the first component for use according to any one of claims 5 to 11, wherein the payload drug in the first component comprises a STING agonist of one of the following structures.



20. The system according to any one of claims 1 to 4 and 8 to 19 or the first component for use according to 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:



21. Use of a first component in the preparation of a medicament to rejuvenate an exhausted CAR T cell, wherein:

a. the first component comprises a conjugate, the conjugate comprising a targeting ligand covalently linked to a payload drug through a releasable or nonreleasable linker;

b. the CAR T cell comprises a second component comprising a fusion receptor, the fusion receptor comprising a targeting ligand-binding module and a membrane-anchoring module;

c. the targeting ligand-binding module of the second component binds to the targeting ligand in the first component to form a complex;

d. the membrane-anchoring module mediates internalization of the first component into the exhausted CAR T cell;

e. the payload drug either blocks the inhibitory signaling of the exhausted CAR T cell, or re-activates the exhausted CAR T cell through an antigen independent pathway.

22. The use of the first component according to claim 21, wherein the payload drug executes its function within the endosome of the exhausted CAR T cell, and the targeting ligand and the payload drug are linked by a nonreleasable linker.

23. The use of the first component according to claim 21, wherein the payload drug executes its function as a free drug in the cytosol of the exhausted CAR T cell, and the targeting ligand and the payload drug are linked by a releasable linker.