CLAIMS

WHAT IS CLAIMED IS:

1. A prodrug comprising:

(i) a targeting moiety that specifically binds to an extracellular antigen;

(ii) a first enzyme-cleavable linker; and

(iii) a first innate immune system activator,

wherein the first linker covalently links the targeting moiety to the innate immune system activator.

2. The prodrug of claim 1, wherein the extracellular antigen is a prostate-specific membrane antigen (PSMA), carbonic anhydrase 9 (CA9), or fibroblast activation protein (FAP).

3. The prodrug of claim 1 or claim 2, wherein the targeting moiety is PSMA-11, PSMA-617, a CA9 small molecule binder, or a FAP inhibitor.

4. The prodrug of claim 3, wherein the FAP inhibitor is FAPI-04.

5. The prodrug of any one of claims 1 to 4, wherein the first enzyme-cleavable linker is a cathepsin-cleavable linker or a legumain-cleavable linker.

6. The prodrug of any one of claims 1 to 4, wherein the first enzyme-cleavable linker is an azide – polyethylene glycol (PEG) – valine – citrulline – p-aminobenzyl (PAB) – p-nitrophenol (PNP) linker or an alanine – alanine – asparagine legumain linker.

7. The prodrug of any one of claims 1 to 6, further comprising a spacer linker between the targeting moiety and the first linker.

8. The prodrug of claim 7, wherein spacer linker is an azide – PEG – maleimide spacer linker or an N-hydroxysuccinimide (NHS) – PEG – Alkyne spacer linker.

9. The prodrug of any one of claims 1 to 8, further comprising an albumin binding motif.

10. The prodrug of any one of claims 1 to 9, wherein the first innate immune system activator comprises a Toll-like Receptor (TLR) agonist or a Stimulator of Interferon Genes (STING) agonist.

11. The prodrug of claim 10, wherein the TLR agonist is a TLR7 agonist, TLR8 agonist, a TLR9 agonist, or a mixed TLR7/8 agonist.

12. The prodrug of claim 11, wherein the TLR7 agonist is gardiquimod, imiquimod, or telratolimod.

13. The prodrug of claim 11, wherein the mixed TLR7/8 agonist is resiquimod.

14. The prodrug of claim 11, wherein the TLR9 agonist is ODN-2395, CMP-001, or MGN1703.

15. The prodrug of claim 10, wherein the STING agonist is a cyclic dinucleotide.

16. The prodrug of any one of claims 1 to 15, further comprising a radiolabel moiety, a second activator of the innate immune system, or a combination thereof.

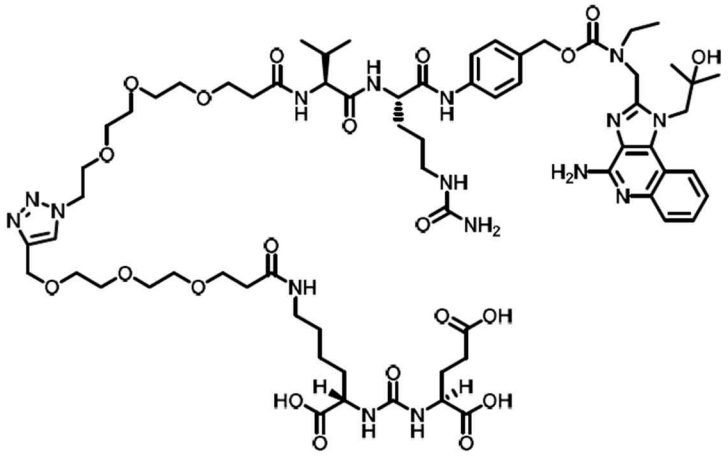
17. The prodrug of claim 16, wherein the radiolabel moiety is linked to the prodrug by a prosthetic group or a chelator.

18. The prodrug of claim 17, wherein the prosthetic group comprises a benzoate moiety for labeling with a radionuclide selected from ^{18}F, ^{123}I, ^{124}I, ^{131}I, ^{75}Br or ^{76}Br linked to the prodrug by a second linker.

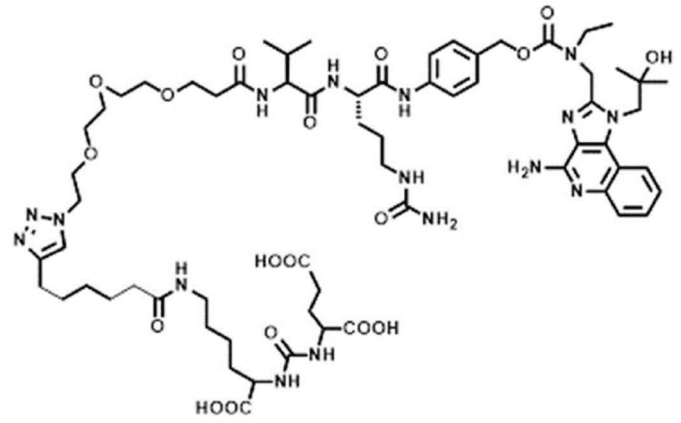
19. The prodrug of claim 17, wherein the chelator comprises a 1,4,7,10-tetraazacyclodecane-1,4,7,10-tetraacetic acid (DOTA) derivative for labeling with a radionuclide for imaging selected from ^{67}Ga, ^{68}Ga, ^{60}Cu, ^{61}Cu, $^{/62}Cu$, ^{64}Cu, ^{89}Zr, ^{177}Lu, and ^{99m}Tc and/or a radionuclide for radiation therapy selected from ^{67}Cu, ^{177}Lu, ^{90}Y, and ^{223}Ra.

20. The prodrug of claim 16, wherein the second innate immune activator comprises a proinflammatory molecule linked to the prodrug by a third linker.

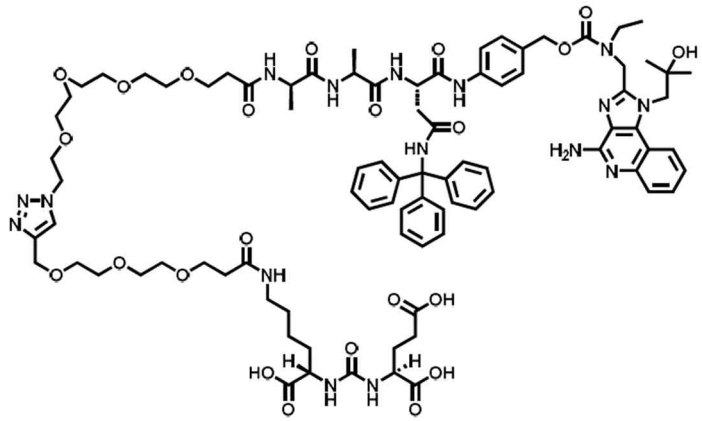
21. A prodrug selected from:



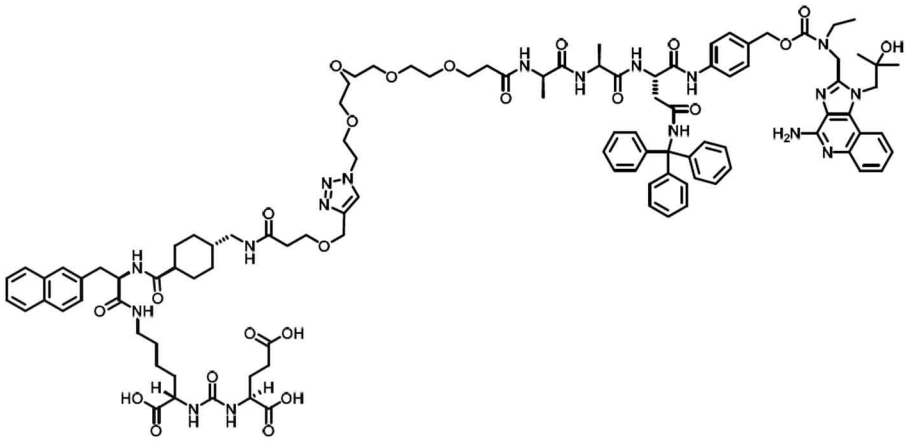
(1) ;



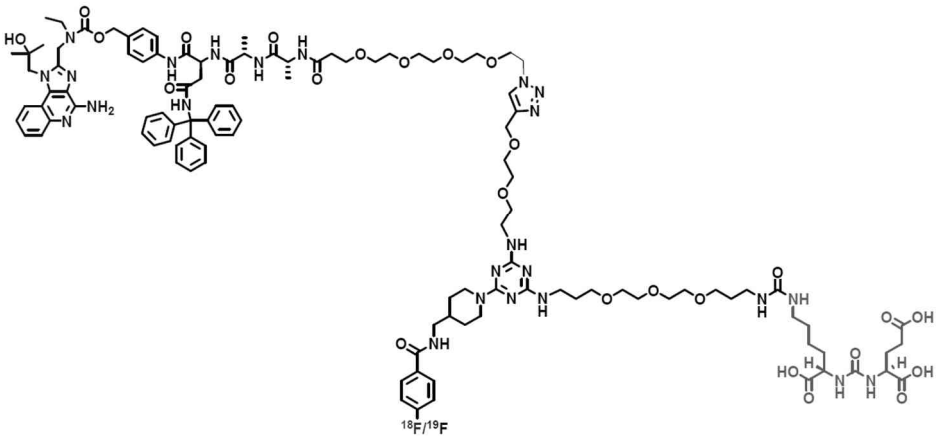
(2) ;



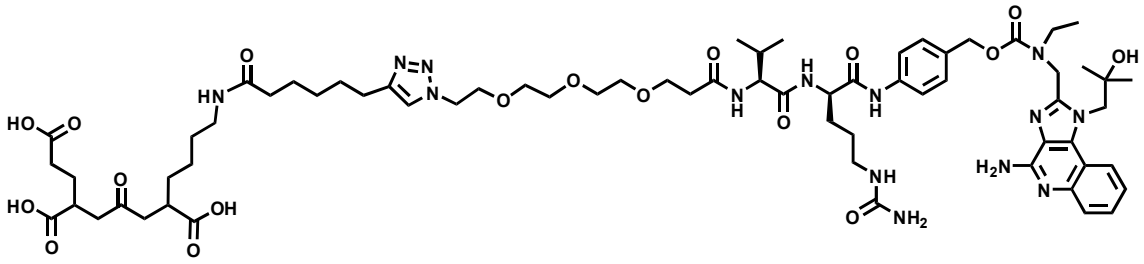
(3);



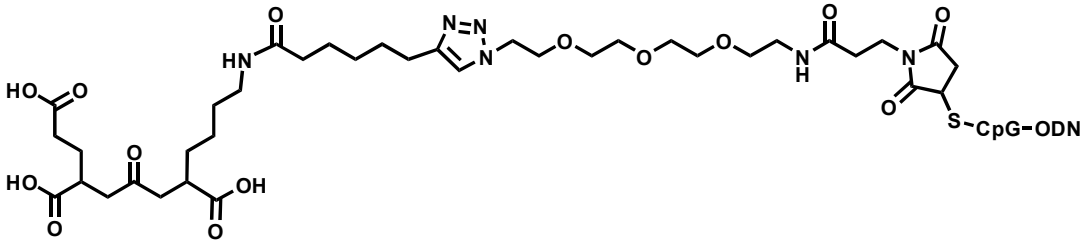
(4);



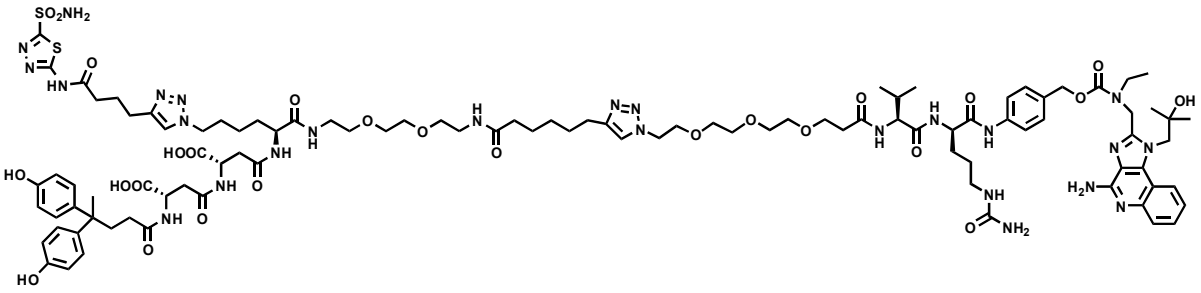
(5);



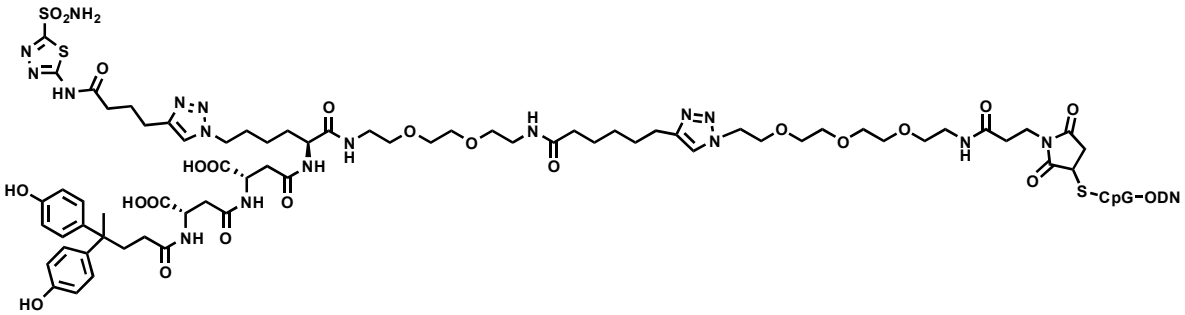
(6);



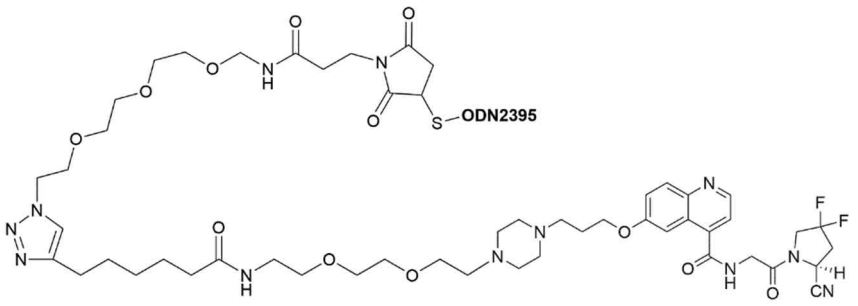
(7);



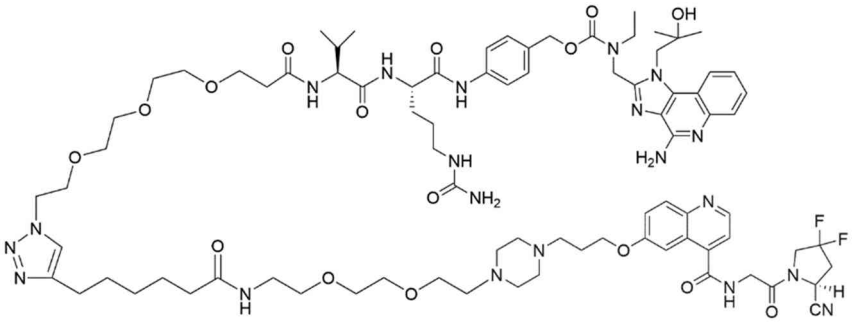
(8);



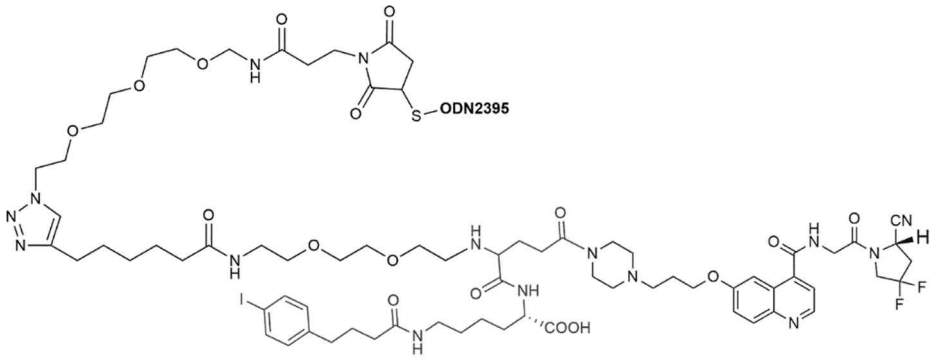
(9)



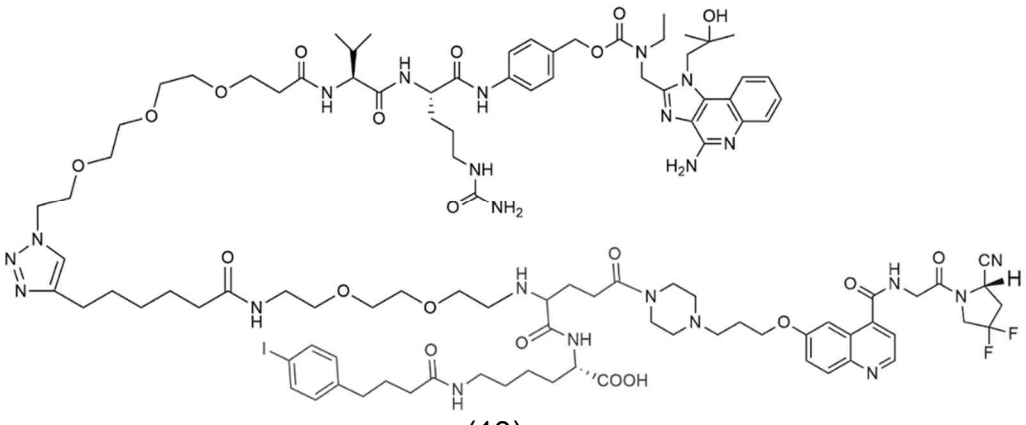
(10);



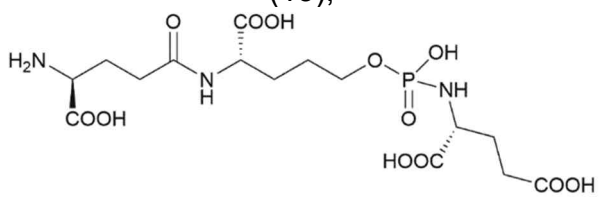
(11);



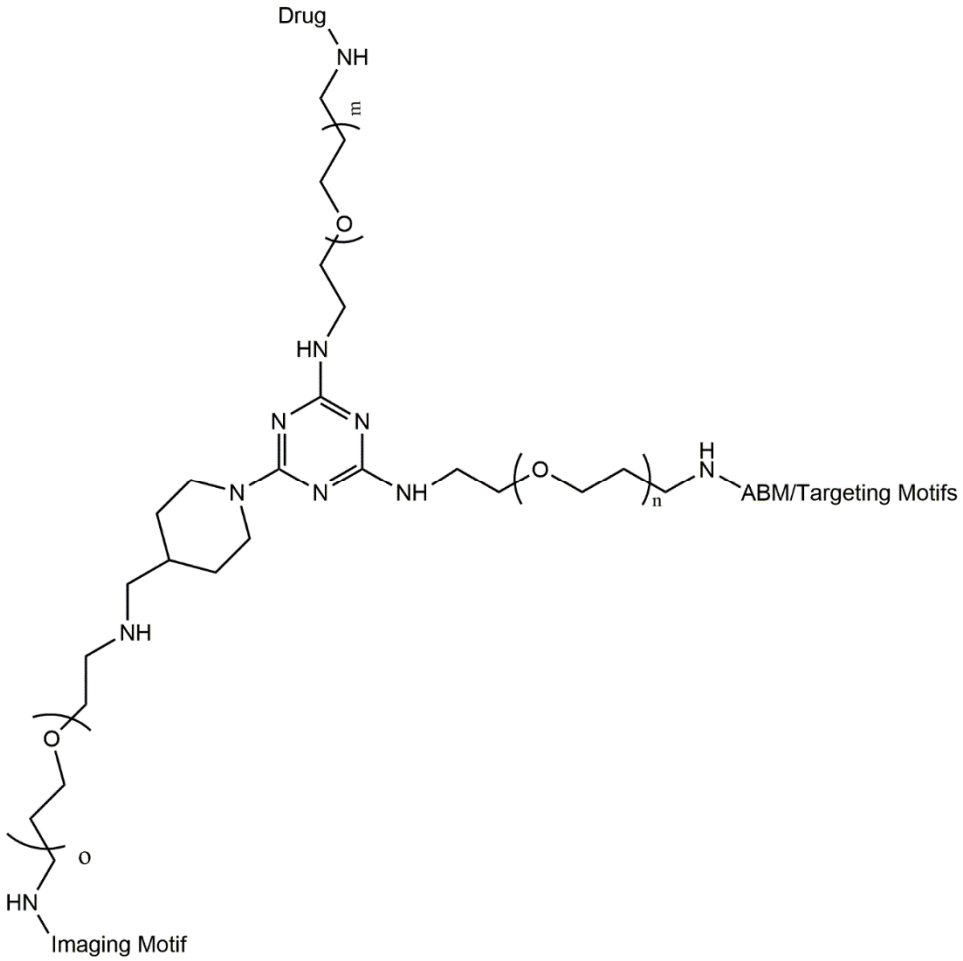
(12);



(13);



(14); and



(15).

22. The use of a prodrug of any one of claims 1 to 21 in the manufacture of a medicament for ~~A method of~~ treating cancer in a subject ~~comprising: administering to the subject an effective amount of the prodrug of claim 1 or 21, thereby treating the cancer~~.

23. The use~~method~~ of claim 22, wherein the cancer is kidney cancer, renal cancer, prostate cancer, lung cancer, colon cancer, rectal cancer, urinary bladder cancer, melanoma, oral cavity cancer, pharynx cancer, pancreatic cancer, uterine cancer, thyroid cancer, skin cancer, head and neck cancer, cervical cancer, ovarian cancer, breast cancer, or hematopoietic cancer.

24. The ~~method~~ use of claim 22 or claim 23, wherein the medicament is to be administered ~~further comprising administering the prodrug~~ prior to, simultaneously with, or following administration of an immunotherapy.

25. The ~~method~~ use of claim 24, wherein the immunotherapy is an interleukin, a cytokine, a chemokine, an immunomodulatory imide drug, CAR-T cells, TCR therapy, a monoclonal antibody, a cancer vaccine, a checkpoint inhibitor, or combinations thereof.

26. The use of a prodrug of any one of claims 16-19 in the manufacture of a medicament for~~A method of~~ imaging cancer in a subject, the imaging comprising:

(i) the medicament is to be administered ~~administering~~ to the subject ~~a prodrug of any one of claim 16-19~~;

(ii) optionally ~~administering to the subject~~ an immunotherapy is to be administered to the subject after, simultaneously with, or before ~~administration of~~ the ~~prodrug~~medicament; and

(iii) ~~performing~~ a functional imaging is to be performed on the subject.

27. The use of a prodrug of claim 16 in the manufacture of a medicament for~~A method of~~ monitoring treatment of cancer in a subject, the monitoring comprising:

(i) the medicament is to be administered ~~administering~~ to the subject ~~a prodrug of claim 16~~;

(ii) optionally ~~administering to the subject~~ an immunotherapy is to be administered to the subject after, simultaneously with, or before ~~administration of the prodrug~~the medicament; and

(iii) ~~performing~~ a functional imaging is to be performed on the subject.

28. The ~~method~~ use of claim 26 or claim 27, wherein the functional imaging is positron emission tomography (PET), single-photon emission computed tomography (SPECT), computed tomography (CT), or any combination thereof.