CLAIMS:

1. A legumain-targeting lipid comprising a lipid component covalently bound to a legumain-binding moiety.

2. The legumain-targeting lipid of claim 1 wherein the legumain-binding moiety comprises an aza-ASN peptide-type legumain inhibitor.

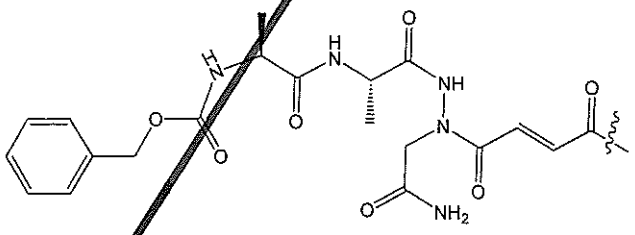
3. The legumain-targeting lipid of claim 2 wherein the aza-Asn-type legumain inhibitor is an aza-Asn Michael acceptor-type legumain inhibitor.

4. The legumain-targeting lipid of any one of claims 1 to 3 wherein the lipid component comprises a 1,2-diacylglycero-phosphoalkanolamine and the legumain-binding moiety is bound to the amine group of the 1,2- diacylglycero-phosphoalkanolamine.

5. The legumain-targeting lipid of claim 4 wherein the 1,2-diacylglycero-phosphoalkanolamine comprises 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine (DOPE).

6. The legumain-targeting lipid of any one of claims 1 to 5 wherein the legumain-binding moiety comprises a group represented by Formula (I):

(I)



which is an aza-Asn Michael acceptor-type legumain inhibitor.

7. A legumain-targeting nanoparticle composition comprising lipid nanoparticles in which the nanoparticles include a legumain-targeting lipid of any one of claims 1 to 6 as a component thereof.

8. The legumain-targeting nanoparticle composition of claim 7 wherein the legumain-targeting lipid is admixed with one or more other micelle or vesicle-forming lipid materials in the nanoparticles.

9. The legumain-targeting nanoparticle composition of claim 7 or claim 8 wherein the nanoparticles comprise (a) the legumain-targeting lipid, (b) a zwitterionic lipid component, (c) an amino-substituted lipid component, (d) a neutral lipid component, and (e) polyethylene glycol-conjugated lipid component; and wherein, optionally, the components (a), (b), (c), (d) and (e) are present in the nanoparticles in a molar ratio of (a):(b):(c):(d):(e) of about 1.1:6.7:6.7:2.2:1.

10. The legumain-targeting nanoparticle composition of claim 9 wherein the zwitterionic lipid component (b) comprises a 1,2-diacylglycero-phosphocholine compound, and/or the amino-substituted lipid component (c) comprises a 1,2-diacylglycero-phosphoalkanolamine compound, and/or the neutral lipid component (d) comprises cholesterol, and/or the polyethylene glycol-conjugated lipid component (e) comprises a polyethylene glycol-conjugated 1,2-diacylglycero-phosphoalkanolamine compound.

11. The composition of claim 10 wherein the 1,2-diacylglycero-phosphocholine compound comprises 1,2-di-(9Z-octadecenoyl)-*sn*-glycero-3-phosphocholine; the 1,2-diacylglycero-phosphoalkanolamine compound comprises 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine; and the polyethylene glycol-conjugated 1,2-diacylglycero-phosphoalkanolamine compound comprises 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol] wherein the polyethylene glycol portion of the compound has an average molecular weight of about 2000 atomic mass units (amu).

12. The legumain-targeting nanoparticle composition of any one of claims 7 to 11 wherein a cancer therapeutic agent is encapsulated within the nanoparticles.

13. The legumain-targeting nanoparticle composition of claim 12 wherein the cancer therapeutic agent comprises at least one compound selected from the group consisting of cisplatin; carboplatin; oxaliplatin; mechlorethamine; cyclophosphamide;

chlorambucil; ifosfamide; 5-fluorouricil; floxuridine; cytosine arabinoside; mercaptopurine; thioguanine; azathioprine; fludarabine; pentostatin; cladribine; etoposide; etoposide phosphate; teniposide; amsacrine; paclitaxel; methotrexate; trimethoprim; pyrimethamine; pemetrexed; vitaxin; anecorvate; angiostatin; endostatin; squalamine; an antiangiogenic tryptophanyl-t-RNA sythetase peptide fragment; bevacizumab; tivozanib; vandetanib; vatalanib; alemtuzumab; cetuximab; gemtuzumab; ibritumomab; pantitumumab; rituximab; tositumomab; trastuzumab; actinomycin; bleomycin; plicamycin; mitomycin; doxorubicin; epirubicin; daunorubicin; valrubicin; idarubicin); ursolic acid; a 2-cyano-3,12-dioxooleana-1,9-dien-28-oic ester, a 2-cyano-3,12-dioxooleana-1,9-dien-28-oic amide; 1-[2-cyano-3-,12-dioxooleana-1,9(11)-dien-28-oyl]imidazole (also known as CDDO-Im); as well as physiologically acceptable salts and prodrugs thereof.

14. The legumain-targeting nanoparticle composition of claim 12 or claim 13 wherein the cancer therapeutic agent comprises a Stat3 inhibitor, an anti-tumor agent, or a compound that is an agonist or antagonist of a receptor or a receptor ligand involved in tumor growth.

15. Use of a composition of any one of claims 1 to 14 for treatment of a legumain-expressing tumor or cancer disease.

16. Use of a composition of any one of claims 1 to 11 for encapsulating a cancer therapeutic agent.

17. A composition of any one of claims 1 to 14 for treating a legumain-expressing tumor or cancer disease.

18. A composition of any one of claims 1 to 11 for encapsulating a cancer therapeutic agent.

19. Use of a composition of any one of claims 1 to 14 for the preparation of a medicament for treating a legumain-expressing tumor or cancer disease.

20. A method of targeting and treating a legumain-expressing cancer disease comprising administering to a subject with a legumain-expressing cancer disease an

effective amount of a legumain-targeting nanoparticle composition of any one of claims 12 to 14.

21. A method of targeting and treating a legumain-expressing tumor comprising administering to a subject with a legumain-expressing tumor an effective amount of a legumain-targeting nanoparticle composition of any one of claims 12 to 14.

CLAIMS:

1. A legumain-targeting lipid comprising a lipid component covalently bound to a legumain-binding moiety wherein the legumain-binding moiety comprises an aza-ASN peptide-type legumain inhibitor.

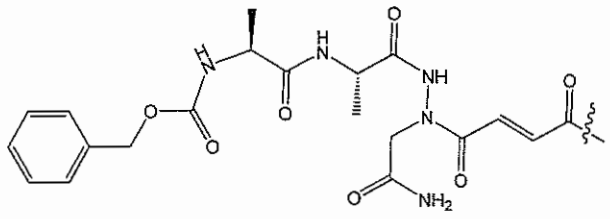
2. The legumain-targeting lipid of claim 1 wherein the aza-Asn-type legumain inhibitor is an aza-Asn Michael acceptor-type legumain inhibitor.

3. The legumain-targeting lipid of claim 1 wherein the lipid component comprises a 1,2-diacylglycero-phosphoalkanolamine and the legumain-binding moiety is bound to the amine group of the 1,2- diacylglycero-phosphoalkanolamine.

4. The legumain-targeting lipid of claim 3 wherein the 1,2-diacylglycero-phosphoalkanolamine comprises 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine (DOPE).

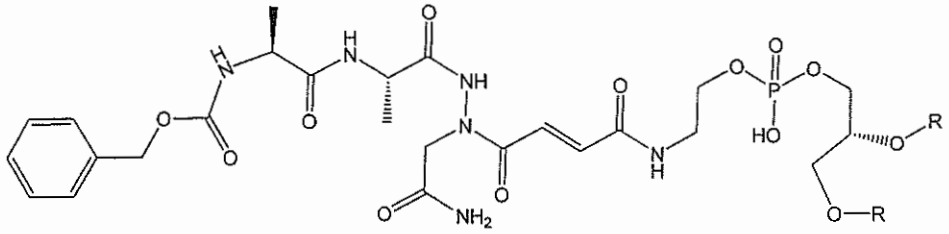
5. The legumain-targeting lipid of claim 1 wherein the legumain-binding moiety comprises a group represented by Formula (I):

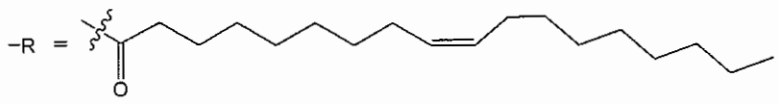
(I)



6. The legumain-targeting lipid of claim 1 wherein the legumain-targeting lipid comprises a compound of Formula (II):

(II)





7. A legumain-targeting nanoparticle composition comprising lipid nanoparticles in which the nanoparticles include a legumain-targeting lipid comprising a lipid component covalently bound to a legumain-binding moiety; wherein the legumain-targeting lipid is admixed with one or more other micelle or vesicle-forming lipid materials in the nanoparticles; and the legumain-binding moiety comprises an aza-Asn-type legumain inhibitor.

8. The legumain-targeting nanoparticle composition of claim 7 wherein the aza-Asn-type legumain inhibitor is an aza-Asn Michael acceptor-type legumain inhibitor.

9. The legumain-targeting nanoparticle composition of claim 7 wherein the lipid component comprises a 1,2-diacylglycero-phosphoalkanolamine and the legumain-binding moiety is bound to the amine group of the 1,2- diacylglycero-phosphoalkanolamine.

10. The legumain-targeting nanoparticle composition of claim 7 wherein the nanoparticles comprise (a) the legumain-targeting lipid, (b) a zwitterionic lipid component, (c) an amino-substituted lipid component, (d) a neutral lipid component, and (e) a polyethylene glycol-conjugated lipid component; and wherein, optionally, the components (a), (b), (c), (d) and (e) are present in the nanoparticles in a molar ratio of (a):(b):(c):(d):(e) of about 1.1:6.7:6.7:2.2:1.

11. The legumain-targeting nanoparticle composition of claim 10 wherein at least one of components (a), (b), (c), (d), and (e) is selected from the group consisting of:

(A) a legumain-targeting lipid (a) comprising an aza-Asn-type legumain inhibitor bound to the amine group of a 1,2-diacylglycero-phosphoalkanolamine,

(B) a zwitterionic lipid component (b) comprising a 1,2-diacylglycero-phosphocholine compound,

(C) a amino-substituted lipid component (c) comprising a 1,2-diacylglycero-phosphoalkanolamine compound,

(D) a neutral lipid component (d) comprising cholesterol, and

(E) a polyethylene glycol-conjugated lipid component (e) comprising a polyethylene glycol-conjugated 1,2-diacylglycero-phosphoalkanolamine compound.

12. The legumain-targeting nanoparticle composition of claim 10 wherein at least one of components (a), (b), (c), (d) and (e) is selected from the group consisting of:

(A) a legumain-targeting lipid (a) comprising an aza-Asn Michael acceptor-type legumain inhibitor bound to the amine group of a 1,2-diacylglycero-phosphoalkanolamine;

(B) a zwitterionic lipid component (b) comprising 1,2-di-(9Z-octadecenoyl)-*sn*-glycero-3-phosphocholine;

(C) a amino-substituted lipid component (c) comprising 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine;

(D) a neutral lipid component (d) comprising cholesterol; and

(E) a polyethylene glycol-conjugated lipid component (e) comprising 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol] wherein the polyethylene glycol portion of the compound has an average molecular weight of about 2000 atomic mass units (amu).

13. A legumain-targeting nanoparticle composition comprising lipid nanoparticles in which the nanoparticles include a legumain-targeting lipid comprising a lipid component covalently bound to a legumain-binding moiety; wherein the legumain-targeting lipid is admixed with one or more other micelle or vesicle-forming lipid materials in the nanoparticles; and the legumain-binding moiety comprises an aza-Asn-type legumain inhibitor; wherein a cancer therapeutic agent is encapsulated within the nanoparticles.

14. The legumain-targeting nanoparticle composition of claim 13 wherein the aza-Asn-type legumain inhibitor is an aza-Asn Michael acceptor-type legumain inhibitor.

15. The legumain-targeting nanoparticle composition of claim 13 wherein the lipid component comprises a 1,2-diacylglycero-phosphoalkanolamine and the legumain-binding moiety is bound to the amine group of the 1,2- diacylglycero-phosphoalkanolamine.

16. The legumain-targeting nanoparticle composition of claim 13 wherein the nanoparticles comprise (a) the legumain-targeting lipid, (b) a zwitterionic lipid component, (c) an amino-substituted lipid component, (d) a neutral lipid component, and (e) a polyethylene glycol-conjugated lipid component; and wherein, optionally, the components (a), (b), (c), (d) and (e) are present in the nanoparticles in a molar ratio of (a):(b):(c):(d):(e) of about 1.1:6.7:6.7:2.2:1.

17. The legumain-targeting nanoparticle composition of claim 16 wherein at least one of components (a), (b), (c), (d), and (e) is selected from the group consisting of:

(A) a legumain-targeting lipid (a) comprising an aza-ASN-type legumain inhibitor bound to the amine group of a 1,2-diacylglycero-phosphoalkanolamine,

(B) a zwitterionic lipid component (b) comprising a 1,2-diacylglycero-phosphocholine compound,

(C) a amino-substituted lipid component (c) comprising a 1,2-diacylglycero-phosphoalkanolamine compound,

(D) a neutral lipid component (d) comprising cholesterol, and

(E) a polyethylene glycol-conjugated lipid component (e) comprising a polyethylene glycol-conjugated 1,2-diacylglycero-phosphoalkanolamine compound.

18. The legumain-targeting nanoparticle composition of claim 16 wherein at least one of components (a), (b), (c), (d) and (e) is selected from the group consisting of:

(A) a legumain-targeting lipid (a) comprising an aza-Asn Michael acceptor-type legumain inhibitor bound to the amine group of a 1,2-diacylglycero-phosphoalkanolamine;

(B) a zwitterionic lipid component (b) comprising 1,2-di-(9Z-octadecenoyl)-*sn*-glycero-3-phosphocholine;

(C) a amino-substituted lipid component (c) comprising 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine;

(D) a neutral lipid component (d) comprising cholesterol; and

(E) a polyethylene glycol-conjugated lipid component (e) comprising 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol] wherein the polyethylene glycol portion of the compound has an average molecular weight of about 2000 atomic mass units (amu).

19. The legumain-targeting nanoparticle composition of claim 13 wherein the cancer therapeutic agent comprises at least one compound selected from the group consisting of cisplatin; carboplatin; oxaliplatin; mechlorethamine; cyclophosphamide; chlorambucil; ifosfamide; 5-fluorouricil; floxuridine; cytosine arabinoside; mercaptopurine; thioguanine; azathioprine; fludarabine; pentostatin; cladribine; etoposide; etoposide phosphate; teniposide; amsacrine; paclitaxel; methotrexate; trimethoprim; pyrimethamine; pemetrexed; vitaxin; anecorvate; angiostatin; endostatin; squalamine; an antiangiogenic

tryptophanyl-t-RNA sythetase peptide fragment; bevacizumab; tivozanib; vandetanib; vatalanib; alemtuzumab; cetuximab; gemtuzumab; ibritumomab; pantitumumab; rituximab; tositumomab; trastuzumab; actinomycin; bleomycin; plicamycin; mitomycin; doxorubicin; epirubicin; daunorubicin; valrubicin; idarubicin); ursolic acid; a 2-cyano-3,12-dioxooleana-1,9-dien-28-oic ester, a 2-cyano-3,12-dioxooleana-1,9-dien-28-oic amide; 1-[2-cyano-3-,12-dioxooleana-1,9(11)-dien-28-oyl]imidazole (also known as CDDO-Im); as well as physiologically acceptable salts and prodrugs thereof.

20. The legumain-targeting nanoparticle composition of claim 13 wherein the cancer therapeutic agent comprises a Stat3 inhibitor, an anti-tumor agent, or a compound that is an agonist or antagonist of a receptor or a receptor ligand involved in tumor growth.

21. Use of a legumain-targeting nanoparticle composition comprising lipid nanoparticles in which the nanoparticles include a legumain-targeting lipid comprising a lipid component covalently bound to a legumain-binding moiety; wherein the legumain-targeting lipid is admixed with one or more other micelle or vesicle-forming lipid materials in the nanoparticles; and the legumain-binding moiety comprises an aza-Asn-type legumain inhibitor; wherein a cancer therapeutic agent is encapsulated within the nanoparticles in the manufacture of a medicament for the treatment of a legumain-expressing disease.

22. Use of a legumain-targeting nanoparticle composition comprising lipid nanoparticles in which the nanoparticles include a legumain-targeting lipid comprising a lipid component covalently bound to a legumain-binding moiety; wherein the legumain-targeting lipid is admixed with one or more other micelle or vesicle-forming lipid materials in the nanoparticles; and the legumain-binding moiety comprises an aza-Asn-type legumain inhibitor; wherein a cancer therapeutic agent is encapsulated within the nanoparticles in the manufacture of a medicament for the treatment of a legumain-expressing tumor.