[0005] The central role of STING in controlling anticancer immune responses was exemplified by observations that spontaneous and radiation-induced adaptive anticancer immunity was reduced in the absence of STING, illustrating the potential of STING-targeting for cancer immunotherapy.

[0006] Bioorthogonal conjugation or click reactions are selective and orthogonal (non-interacting with) functionalities found in biological systems, and have found use in various applications in the fields of chemistry, chemical biology, molecular diagnostics, and medicine, where they can be used to facilitate the selective manipulation of molecules, cells, particles and surfaces, and the tagging and tracking of biomolecules *in vitro* and *in vivo*. These reactions include the Staudinger ligation, the azide-cyclooctyne cycloaddition, and the inverse-electron-demand Diels-Alder reaction.

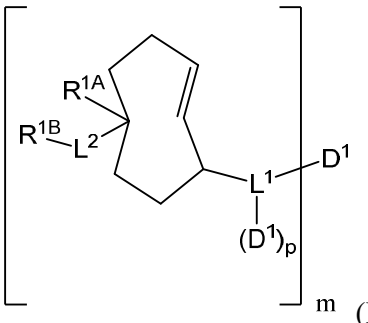
[0007] WO2017/044983 describes anti-tumor effects of a trans-cyclooctene conjugate of doxorubicin through release of doxorubicin at a tumor site by bioorthogonal reaction with a tetrazine-functionalized alginate implanted at the tumor site.

SUMMARY

[0008] The present disclosure provides trans-cyclooctene derivatives for delivering payload molecules in a subject using bioorthogonal chemistry. The disclosure also provides methods of producing the compositions, as well as methods of using the same.

[0008a] In an aspect, there is provided a pharmaceutical combination for use in the treatment of a tumor, the combination comprising:

(a) a compound of formula (II-A'), or a pharmaceutically acceptable salt, or composition thereof;



(II-A')

wherein

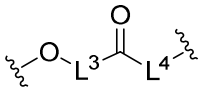
R^{1A} is $C_{1\text{-}4}$alkyl;

R^{1B} is OH, $–N(R^{1c})CHR^{1e}CO_2H$, or $–N(R^{1c})–C_{1\text{-}6}$alkylene$–CO_2H$;

R^{1c} is hydrogen;

R^{1e} is $–C_{1\text{-}4}$alkylene$–CO_2H$;

D^1, at each occurrence, is independently an anticancer agent payload;

L^1 is ;

L^2 is –C(O)–;

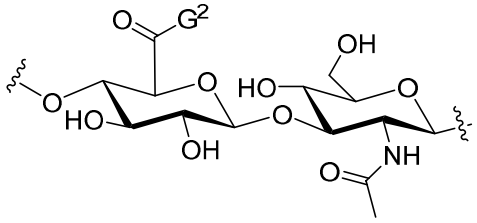
L^3 is a bond;

L^4 is a bond;

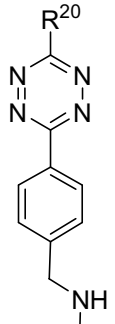
m is 1, 2, or 3; and

p is 0;

b) a therapeutic support composition that is substituted hyaluronic acid comprising units of formula (II):



(II)

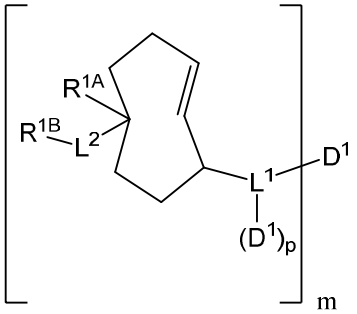


wherein G^2 is tetrazine-containing group ; and R^{20} is $C_{1\text{-}4}$alkyl and

(c) one or more immunomodulatory agents, wherein the immunomodulatory agent(s) are selected from the group consisting of a toll-like receptor (TLR) agonist and a stimulator of interferon genes (STING) agonist.

[0008b] In another aspect, there is providec the use of a pharmaceutical combination in the manufacture of a medicament for the treatment of a tumor, the combination comprising:

(a) a compound of formula (II-A'), or a pharmaceutically acceptable salt, or composition thereof;



(II-A')

wherein

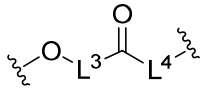
R^{1A} is $C_{1\text{-}4}$alkyl;

R^{1B} is OH, $-N(R^{1c})CHR^{1e}CO_2H$, or $-N(R^{1c})-C_{1\text{-}6}$alkylene$-CO_2H$;

R^{1c} is hydrogen;

$R^{1e}-$ is $C_{1\text{-}4}$alkylene$-CO_2H$;

D^1, at each occurrence, is independently an anticancer agent payload;

L^1 is 

;

L^2 is $-C(O)-$;

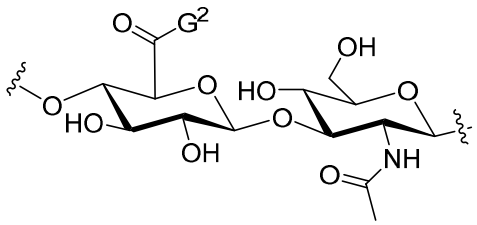
L^3 is a bond;

L^4 is a bond;

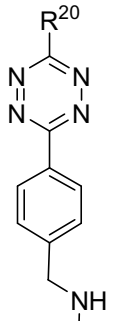
m is 1, 2, or 3; and

p is 0;

b) a therapeutic support composition that is a substituted hyaluronic acid comprising units of formula (II):



(II)



wherein G^2 is tetrazine-containing group ; and R^{20} is $C_{1\text{-}4}$alkyl and

(c) one or more immunomodulatory agents, wherein the immunomodulatory agent(s) are selected from the group consisting of a toll-like receptor (TLR) agonist and a stimulator of interferon genes (STING) agonist.

[0008c] In another aspect, there is provided a kit comprising:

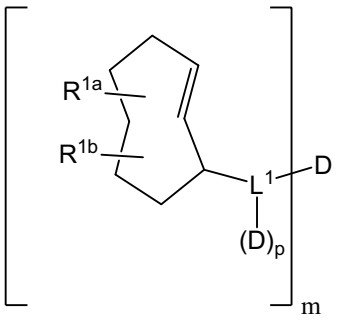
a) the compound of formula (II-A'), as defined above, or a pharmaceutically acceptable salt or composition thereof;

b) one or more immunomodulatory agents, wherein the immunomodulatory agent(s) are selected from the group consisting of a toll-like receptor (TLR) agonist and a stimulator of interferon genes (STING) agonist, or a pharmaceutically acceptable salt or composition thereof;

c) a substituted hyaluronic acid, as defined above; and

d) instructions for use.

[0009] In one example, the disclosure provides compounds of formula (I), or a pharmaceutically acceptable salt thereof,



(I)

wherein

R^{1a}, at each occurrence, is independently selected from the group consisting of hydrogen, C_{1-4}alkyl, and C_{1-4}haloalkyl;

R^{1b}, at each occurrence, is independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}haloalkyl, C(O)OH, $C(O)OC_{1-4}$alkyl, $C(O)N(R^{1c})CHR^{1e}CO_2H$, $C(O)N(R^{1c})CHR^{1e}C(O)OC_{1-4}$alkyl, $C(O)N(R^{1c})–C_{1-6}$alkylene–CO_2H, and $C(O)N(R^{1c})–C_{1-6}$alkylene–$C(O)OC_{1-4}$alkyl;

R^{1c}, at each occurrence, is independently hydrogen or C_{1-4}alkyl;

R^{1e}, at each occurrence, is independently –C_{1-4}alkylene–CO_2H, –C_{1-4}alkylene–$CONH_2$, or –C_{1-4}alkylene–OH;

D, at each occurrence, is independently a payload selected from the group consisting of a toll-like receptor (TLR) agonist and a stimulator of interferon genes (STING) agonist;

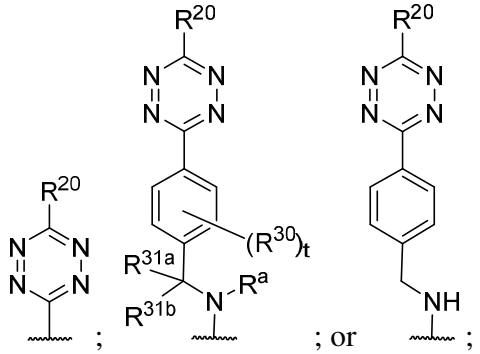
L^1, at each occurrence, is independently a linker;

m, at each occurrence, is independently 1, 2, or 3; and

p, at each occurrence, is independently 0, 1, or 2.

[0010] In another example, the disclosure provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0011] In another example, the disclosure provides a method of treating or preventing a condition or disorder or enhancing or eliciting an immune response, the method comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or composition thereof; and a therapeutic support composition, the therapeutic support composition comprising a biocompatible support and a tetrazine-containing group of formula



wherein

R^{20} is selected from the group consisting of hydrogen, halogen, cyano, nitro, alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, cycloalkenyl, CF_3, CF_2-R', NO_2, OR', SR', C(=O)R', C(=S)R', OC(=O)R'", SC(=O)R'", OC(=S)R'", SC(=S)R'", S(=O)R', $S(=O)_2$R'", $S(=O)_2$NR' R", C(=O)O-R', C(=O)S-R', C(=S)O-R', C(=S)S-R', C(=O)NR'R", C(=S)NR' R", NR'R", NR'C(=O)R", NR'C(=S)R", NR'C(=O)OR", NR'C(=S)OR", NR'C(=O)SR", NR'C(=S)SR", OC(=O)NR'R", SC(=O)NR'R", OC(=S) R'R'", SC(=S)R'R", NR'C(=O)NR"R", and NR'C(=S)NR"R";

R' and R" at each occurrence are independently selected from hydrogen, aryl and alkyl;

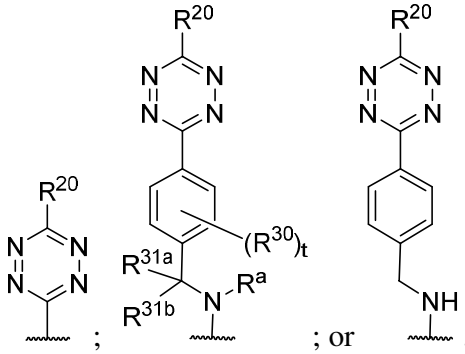
R'" at each occurrence is independently selected from aryl and alkyl;

R^{30} is halogen, cyano, nitro, hydroxy, alkyl, haloalkyl; alkenyl, alkynyl, alkoxy; halalkoxy; heteroalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, or cycloalkenyl;

R^a, R^{31a} and R^{31b} are each independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl; and

t is 0, 1, 2, 3, or 4.

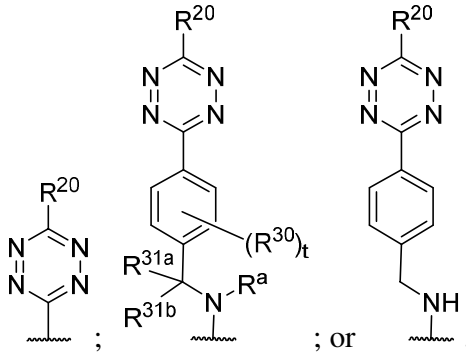
[0012] In another example, the disclosure provides a pharmaceutical combination comprising a compound of formula (I), or a pharmaceutically acceptable salt, or composition thereof; and a therapeutic support composition, the therapeutic support composition comprising a biocompatible support and a tetrazine-containing group of formula



; ; or , as defined herein for use in the treatment or prevention of a disease or disorder, such as cancer, infections, tissue injury, stenosis, ischemia, re-vascularization, myocardial infarction, arrhythmias, vascular occlusion, inflammation, autoimmune disorders, transplant rejection, macular degeneration, rheumatoid arthritis, osteoarthritis, peri-prosthetic infections, and pigmented villonodular synovitis; or for use in enhancing or eliciting an immune response.

[0013] In another example, the disclosure provides the use of a combination comprising a compound of formula (I), or a pharmaceutically acceptable salt, or composition thereof; and a

therapeutic support composition, the therapeutic support composition comprising a biocompatible support and a tetrazine-containing group of formula


; ; or , as defined herein

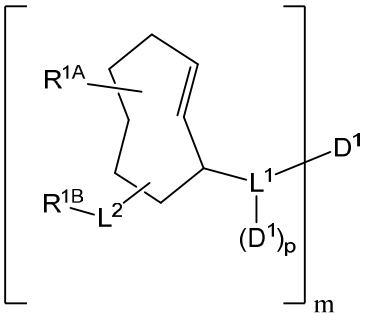
in the manufacture of a medicament for the treatment or prevention of a condition or disorder such as cancer, infections, tissue injury, stenosis, ischemia, re-vascularization, myocardial infarction, arrhythmias, vascular occlusion, inflammation, autoimmune disorders, transplant rejection, macular degeneration, rheumatoid arthritis, osteoarthritis, peri-prosthetic infections, and pigmented villonodular synovitis; or for use in enhancing or eliciting an immune response.

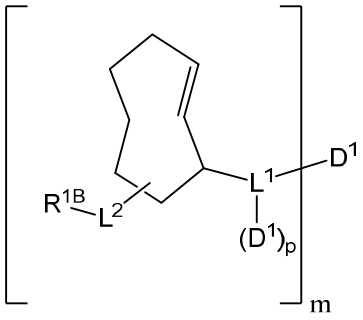
[0014] Examples of the present disclosure include a method for delivering an effective amount of a payload to a target location in a subject, where the method includes administering to the subject a therapeutic support composition, as defined herein.

[0015] Examples of the present disclosure also include a kit comprising a compound of formula (I), a therapeutic support composition as defined herein, and optionally a compound of formula (I-B), as defined herein.

[0016] Another example of the disclosure provides a method of treating cancer or enhancing or eliciting an immune response comprising administering to a subject in need thereof:

a) a therapeutically effective amount of a compound of formula (II-A) or (III-A), or a pharmaceutically acceptable salt thereof,


(II-A)


(III-A)

wherein R^{20} is selected from the group consisting of hydrogen, halogen, cyano, nitro, alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, cycloalkenyl, CF_3, CF_2-R', NO_2, OR', SR', C(=O)R', C(=S)R', OC(=O)R'", SC(=O)R'", OC(=S)R'", SC(=S)R'", S(=O)R', $S(=O)_2$R'", $S(=O)_2$NR' R", C(=O)O-R', C(=O)S-R', C(=S)O-R', C(=S)S-R', C(=O)NR'R", C(=S)NR' R", NR'R", NR'C(=O)R", NR'C(=S)R", NR'C(=O)OR", NR'C(=S)OR", NR'C(=O)SR", NR'C(=S)SR", OC(=O)NR'R", SC(=O)NR'R", OC(=S) R'R'", SC(=S)R'R", NR'C(=O)NR"R", and NR'C(=S)NR"R"; R' and R" at each occurrence are independently selected from hydrogen, aryl and alkyl; and R'" at each occurrence is independently selected from aryl and alkyl; R^{30} is halogen, cyano, nitro, hydroxy, alkyl, haloalkyl; alkenyl, alkynyl, alkoxy; halalkoxy; heteroalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, or cycloalkenyl; R^a, R^{31a} and R^{31b} are each independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl; and t is 0, 1, 2, 3, or 4;

wherein the tetrazine-containing group is linked or directly bonded to the support;
and

c) a therapeutically effective amount one or more immunomodulatory agents, or a pharmaceutically acceptable salt thereof.

[0017] In another example, the disclosure provides a pharmaceutical combination of a compound of formula (II-A) or (III-A), or a pharmaceutically acceptable salt, or composition thereof; a therapeutic support composition; and immunomodulatory agents for use in the treatment or prevention of a disease or disorder, such as cancer, infections, tissue injury, stenosis, ischemia, re-vascularization, myocardial infarction, arrhythmias, vascular occlusion, inflammation, autoimmune disorders, transplant rejection, macular degeneration, rheumatoid arthritis, osteoarthritis, peri-prosthetic infections, and pigmented villonodular synovitis; or for use in enhancing or eliciting an immune response.

[0018] In another example, the disclosure provides the use of a combination of a compound of formula (II-A) or (III-A), or a pharmaceutically acceptable salt, or composition thereof; a therapeutic support composition; and immunomodulatory agents in the manufacture of a medicament for the treatment or prevention of a condition or disorder such as cancer, infections, tissue injury, stenosis, ischemia, re-vascularization, myocardial infarction, arrhythmias, vascular occlusion, inflammation, autoimmune disorders, transplant rejection, macular degeneration,

rheumatoid arthritis, osteoarthritis, peri-prosthetic infections, and pigmented villonodular synovitis; or for use in enhancing or eliciting an immune response.

[0019] Another example of the disclosure provides a kit comprising a) the compound of formula (II-A) or (III-A), or a pharmaceutically acceptable salt or composition thereof; b) immunomodulatory agents, or a pharmaceutically acceptable salt or composition thereof; and c) instructions for use.

[0020] Another example of the disclosure provides a kit comprising a) the therapeutic support composition; b) immunomodulatory agents, or a pharmaceutically acceptable salt or composition thereof; and c) instructions for use.

[0021] Another example of the disclosure provides a pharmaceutical composition comprising a) the compound of formula (II-A) or (III-A), or a pharmaceutically acceptable salt thereof; b) immunomodulatory agents, or a pharmaceutically acceptable salt thereof; and c) a pharmaceutically acceptable carrier.

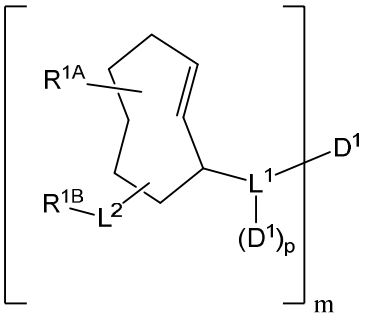
[0022] Another example of the disclosure provides a pharmaceutical composition comprising a) the therapeutic support composition; b) immunomodulatory agents, or a pharmaceutically acceptable salt thereof; and c) a pharmaceutically acceptable carrier.

[0023] Examples of the present disclosure include a method for delivering an effective amount of a payload to a target location in a subject, where the method includes administering to the subject a therapeutic support composition, as defined herein.

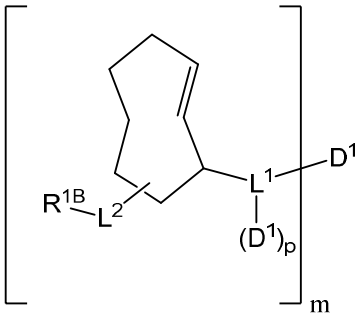
[0024] Another example of the disclosure provides a method of treating cancer comprising:

a) administering to a subject in need thereof, a therapeutically effective amount of a compound of formula (II-A), or a pharmaceutically acceptable salt thereof,

wherein



(II-A)



(III-A)

wherein R^{20} is selected from the group consisting of hydrogen, halogen, cyano, nitro, alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, cycloalkenyl, CF_3, CF_2-R', NO_2, OR', SR', C(=O)R', C(=S)R', OC(=O)R'", SC(=O)R'", OC(=S)R'", SC(=S)R'", S(=O)R', $S(=O)_2$R'", $S(=O)_2$NR' R", C(=O)O-R', C(=O)S-R', C(=S)O-R', C(=S)S-R', C(=O)NR'R", C(=S)NR' R", NR'R", NR'C(=O)R", NR'C(=S)R", NR'C(=O)OR", NR'C(=S)OR", NR'C(=O)SR", NR'C(=S)SR", OC(=O)NR'R", SC(=O)NR'R", OC(=S) R'R'", SC(=S)R'R", NR'C(=O)NR"R", and NR'C(=S)NR"R"; R' and R" at each occurrence are independently selected from hydrogen, aryl and alkyl; and R'" at each occurrence is independently selected from aryl and alkyl; R^{30} is halogen, cyano, nitro, hydroxy, alkyl, haloalkyl; alkenyl, alkynyl, alkoxy; halalkoxy; heteroalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, or cycloalkenyl; R^a, R^{31a} and R^{31b} are each independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl; and t is 0, 1, 2, 3, or 4;

wherein the tetrazine-containing group is linked or directly bonded to the support;

wherein the subject has a second tumor and the administration of a) and the administration of b) inhibits growth of a second tumor in the patient.

[0025] In another example, the disclosure provides a method of enhancing or eliciting an immune response against a second tumor in a subject comprising a) administering a compound of formula (II-A) or (III-A), or a pharmaceutically acceptable salt thereof to the subject; b) locally administering a therapeutic support composition to the subject at a first tumor; wherein the compound of formula (II-A) or (III-A) and the therapeutic support composition are as defined herein, and the administration of a) and the administration of b) enhances or elicits an immune response against the second tumor.

[0026] In another example, the disclosure provides a method of inhibiting tumor metastasis in a subject at risk of tumor metastasis comprising a) administering a compound of formula (II-A) or (III-A), or a pharmaceutically acceptable salt thereof to the subject; and b) locally administering a therapeutic support composition to the subject at a first tumor; wherein the compound of formula (II-A) or (III-A) and the therapeutic support composition are as defined herein.

[0027] In another example, the disclosure provides a pharmaceutical combination comprising a) a compound of formula (II-A) or (III-A), or a pharmaceutically acceptable salt, or composition thereof; and b) a therapeutic support composition; for use in a method of inhibiting growth of a second tumor in a subject, wherein the therapeutic support composition is locally administered at

a first tumor in the subject and the compound of formula (II-A) or (III-A), or a pharmaceutically acceptable salt, or composition thereof is administered to the subject.

[0028] In another example, the disclosure provides a pharmaceutical combination comprising a) a compound of formula (II-A) or (III-A), or a pharmaceutically acceptable salt, or composition thereof; and b) a therapeutic support composition; for use in a method of enhancing or eliciting an immune response against a second tumor in a subject, wherein the therapeutic support composition is locally administered at a first tumor in the subject and the compound of formula (II-A) or (III-A), or a pharmaceutically acceptable salt, or composition thereof is administered to the subject.

[0029] In another example, the disclosure provides a pharmaceutical combination comprising a) a compound of formula (II-A) or (III-A), or a pharmaceutically acceptable salt, or composition thereof; and b) a therapeutic support composition; for use in a method of inhibiting tumor metastasis in a subject at risk of tumor metastasis, wherein the therapeutic support composition is locally administered at a first tumor in the subject and the compound of formula (II-A) or (III-A), or a pharmaceutically acceptable salt, or composition thereof is administered to the subject.

[0030] In another example, the disclosure provides the use of a combination comprising a) a compound of formula (II-A) or (III-A), or a pharmaceutically acceptable salt, or composition thereof; and b) a therapeutic support composition; in the manufacture of a medicament for inhibiting growth of a second tumor, wherein the therapeutic support composition is locally administered at a first tumor in the subject and the compound of formula (II-A) or (III-A), or a pharmaceutically acceptable salt, or composition thereof is administered to the subject.

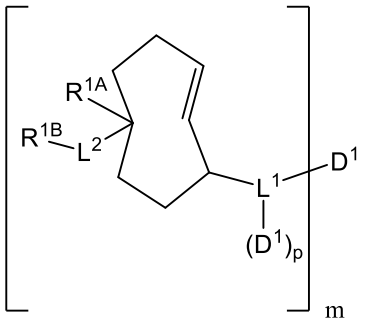
[0031] In another example, the disclosure provides use of a combination comprising a) a compound of formula (II-A) or (III-A), or a pharmaceutically acceptable salt, or composition thereof; and b) a therapeutic support composition; in the manufacture of a medicament for enhancing or eliciting an immune response against a second tumor, wherein the therapeutic support composition is locally administered at a first tumor in the subject and the compound of formula (I-A), or a pharmaceutically acceptable salt, or composition thereof is administered to the subject.

[0032] In another example, the disclosure provides use of a combination comprising a) a compound of formula (II-A) or (III-A), or a pharmaceutically acceptable salt, or composition thereof; and b) a therapeutic support composition; in the manufacture of a medicament for

CLAIMS

1. A pharmaceutical combination for use in the treatment of a tumor, the combination comprising:

(a) a compound of formula (II-A'), or a pharmaceutically acceptable salt, or composition thereof;



(II-A')

wherein

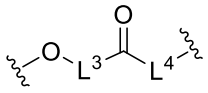
R^{1A} is $C_{1\text{-}4}$alkyl;

R^{1B} is OH, $–N(R^{1c})CHR^{1e}CO_2H$, or $–N(R^{1c})–C_{1\text{-}6}$alkylene$–CO_2H$;

R^{1c} is hydrogen;

R^{1e} is $–C_{1\text{-}4}$alkylene$–CO_2H$;

D^1, at each occurrence, is independently an anticancer agent payload;

L^1 is 

;

L^2 is –C(O)–;

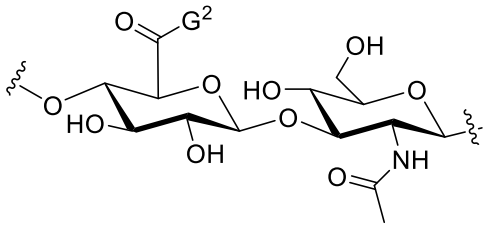
L^3 is a bond;

L^4 is a bond;

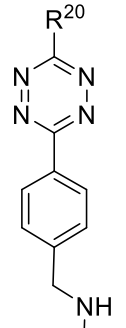
m is 1, 2, or 3; and

p is 0;

b) a therapeutic support composition that is substituted hyaluronic acid comprising units of formula (II):



(II)



wherein G^2 is tetrazine-containing group ; and R^{20} is $C_{1\text{-}4}$alkyl and

(c) one or more immunomodulatory agents, wherein the immunomodulatory agent(s) are selected from the group consisting of a toll-like receptor (TLR) agonist and a stimulator of interferon genes (STING) agonist.

2. The pharmaceutical combination of claim 1, wherein the tumor is of a cancer selected from the group consisting of melanoma, renal cancer, prostate cancer, ovarian cancer, breast cancer, glioma, lung cancer, soft tissue carcinoma, soft tissue sarcoma, osteosarcoma, rhabdomyosarcoma, colon cancer and pancreatic cancer.

3. The pharmaceutical combination of claim 1 or 2, wherein the immunomodulatory agent is a toll-like receptor (TLR) agonist.

4. The pharmaceutical combination of claim 3, wherein the TLR agonist is a TLR9 agonist.

5. The pharmaceutical combination of claim 1 or 2, wherein the immunomodulatory agent is a stimulator of interferon genes (STING) agonist.

6. The pharmaceutical combination of any of claims 1-5, wherein:

R^{1A} is CH_3; and

R^{1e} is $–CH_2CO_2H$.

7. The pharmaceutical combination of claim 6, wherein R^{1B} is OH.

8. The pharmaceutical combination of claim 6, wherein R^{1B} is $–N(R^{1c})CH_2CO_2H$.

9. The pharmaceutical combination of claim 6, wherein R^{1B} is $–N(R^{1c})CHR^{1e}CO_2H$.

10. The pharmaceutical combination of any of claims 1-9, wherein m is 1.

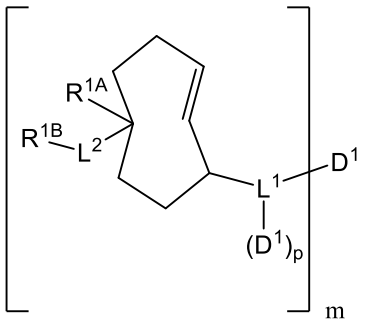
11. The pharmaceutical combination of any of claims 1-10, wherein D^1 is paclitaxel, doxorubicin, docetaxel, SN38, auristatin, or monomethyl auristatin E.

12. The pharmaceutical combination of claim 11, wherein D^1 is doxorubicin.

13. The pharmaceutical combination of any of claims 1-12, wherein the tetrazine-containing group is incorporated into the hyaluronic acid from 10% to 50%, as measured by the % of carboxylic acids being linked or conjugated to the tetrazine-containing group.

14. Use of a pharmaceutical combination in the manufacture of a medicament for the treatment of a tumor, the combination comprising:

(a) a compound of formula (II-A'), or a pharmaceutically acceptable salt, or composition thereof;



(II-A')

wherein

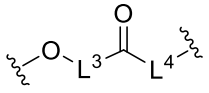
R^{1A} is $C_{1\text{-}4}$alkyl;

R^{1B} is OH, –N(R^{1c})CH$R^{1e}$$CO_2H$, or –N($R^{1c}$)–$C_{1\text{-}6}$alkylene–$CO_2H$;

R^{1c} is hydrogen;

R^{1e}– is $C_{1\text{-}4}$alkylene–CO_2H;

D^1, at each occurrence, is independently an anticancer agent payload;

L^1 is ;

L^2 is –C(O)–;

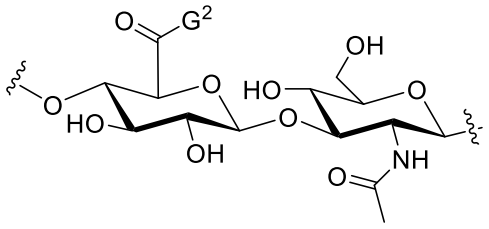
L^3 is a bond;

L^4 is a bond;

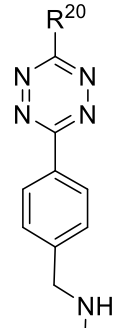
m is 1, 2, or 3; and

p is 0;

b) a therapeutic support composition that is a substituted hyaluronic acid comprising units of formula (II):



(II)



wherein G^2 is tetrazine-containing group ; and R^{20} is $C_{1\text{-}4}$alkyl and

(c) one or more immunomodulatory agents, wherein the immunomodulatory agent(s) are selected from the group consisting of a toll-like receptor (TLR) agonist and a stimulator of interferon genes (STING) agonist.

15. The use of claim 14, wherein the tumor is of a cancer selected from the group consisting of melanoma, renal cancer, prostate cancer, ovarian cancer, breast cancer, glioma, lung cancer, soft tissue carcinoma, soft tissue sarcoma, osteosarcoma, rhabdomyosarcoma, colon cancer and pancreatic cancer.

16. The use of claim 14 or 15, wherein the immunomodulatory agent is a toll-like receptor (TLR) agonist.

17. The use of claim 16, wherein the TLR agonist is a TLR9 agonist.

18. The use of claim 14 or 15, wherein the immunomodulatory agent is a stimulator of interferon genes (STING) agonist.

19. The use of any of claims 14-18, wherein:
R^{1A} is CH_3; and
R^{1e} is $–CH_2CO_2H$.

20. The use of claim 19, wherein R^{1B} is OH.

21. The use of claim 19, wherein R^{1B} is $–N(R^{1c})CH_2CO_2H$.

22. The use of claim 19, wherein R^{1B} is $–N(R^{1c})CHR^{1e}CO_2H$.

23. The use of any of claims 14-22, wherein m is 1.

24. The use of any of claims 14-23, wherein D^1 is paclitaxel, doxorubicin, docetaxel, SN38, auristatin, or monomethyl auristatin E.

25. The use of claim 24, wherein D^1 is doxorubicin.

26. The use of any of claims 14-25, wherein the tetrazine-containing group is incorporated into the hyaluronic acid from 10% to 50%, as measured by the % of carboxylic acids being linked or conjugated to the tetrazine-containing group.

27. A kit comprising:

a) the compound of formula (II-A'), as defined in claim 1, or a pharmaceutically acceptable salt or composition thereof;

b) one or more immunomodulatory agents, wherein the immunomodulatory agent(s) are selected from the group consisting of a toll-like receptor (TLR) agonist and a stimulator of interferon genes (STING) agonist, or a pharmaceutically acceptable salt or composition thereof;

c) a substituted hyaluronic acid, as defined in claim 1; and

d) instructions for use.