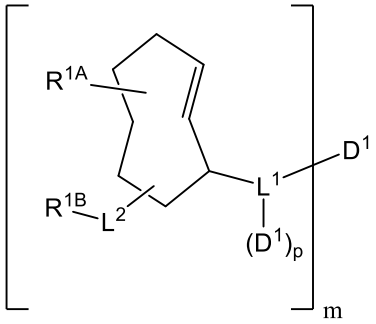
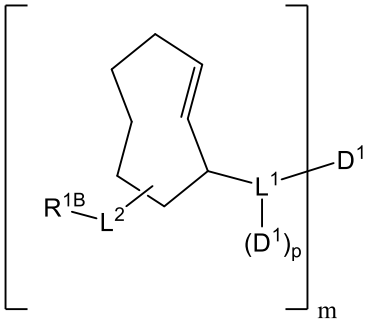
CLAIMS

1. A pharmaceutical combination 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, the combination comprising:

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



(II-A)



(III-A)

wherein

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

R^{1B}, at each occurrence, is independently selected from the group consisting of G^1, OH, $–NR^{1c}–C_{1-4}$alkylene$–G^1$, $–NR^{1c}–C_{1-4}$alkylene$–N(R^{1d})_2$, $–N(R^{1c})CHR^{1e}CO_2H$, $–N(R^{1c})–C_{1-6}$alkylene$–CO_2H$, $–N(R^{1f})–C_{2-4}$alkylene$–(N(C_{1-4}$alkylene$–CO_2H)–C_{2-4}$alkylene$)_n–N(C_{1-4}$alkylene$–CO_2H)_2$, $–N(R^{1c})CHR^{1e}C(O)OC_{1-6}$alkyl, $–N(R^{1c})–C_{1-6}$alkylene$–C(O)OC_{1-6}$alkyl, and $–N(R^{1f})–C_{2-4}$alkylene$–(N(C_{1-4}$alkylene$–C(O)OC_{1-6}$alkyl$)–C_{2-4}$alkylene$)_n–N(C_{1-4}$alkylene$–C(O)OC_{1-6}$alkyl$)_2$;

R^{1c} and R^{1d}, at each occurrence, are 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;

R^{1f}, at each occurrence, is independently hydrogen, C_{1-6}alkyl, or C_{1-4}alkylene$–CO_2H$;

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

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

L^2, at each occurrence, is independently selected from the group consisting of –C(O)– and C_{1-3}alkylene;

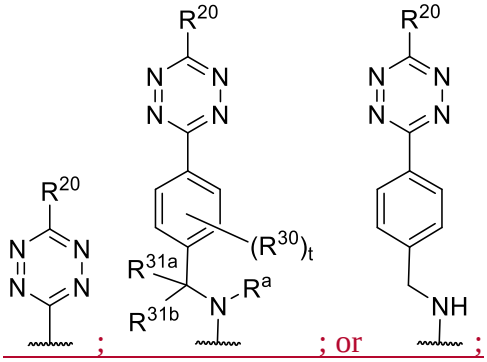
G^1, at each occurrence, is independently an optionally substituted heterocyclyl;

m is 1, 2, or 3

n, at each occurrence, is independently 0, 1, 2, or 3; and

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

b) a therapeutic support composition comprising a support and a tetrazine-containing group of formula



; ; or ;

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) one or more immunomodulatory agents.

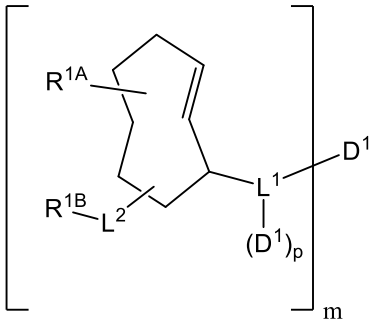
2. The combination of claim 1 for use in enhancing or eliciting an immune response.

3. The combination of claim 1 for use in the treatment or prevention of cancer.

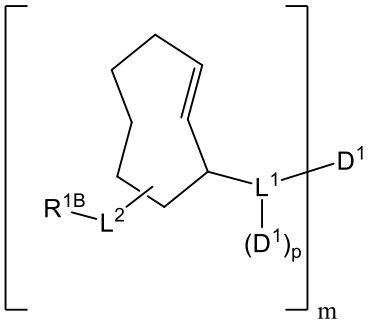
4. The combination of any of claims 1-3, wherein the immunomodulatory agent is a toll-like receptor (TLR) agonist.

5. Use of a pharmaceutical combination in the manufacture of a medicament for 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, the combination comprising:

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



(II-A)



(III-A)

wherein

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

R^{1B}, at each occurrence, is independently selected from the group consisting of G^1, OH, $–NR^{1c}–C_{1-4}$alkylene$–G^1$, $–NR^{1c}–C_{1-4}$alkylene$–N(R^{1d})_2$, $–N(R^{1c})CHR^{1e}CO_2H$, $–N(R^{1c})–C_{1-6}$alkylene–

CO_2H, $–N(R^{1f})–C_{2-4}alkylene–(N(C_{1-4}alkylene–CO_2H)–C_{2-4}alkylene)_n–N(C_{1-4}alkylene–CO_2H)_2$, $–N(R^{1c})CHR^{1e}C(O)OC_{1-6}alkyl$, $–N(R^{1c})–C_{1-6}alkylene–C(O)OC_{1-6}alkyl$, and $–N(R^{1f})–C_{2-4}alkylene–(N(C_{1-4}alkylene–C(O)OC_{1-6}alkyl)–C_{2-4}alkylene)_n–N(C_{1-4}alkylene–C(O)OC_{1-6}alkyl)_2$;

R^{1c} and R^{1d}, at each occurrence, are 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 $–C_{1-4}alkylene–OH$;

R^{1f}, at each occurrence, is independently hydrogen, $C_{1-6}alkyl$, or $C_{1-4}alkylene–CO_2H$;

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

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

L^2, at each occurrence, is independently selected from the group consisting of –C(O)– and $C_{1-3}alkylene$;

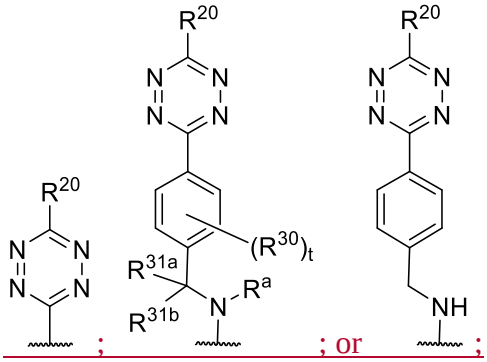
G^1, at each occurrence, is independently an optionally substituted heterocyclyl;

m is 1, 2, or 3

n, at each occurrence, is independently 0, 1, 2, or 3; and

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

b) a therapeutic support composition comprising a support and a tetrazine-containing group of formula



; ; or ;

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) one or more immunomodulatory agents.

6. The use of claim 5 for enhancing or eliciting an immune response.

7. The use of claim 5 for the treatment or prevention of cancer.

8. The use of any of claims 5-7, wherein the immunomodulatory agent is a toll-like receptor (TLR) agonist.

9. A kit comprising:

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

b) one or more immunomodulatory agents, or a pharmaceutically acceptable salt or composition thereof; and

c) instructions for use.

10. A kit comprising:

a) the therapeutic support composition, as defined in claim 1;

b) one or more immunomodulatory agents, or a pharmaceutically acceptable salt or composition thereof; and

c) instructions for use.

11. A pharmaceutical composition comprising:

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

b) one or more immunomodulatory agents, or a pharmaceutically acceptable salt thereof; and

c) a pharmaceutically acceptable carrier.

12. A pharmaceutical composition comprising:

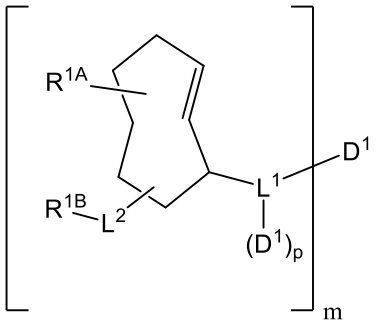
a) the therapeutic support composition, as defined in claim 1;

b) one or more immunomodulatory agents, or a pharmaceutically acceptable salt thereof; and

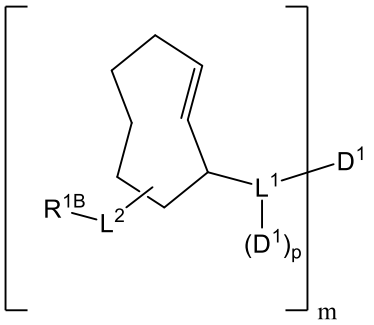
c) a pharmaceutically acceptable carrier.

13. A pharmaceutical combination for use in inhibiting growth of a secondary tumor, or enhancing or eliciting an immune response against a secondary tumor, the combination comprising:

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



(II-A)



(III-A)

wherein

R^{1A} is selected from the group consisting of C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}alkoxy;

R^{1B} is selected from the group consisting of G^1, OH, $–NR^{1c}–C_{1-4}$alkylene$–G^1$, $–NR^{1c}–C_{1-4}$alkylene$–N(R^{1d})_2$, $–N(R^{1c})CHR^{1e}CO_2H$, $–N(R^{1c})–C_{1-6}$alkylene$–CO_2H$, $–N(R^{1f})–C_{2-4}$alkylene$–(N(C_{1-4}$alkylene$–CO_2H)–C_{2-4}$alkylene$)_n–N(C_{1-4}$alkylene$–CO_2H)_2$, $–N(R^{1c})CHR^{1e}C(O)OC_{1-6}$alkyl, $–N(R^{1c})–C_{1-6}$alkylene$–C(O)OC_{1-6}$alkyl, and $–N(R^{1f})–C_{2-4}$alkylene$–(N(C_{1-4}$alkylene$–C(O)OC_{1-6}$alkyl$)–C_{2-4}$alkylene$)_n–N(C_{1-4}$alkylene$–C(O)OC_{1-6}$alkyl$)_2$;

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

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

R^{1f} is hydrogen, C_{1-6}alkyl, or C_{1-4}alkylene$–CO_2H$;

D^1, at each occurrence, is independently a payload;

$–L^1–$ is a linker;

$–L^2–$ is selected from the group consisting of –C(O)– and C_{1-3}alkylene;

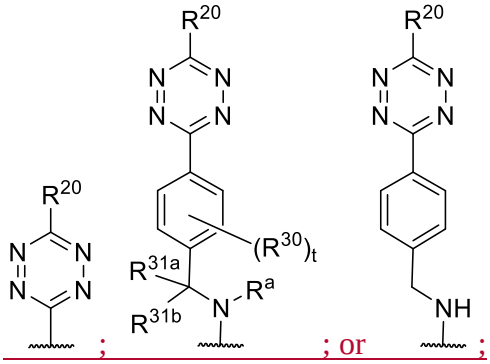
G^1 is an optionally substituted heterocyclyl;

m is 1, 2, or 3

n is 0, 1, 2, or 3; and

p is 0, 1, or 2; and

b) a therapeutic support composition comprising a support and a tetrazine-containing group of formula



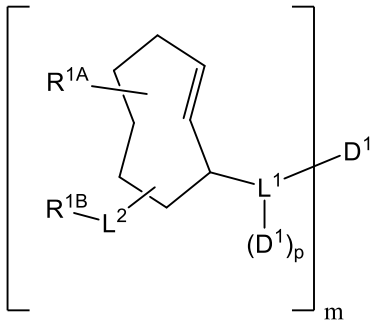
; ; or ;

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;

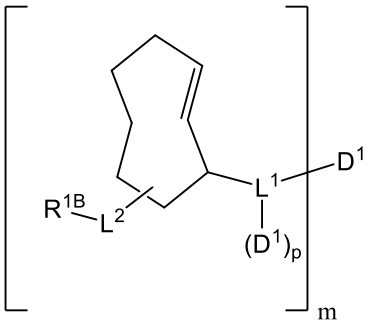
wherein the tetrazine-containing group is linked or directly bonded to the support.

14. Use of a pharmaceutical combination in the manufacture of a medicament for inhibiting growth of a secondary tumor, or enhancing or eliciting an immune response against a secondary tumor, the combination comprising:

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



(II-A)



(III-A)

wherein

R^{1A} is selected from the group consisting of C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}alkoxy;

R^{1B} is selected from the group consisting of G^1, OH, $–NR^{1c}–C_{1-4}$alkylene$–G^1$, $–NR^{1c}–C_{1-4}$alkylene$–N(R^{1d})_2$, $–N(R^{1c})CHR^{1e}CO_2H$, $–N(R^{1c})–C_{1-6}$alkylene$–CO_2H$, $–N(R^{1f})–C_{2-4}$alkylene$–(N(C_{1-4}$alkylene$–CO_2H)–C_{2-4}$alkylene$)_n–N(C_{1-4}$alkylene$–CO_2H)_2$, $–N(R^{1c})CHR^{1e}C(O)OC_{1-6}$alkyl, $–N(R^{1c})–C_{1-6}$alkylene$–C(O)OC_{1-6}$alkyl, and $–N(R^{1f})–C_{2-4}$alkylene$–(N(C_{1-4}$alkylene$–C(O)OC_{1-6}$alkyl$)–C_{2-4}$alkylene$)_n–N(C_{1-4}$alkylene$–C(O)OC_{1-6}$alkyl$)_2$;

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

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

R^{1f} is hydrogen, C_{1-6}alkyl, or C_{1-4}alkylene$–CO_2H$;

D^1, at each occurrence, is independently a payload;

$–L^1–$ is a linker;

$–L^2–$ is selected from the group consisting of $–C(O)–$ and C_{1-3}alkylene;

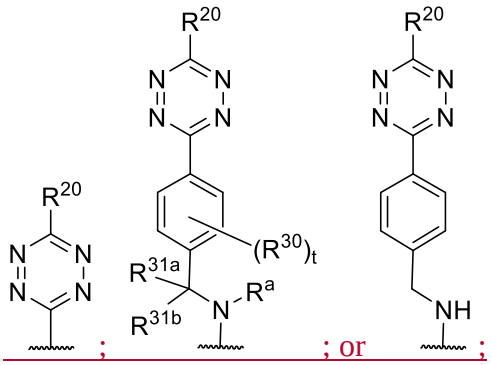
G^1 is an optionally substituted heterocyclyl;

m is 1, 2, or 3

n is 0, 1, 2, or 3; and

p is 0, 1, or 2; and

b) a therapeutic support composition comprising a support and a tetrazine-containing group of formula



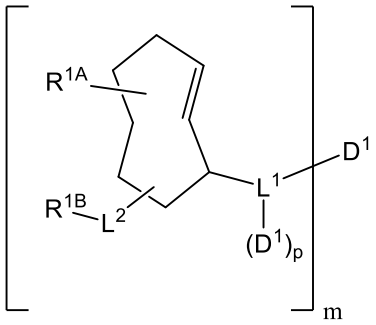
; ; or ;

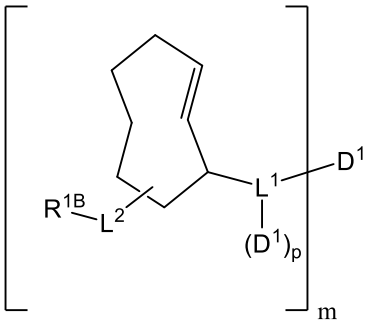
wherein R^{20} is selected from the group consisting of hydrogen, halogen, cyano, nitro, alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, cycloalkenyl, CF_3, CF_2-R', NO_2, OR', SR', C(=O)R', C(=S)R', OC(=O)R'", SC(=O)R'", OC(=S)R'", SC(=S)R'", S(=O)R', $S(=O)_2$R'", $S(=O)_2$NR'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

15. A pharmaceutical combination for use in inhibiting tumor metastasis in a subject at risk of tumor metastasis, the combination comprising

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





(II-A) (III-A)

wherein

R^{1A} is selected from the group consisting of C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}alkoxy;

R^{1B} is selected from the group consisting of G^1, OH, $–NR^{1c}–C_{1-4}$alkylene$–G^1$, $–NR^{1c}–C_{1-4}$alkylene$–N(R^{1d})_2$, $–N(R^{1c})CHR^{1e}CO_2H$, $–N(R^{1c})–C_{1-6}$alkylene$–CO_2H$, $–N(R^{1f})–C_{2-4}$alkylene$–(N(C_{1-4}$alkylene$–CO_2H)–C_{2-4}$alkylene$)_n–N(C_{1-4}$alkylene$–CO_2H)_2$, $–N(R^{1c})CHR^{1e}C(O)OC_{1-6}$alkyl, $–N(R^{1c})–C_{1-6}$alkylene$–C(O)OC_{1-6}$alkyl, and $–N(R^{1f})–C_{2-4}$alkylene$–(N(C_{1-4}$alkylene$–C(O)OC_{1-6}$alkyl$)–C_{2-4}$alkylene$)_n–N(C_{1-4}$alkylene$–C(O)OC_{1-6}$alkyl$)_2$;

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

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

R^{1f} is hydrogen, C_{1-6}alkyl, or C_{1-4}alkylene$–CO_2H$;

D^1, at each occurrence, is independently a payload;

$–L^1–$ is a linker;

$–L^2–$ is selected from the group consisting of $–C(O)–$ and C_{1-3}alkylene;

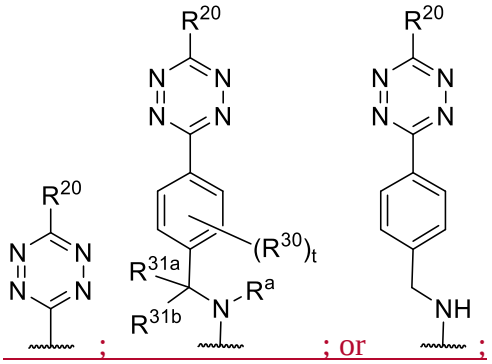
G^1 is an optionally substituted heterocyclyl;

m is 1, 2, or 3

n is 0, 1, 2, or 3; and

p is 0, 1, or 2;and

b) a therapeutic support composition comprising a support and a tetrazine-containing group of formula



; ; or ;

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;

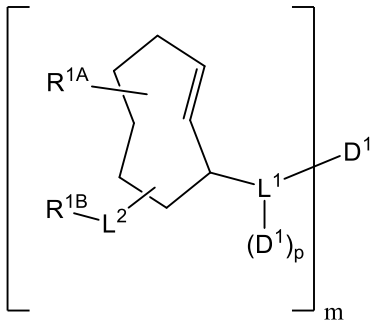
wherein the tetrazine-containing group is linked or directly bonded to the support.

16. The combination of claim 15, further comprising one or more immunomodulatory agents.

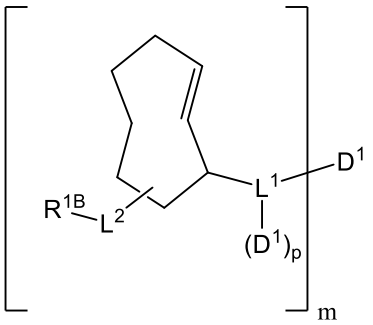
17. The combination of claim 16, wherein the one or more immunomodulatory agents is one or more of an immune checkpoint inhibitor, a toll-like receptor (TLR) agonist, a stimulator of interferon genes (STING) agonist, a cytokine, a cytokine inhibitor, a cytokine receptor agonist, a cytokine receptor antagonist, a chemokine, a chemokine inhibitor, a chemokine receptor agonist, or a chemokine receptor antagonist.

18. Use of a pharmaceutical combination in the manufacture of a medicament for inhibiting tumor metastasis, the combination comprising

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



(II-A)



(III-A)

wherein

R^{1A} is selected from the group consisting of C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}alkoxy;

R^{1B} is selected from the group consisting of G^1, OH, $–NR^{1c}–C_{1-4}$alkylene$–G^1$, $–NR^{1c}–C_{1-4}$alkylene$–N(R^{1d})_2$, $–N(R^{1c})CHR^{1e}CO_2H$, $–N(R^{1c})–C_{1-6}$alkylene$–CO_2H$, $–N(R^{1f})–C_{2-4}$alkylene$–(N(C_{1-4}$alkylene$–CO_2H)–C_{2-4}$alkylene$)_n–N(C_{1-4}$alkylene$–CO_2H)_2$, $–N(R^{1c})CHR^{1e}C(O)OC_{1-6}$alkyl, $–N(R^{1c})–C_{1-6}$alkylene$–C(O)OC_{1-6}$alkyl, and $–N(R^{1f})–C_{2-4}$alkylene$–(N(C_{1-4}$alkylene$–C(O)OC_{1-6}$alkyl$)–C_{2-4}$alkylene$)_n–N(C_{1-4}$alkylene$–C(O)OC_{1-6}$alkyl$)_2$;

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

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

R^{1f} is hydrogen, C_{1-6}alkyl, or C_{1-4}alkylene$–CO_2H$;

D^1, at each occurrence, is independently a payload;

$–L^1–$ is a linker;

$–L^2–$ is selected from the group consisting of $–C(O)–$ and C_{1-3}alkylene;

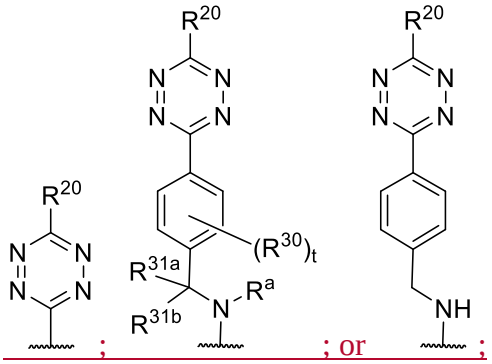
G^1 is an optionally substituted heterocyclyl;

m is 1, 2, or 3

n is 0, 1, 2, or 3; and

p is 0, 1, or 2;and

b) a therapeutic support composition comprising a support and a tetrazine-containing group of formula



; ; or ;

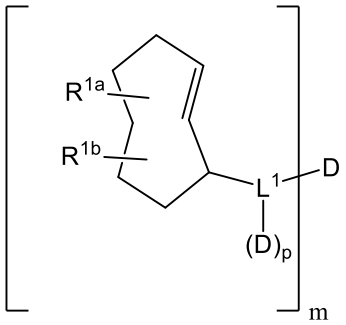
wherein R^{20} is selected from the group consisting of hydrogen, halogen, cyano, nitro, alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, cycloalkenyl, CF_3, CF_2-R', NO_2, OR', SR', C(=O)R', C(=S)R', OC(=O)R'", SC(=O)R'", OC(=S)R'", SC(=S)R'", S(=O)R', $S(=O)_2$R'", $S(=O)_2$NR'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

19. The use of claim 18, wherein the combination further comprises one or more immunomodulatory agents.

20. The use of claim 19, wherein the one or more immunomodulatory agents is one or more of an immune checkpoint inhibitor, a toll-like receptor (TLR) agonist, a stimulator of interferon genes (STING) agonist, a cytokine, a cytokine inhibitor, a cytokine receptor agonist, a cytokine receptor antagonist, a chemokine, a chemokine inhibitor, a chemokine receptor agonist, or a chemokine receptor antagonist.

21. A compound of formula (I), or a pharmaceutically acceptable salt thereof



(I)

wherein

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

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

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;

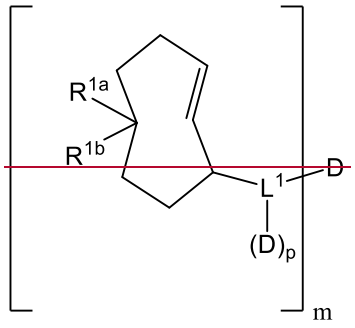
D, at each occurrence, is independently a payload selected from the group consisting of a toll-like receptor (TLR) agonist and a stimulator of interferon genes (STING) agonist~~cyclic dinucleotide~~;

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.

~~2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, of formula (I-A)~~



~~(I-A).~~

~~3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is hydrogen.~~

~~4. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is C_{1-4}alkyl.~~

~~5. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is CH_3.~~

~~6. The compound of any of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein R^{1b} is hydrogen.~~

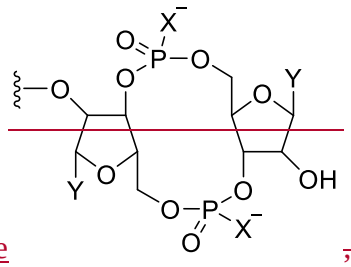
~~7. The compound of any of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein R^{1b} is $C(O)N(R^{1c})$-C_{1-6}alkylene-CO_2H.~~

~~8. The compound of claim 7, or a pharmaceutically acceptable salt thereof, wherein R^{1b} is $C(O)N(R^{1c})CH_2CO_2H$.~~

~~9. The compound of any of claims 1-5 or 7-8, or a pharmaceutically acceptable salt thereof, wherein R^{1c} is hydrogen.~~

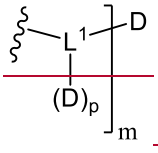
~~10. The compound of any of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein R^{1b} is C(O)OH.~~

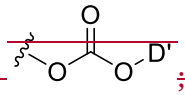
~~11~~22. The compound of ~~any of claims 1-10~~claim 21, or a pharmaceutically acceptable salt thereof, wherein D, at each occurrence, is independently a cyclic



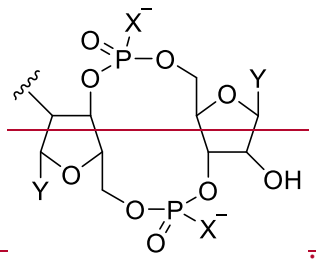
oligodinucleotide ~~, wherein Y is a nucleobase and X is O or S~~.

~~12. The compound of any of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein:~~

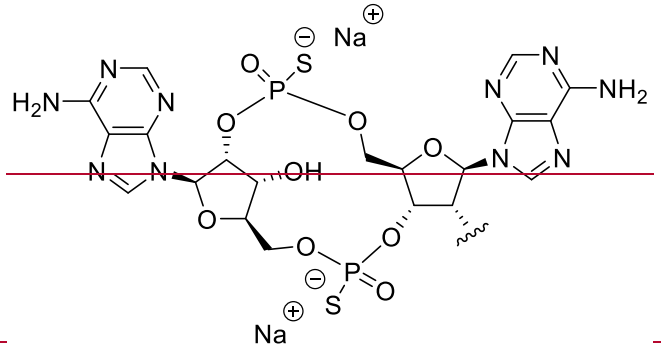


~~is~~  ~~; and~~

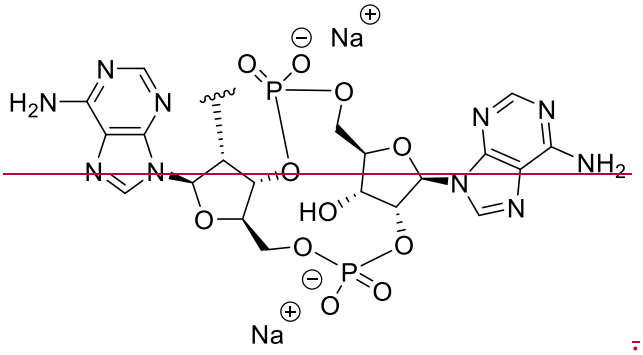
~~D' is a cyclic dinucleotide payload moiety.~~

~~13. The compound of claim 12, or a pharmaceutically acceptable salt thereof, wherein the cyclic dinucleotide payload moiety is~~  ~~.~~

~~14. The compound of claim 12, or a pharmaceutically acceptable salt thereof, wherein the cyclic dinucleotide payload moiety is~~

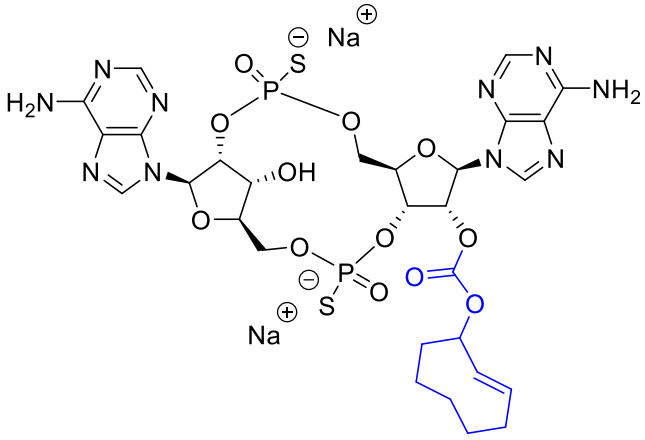


~~or~~



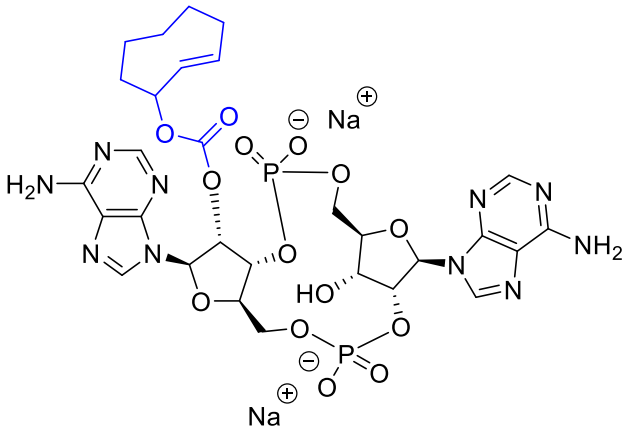
~~.~~

~~15~~23. The compound of claim 21, or a pharmaceutically acceptable salt thereof, selected from the group consisting of



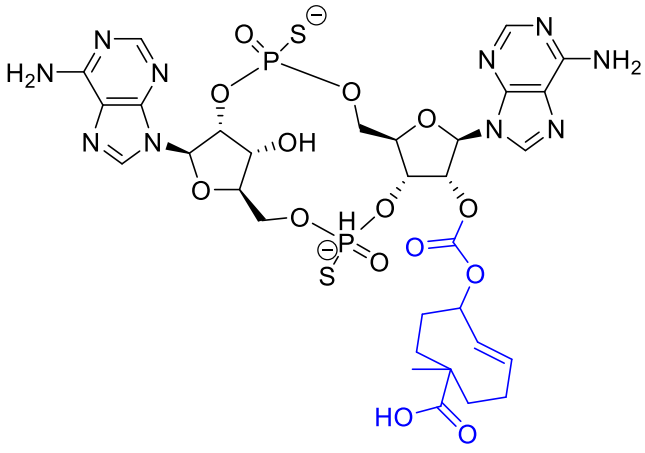
TCO-ADU-S100

,



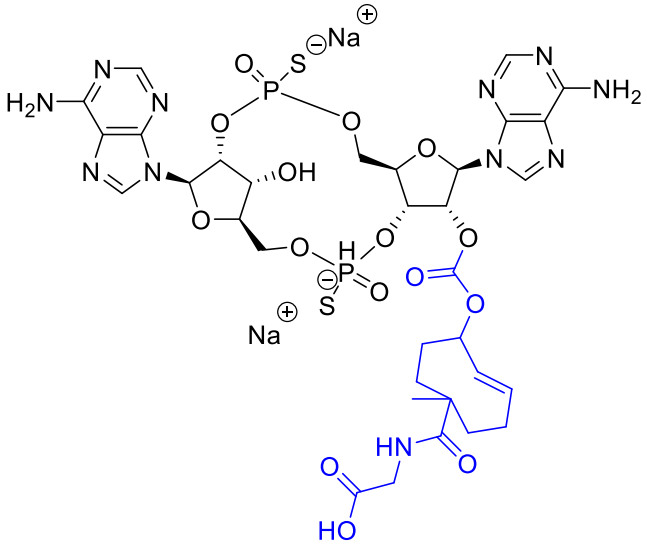
TCO-2’3’-cGAMP

,

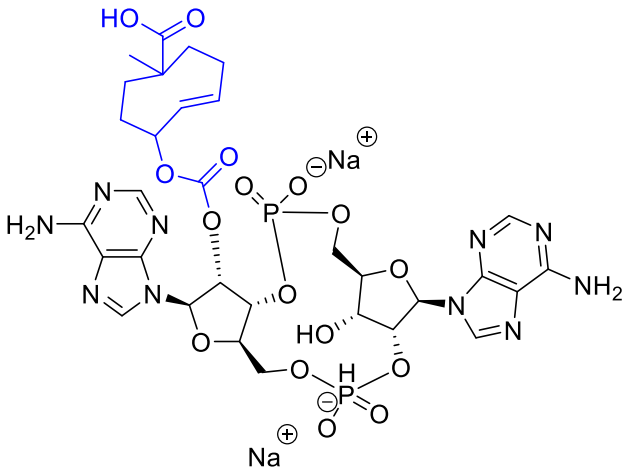


ADU-S100-TCO-Acid

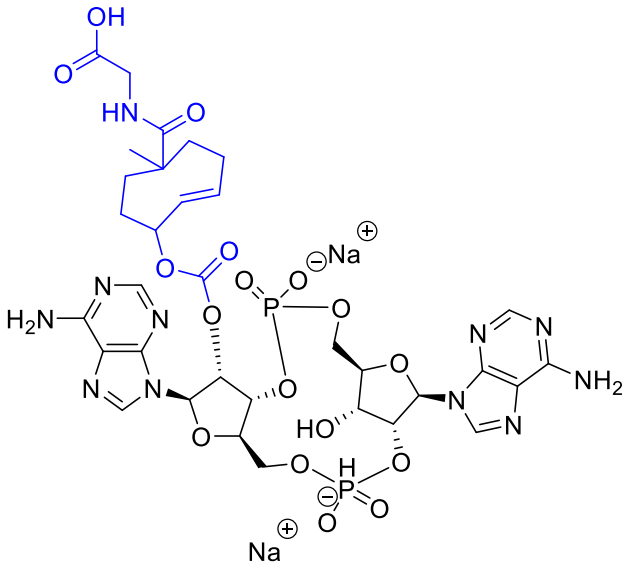
,



ADU-S100-TCO-Glycine ,



2'3'-cGAMP-TCO-Acid , or

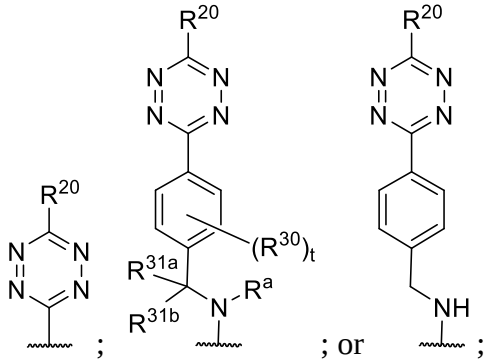


2’3’-cGAMP-TCO-Glycine

.

~~16~~24. A pharmaceutical composition comprising the compound of any of claims ~~1-15~~21-23, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

~~17~~25. A pharmaceutical combination comprising a compound of any of claims ~~1-15~~21-23, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim ~~16~~24, and a therapeutic support composition for use in the treatment of cancer; or for use in enhancing or eliciting an immune response, the therapeutic support composition comprising a biocompatible support and a tetrazine-containing group of formula



; ; or ;

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;

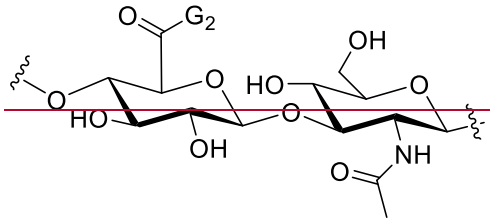
R^{30} is halogen, cyano, nitro, hydroxy, alkyl, haloalkyl; alkenyl, alkynyl, alkoxy; halalkoxy; heteroalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, or cycloalkenyl;

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

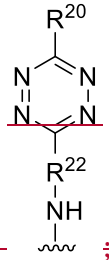
t is 0, 1, 2, 3, or 4.

~~18. The pharmaceutical combination of claim 17, wherein the tetrazine-containing group is linked or directly bonded to a hyaluronic acid biocompatible support.~~

~~19. The pharmaceutical combination of claim 17, wherein the therapeutic support composition comprises substituted hyaluronic acid units of formula (II),~~



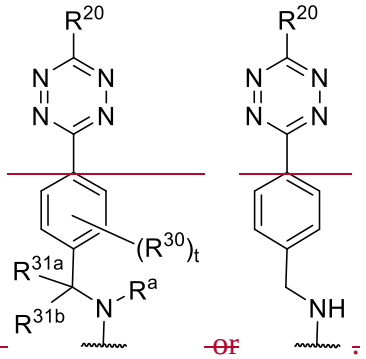
~~(II)~~



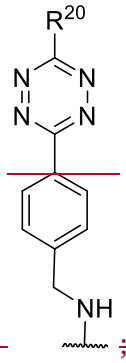
~~wherein G^2 is ; and~~

~~R^{22} is a linker of 1 to 100 linking atoms.~~

~~20. The pharmaceutical combination of claim 19, wherein:~~

~~G^2 is~~  ~~or~~ ~~.~~

~~21. The pharmaceutical combination of claim 19, wherein~~

~~G^2 is~~  ~~; and~~

~~R^{20} is hydrogen or C_{1-4}alkyl.~~

~~22~~26. The pharmaceutical combination of ~~any of claims 17-21~~claim 25, wherein the use is for treating or preventing a cancer.

~~23. The pharmaceutical combination of claim 22, wherein the cancer is a melanoma, renal cancer, prostate cancer, ovarian cancer , breast cancer , glioma, lung cancer, soft tissue carcinoma, soft tissue sarcoma, osteosarcoma, or pancreatic cancer.~~

~~24. The pharmaceutical combination of claim 22 or 23, wherein the cancer is a solid tumor.~~

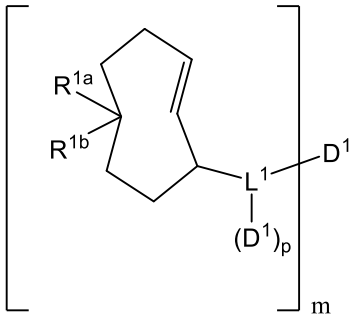
~~25. The pharmaceutical combination of claim 22 or 23, wherein the cancer is a soft tissue sarcoma.~~

~~26. The pharmaceutical combination of claim 25, wherein the soft tissue sarcoma is a fibrosarcoma, rhabdomyosarcoma, or Ewing's sarcoma.~~

~~27. The pharmaceutical combination of any of claims 17-21, wherein the use is for enhancing or eliciting an immune response.~~

~~28. The pharmaceutical combination of claim 27, wherein the immune response is an increase in one or more of leukocytes, lymphocytes, monocytes, and eosinophils.~~

~~29~~27. The pharmaceutical combination of any of claims ~~17-28~~25-26, further comprising an additional therapeutic agent selected from the group consisting of an anticancer agent, an immune checkpoint inhibitor, or a compound of formula (I-B), or a pharmaceutically acceptable salt thereof,



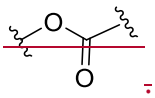
(I-B)

wherein

D^1, at each occurrence, is independently a payload selected from an anticancer drug payload, a microbial immunosuppressive drug payload, an anti-restenosis drug payload, antibiotic drug payload, antifungal drug payload, antiviral drug payload, anti-inflammatory/anti-arthritic drug payload, a corticosteroid drug payload, and an immunosuppressant drug payload; and

R^{1a}, R^{1b}, L^1, p, and m are as defined in any of claims 1-11.

~~30. The pharmaceutical combination of claim 29, wherein p is 0; m is 1; and L^1 is~~



~~.~~

~~31. The pharmaceutical combination of claim 29 or 30, wherein the anticancer drug is doxorubicin.~~

~~32~~28. A kit comprising the compound of any of claims ~~1-15~~21-23, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim ~~16~~24, and instructions for use thereof.

~~33. The kit of claim 32, further comprising the therapeutic support composition as defined in any of claims 19-23.~~

~~34. The kit of claim 32 or 33, further comprising the compound of formula (I-B), as defined in any of claims 29-31.~~