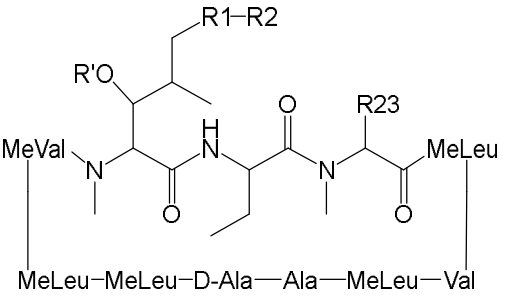
WHAT IS CLAIMED IS:

1. Use of a composition comprising a cyclosporine analogue of Formula L, or a pharmaceutically acceptable salt, solvate, stereoisomer thereof, in the manufacture of a medicament for treating a proliferative disease, for alleviating one or more symptoms of a proliferative disease, for preventing or delaying the onset of one or more symptoms of a proliferative disease, or for preventing a proliferative disease, in a subject, wherein the proliferative disease is cancer,



Formula L

wherein:

a. R' is H or acetyl;

b. R1 is a saturated or unsaturated straight or branched aliphatic carbon chain from 2 to 15 carbon atoms in length;

c. R2 is selected from the group consisting of:

i. H;

ii. an unsubstituted, N–substituted, or N,N-disubstituted amide;

iii. a N-substituted or unsubstituted acyl protected amine;

iv. a N-substituted or unsubstituted amine;

v. a carboxylic acid;

vi. a nitrile;

vii. an ester;

viii. a ketone;

ix. a hydroxy, dihydroxy, trihydroxy, or polyhydroxy alkyl; and

x. a substituted or unsubstituted aryl;

xi. a saturated or unsaturated. straight or branched aliphatic chain optionally containing a substituent selected from the group consisting of a hydrogen, a ketone, a hydroxyl, a nitrile, a carboxylic acid, an ester, a 1,3-dioxolane, a halogen, and an oxo;

xii. an aromatic group containing a substituent selected from the group consisting of a halogen, an ester, and a nitro; and

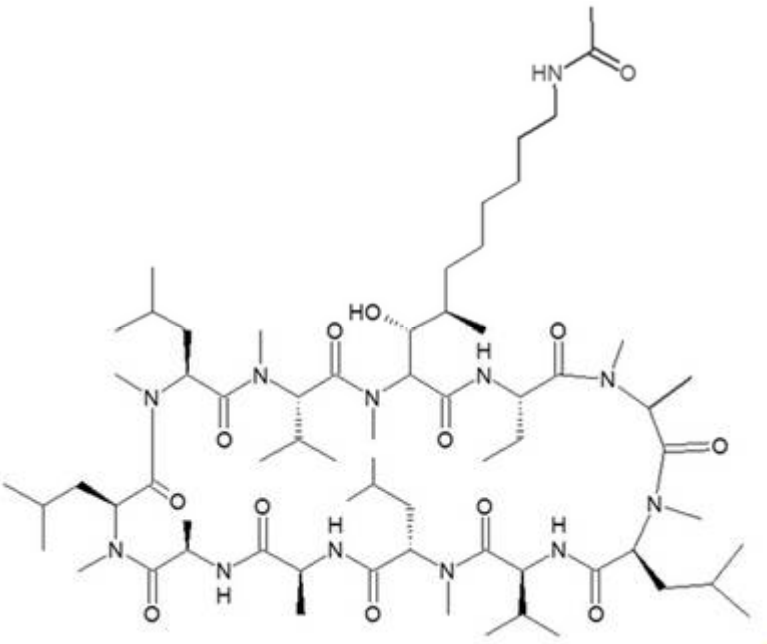
xiii. a combination of the saturated or unsaturated, straight or branched aliphatic chain of (xi) and the aromatic group of (xii); and

d. R23 is a saturated or unsaturated straight chain or branched optionally substituted aliphatic carbon chain.

2. The use of claim 1, wherein the subject is in a partial remission of the proliferative disease, and/or wherein the subject is a subject at a risk of developing the proliferative disease, or a subject at a complete remission of the proliferative disease.

3. The use of any one of claims 1-2, wherein the subject is identified as suffering from the proliferative disease and/or wherein the subject is identified as being at risk of development of the proliferative disease.

4. The use of any one of claims 1-3, wherein the cyclosporine analogue of Formula L is CRV431:



(CRV431).

5. The use of any one of claims 1-4, wherein the liver cancer is primary liver cancer or secondary liver cancer.

6. The use of any one of claims 1-4, wherein the liver cancer is hepatocellular carcinoma (HCC), bile duct cancer, Angiosarcoma, hemangiosarcoma, hepatoblastoma, hemangioma, hepatic adenoma, focal nodular hyperplasia, or a combination thereof.

7. The use of any one of claims 1-6, wherein the composition comprises a therapeutically or prophylactically effective amount of cyclosporine analogue of Formula L, or a pharmaceutically acceptable salt, solvate, stereoisomer thereof.

8. The use of any one of claims 1-7, wherein the subject is a mammal, and optionally the mammal is human.

9. The use of any one of claims 1-**Error! Reference source not found.**, wherein the composition comprises one or more pharmaceutically acceptable excipients, wherein the composition comprises one or more additional therapeutic agents, and/or wherein the composition is to be administered with one or more cancer therapies.

10. The use of claim **Error! Reference source not found.**,

wherein the one or more additional therapeutic agents comprise a radiotherapeutic agent, an anti-immunosuppressive agent or immunostimulatory agent, a chemotherapeutic agent, or a combination thereof,

wherein the one or more additional therapeutic agents comprise an anti-PD-1 agent, an anti-PD-L1 agent, an anti-CTLA4 agent, an anti-TIM-3 agent, an anti-LAG-3 agent, a GITR (glucocorticoid-induced TNFR-related protein) stimulating agent, an anti-IDO agent, an anti-ICOS agent, a proteosome inhibitor(s), an anti-OX40 agent, an anti-CSF1R agent, a chemokine signaling agent, a cytokine signal stimulating agent, or a combination thereof,

wherein the one or more additional therapeutic agents comprise bevacizumab, pembrolizumab, nivolumab, PDR001, REGN2810 (SAR-439684), BGB-A317, BI 754091, IBI308, INCSHR-1210, JNJ-63723283, JS-001, MEDI0680 (AMP-514), MGA-012, PF-06801591, REGN-2810, TSR-042, atezolizumab, avelumab, CX-072, durvalumab, FAZ053, LY3300054, PD-L1 millamolecule, atezolizumab, durvalumab, avelumab, LY3300054, aminoglutethimide, amsacrine, anastrozole, asparaginase, bcg, beta-hydroxy beta-methylbutyrate, bicalutamide, bleomycin, bortezomib, buserelin, busulfan, campothecin, capecitabine, carfilzomib, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, clodronate, colchicine, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, delanzomib, dienestrol, diethylstilbestrol, disulfiram, docetaxel, doxorubicin, epigallocatechin-3-gallate, epirubicin, epoxomicin, estradiol, estramnustine, etoposide, exemestane, filgrastim, fludarabine, fludrocortisone, fluorouracil, fluoxymesterone, flutamide, gemcitabine, genistein, goserelin, hydroxyurea, idarubicin, ifosfamide, imatinib, interferon, irinotecan, ironotecan, letrozole, leucovorin, leuprolide, levamisole, lomustine, ixazomib, marizomib, mechlorethamine, medroxyprogesterone, megestrol, melphalan, mercaptopurine, mesna, methotrexate, mitomycin, mitotane, mitoxantrone, nilutamide, nocodazole, octreotide, oprozomib, oxaliplatin, paclitaxel, pamidronate, pentostatin, plicamycin, porfimer, procarbazine, raltitrexed, rituximab, streptozocin, suramin, tamoxifen, temozolomide, teniposide,

testosterone, thioguanine, thiotepa, titanocene dichloride, topotecan, trastuzumab, tretinoin, vinblastine, vincristine, vindesine, vinorelbine, or a combination thereof,

wherein the one or more cancer therapies comprise surgery, chemotherapy, radiotherapy, immunotherapy, or a combination thereof, and/or

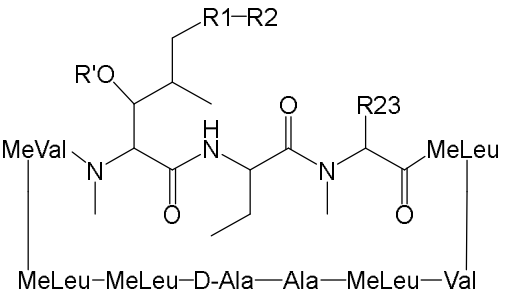
wherein the one or more additional therapeutic agents a proteasome inhibitor, and the cyclosporine analogue of Formula L, or a pharmaceutically acceptable salt, solvate, stereoisomer thereof are formulated to be administered to the subject, optionally wherein the proteasome inhibitor is beta-hydroxy beta-methylbutyrate, bortezomib, carfilzomib, delanzomib, disulfiram, epigallocatechin-3-gallate, epoxomicin, ixazomib, marizomib, or oprozomib.

11. The use of any one of claims **Error! Reference source not found.**-10, wherein at least one of the one or more additional therapeutic agents and/or the one or more cancer therapies is formulated to be co-administered to the subject with the composition, and/or wherein at least one of the one or more additional therapeutic agents and/or the one or more cancer therapies is formulated to be administered to the subject before the administration of the composition, after the administration of the composition, or both.

12. The use of any one of claims 1-11, wherein the composition is formulated to be administered to the subject by intravenous administration, oral administration, parenteral administration, and/or wherein the composition is in the form of a powder, pill, tablet, microtablet, pellet, micropellet, capsule, capsule containing microtablets, liquid, aerosols, or nanoparticles.

13. The use of any one of claims 1-**Error! Reference source not found.**, wherein the composition is formulated to be administered to the subject at an effective daily dose of the cyclosporine analogue or a pharmaceutically acceptable salt, solvate, stereoisomer thereof at from 10 mg to 250 mg.

14. A pharmaceutical composition, comprising a cyclosporine analogue of Formula L, or a pharmaceutically acceptable salt, solvate, stereoisomer thereof, for use in preventing or treating a proliferative disease, or alleviating one or more symptoms of a proliferative disease, or preventing or delaying the onset of one or more symptoms of a proliferative disease, or preventing or delaying the onset of a proliferative disease,



Formula L

wherein:

a. R' is H or acetyl;

b. R1 is a saturated or unsaturated straight or branched aliphatic carbon chain from 2 to 15 carbon atoms in length;

c. R2 is selected from the group consisting of:

i. H;

ii. an unsubstituted, N–substituted, or N,N-disubstituted amide;

iii. a N-substituted or unsubstituted acyl protected amine;

iv. a N-substituted or unsubstituted amine;

v. a carboxylic acid;

vi. a nitrile;

vii. an ester;

viii. a ketone;

ix. a hydroxy, dihydroxy, trihydroxy, or polyhydroxy alkyl; and

x. a substituted or unsubstituted aryl;

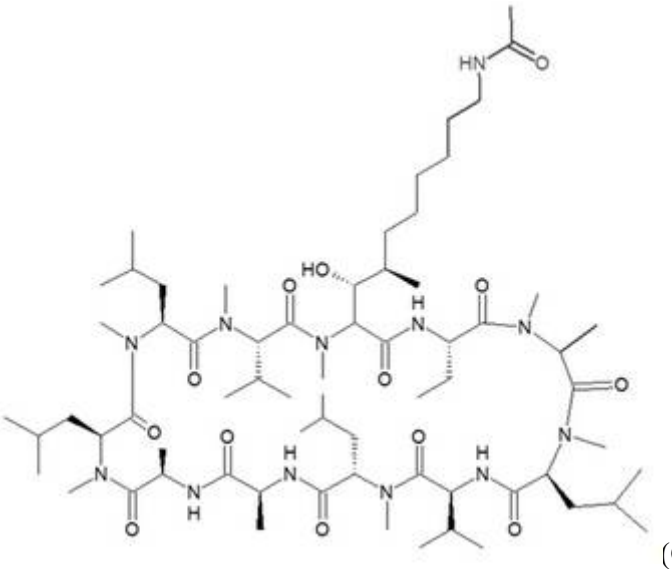
xi. a saturated or unsaturated. straight or branched aliphatic chain optionally containing a substituent selected from the group consisting of a hydrogen, a ketone, a hydroxyl, a nitrile, a carboxylic acid, an ester, a 1,3-dioxolane, a halogen, and an oxo;

xii. an aromatic group containing a substituent selected from the group consisting of a halogen, an ester, and a nitro; and

xiii. a combination of the saturated or unsaturated, straight or branched aliphatic chain of (xi) and the aromatic group of (xii); and

d. R23 is a saturated or unsaturated straight chain or branched optionally substituted aliphatic carbon chain.

15. The pharmaceutically composition of claim 14, wherein the cyclosporine analogue is CRV431:


(CRV431).

16. The pharmaceutical composition of any one of claims 14-15, wherein the pharmaceutical composition is for intravenous administration, oral administration, or parenteral administration, and/or wherein the pharmaceutical composition is in the form of powder, pill, tablet, microtablet, pellet, micropellet, capsule, capsule containing microtablets, liquid, aerosols, or nanoparticles.

17. A kit, comprising

a pharmaceutical composition of any one of claims 14-**Error! Reference source not found.**; and

a label, wherein the label indicating one or more of:

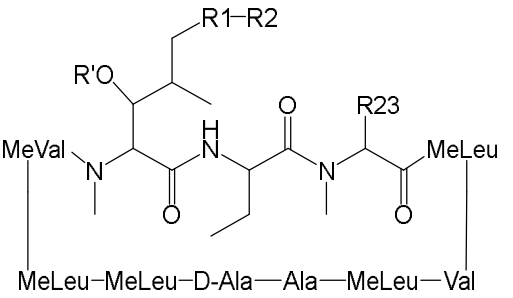
(a) the kit is for preventing or treating a proliferative disease,

(b) the kit is for alleviating one or more symptoms of a proliferative disease, or preventing or delaying the onset of one or more symptoms of a proliferative disease, and

(c) the kit is for preventing or delaying the onset of a proliferative disease.

18. The kit of claim 17, further comprising instructions for identifying a subject at risk of development the proliferative disease, instructions for identifying a subject suffering from the proliferative disease, or both.

19. Use of a composition comprising a cyclosporine analogue of Formula L, or a pharmaceutically acceptable salt, solvate, stereoisomer thereof, in the manufacture of a medicament for sensitizing cancer cells to anti-cancer agents or therapies, wherein the cancer cells comprise cells of liver cancer, thereby sensitizing the cancer cells to one or more anticancer agents, one or more cancer therapies, or both,



Formula L

wherein:

a. R' is H or acetyl;

b. R1 is a saturated or unsaturated straight or branched aliphatic carbon chain from 2 to 15 carbon atoms in length;

c. R2 is selected from the group consisting of:

i. H;

ii. an unsubstituted, N–substituted, or N,N-disubstituted amide;

iii. a N-substituted or unsubstituted acyl protected amine;

iv. a N-substituted or unsubstituted amine;

v. a carboxylic acid;

vi. a nitrile;

vii. an ester;

viii. a ketone;

ix. a hydroxy, dihydroxy, trihydroxy, or polyhydroxy alkyl; and

x. a substituted or unsubstituted aryl;

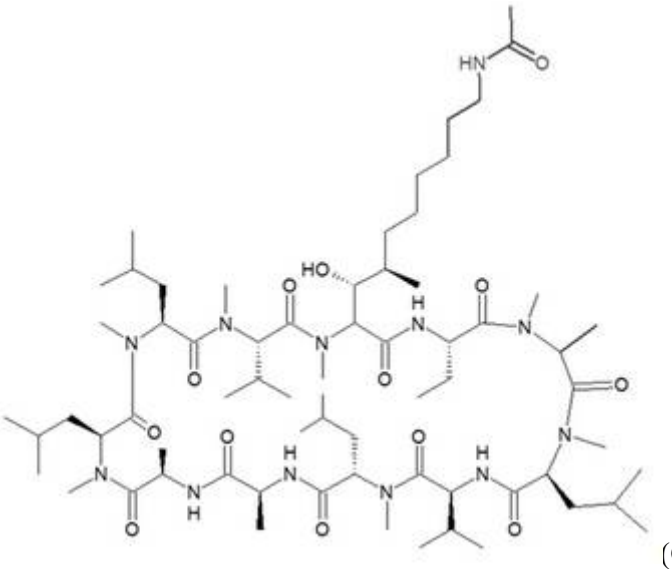
xi. a saturated or unsaturated. straight or branched aliphatic chain optionally containing a substituent selected from the group consisting of a hydrogen, a ketone, a hydroxyl, a nitrile, a carboxylic acid, an ester, a 1,3-dioxolane, a halogen, and an oxo;

xii. an aromatic group containing a substituent selected from the group consisting of a halogen, an ester, and a nitro; and

xiii. a combination of the saturated or unsaturated, straight or branched aliphatic chain of (xi) and the aromatic group of (xii); and

d. R23 is a saturated or unsaturated straight chain or branched optionally substituted aliphatic carbon chain.

20. The use of claim 19, wherein the cyclosporine analogue is CRV431:


(CRV431).

21. The use of any one of claims 19-20, wherein contacting cancer cells with the composition occurs *in vitro*, *ex vivo*, and/or i*n vivo*.

22. The use of any one of claims 19-21, wherein contacting cancer cells with the composition is in a subject.

23. The use of claim 22, wherein the subject did not respond to, or is known to be resistant to, the one or more anticancer agents alone, the one or more cancer therapies alone, or both.

24. The use of any one of claims 22-23, wherein the subject had prior treatment with the one or more anticancer agents, the one or more cancer therapies, or both.

25. The use of any one of claims 22-24, wherein the subject is a mammal, and optionally the mammal is human.

26. The use of any one of claims 19-25, wherein the cancer cells are formulated to determine sensitization to the one or more anticancer agents, the one or more cancer therapies, or both, after being contacted with the composition.

27. The use of any one of claims 19-26, wherein the cancer cells are formulated to contact with the one or more anticancer agents, the one or more cancer therapies, or both.

28. The use of claim 27, wherein the cancer cells are formulated to contact with the one or more anticancer agents, the one or more cancer therapies, or both, in the subject.

29. The use of any one of claims 27-28, wherein a response of the subject to the one or more anticancer agents, the one or more cancer therapies, or both is determined.

30. The use of any one of claims 27-29, wherein the cancer cells are formulated to contact with the one or more anticancer agents, the one or more cancer therapies, or both, so as to be concurrent with the contacting the cancer cells with the composition, or after the contacting the cancer cells with the composition.

31. The use of any one of claims 19-**Error! Reference source not found.**,

wherein the one or more anticancer agents comprise a radiotherapeutic agent, an anti-immunosuppressive agent or immunostimulatory agent, a chemotherapeutic agent, or a combination thereof,

wherein the one or more anticancer agents comprise an anti-PD-1 agent, an anti-PD-L1 agent, an anti-CTLA4 agent, an anti-TIM-3 agent, an anti-LAG-3 agent, a GITR (glucocorticoid-induced TNFR-related protein) stimulating agent, an anti-IDO agent, an anti-ICOS agent, a proteasome inhibitor, an anti-OX40 agent, an anti-CSF1R agent, a chemokine signaling agent, a cytokine signal stimulating agent, or a combination thereof,

wherein the one or more anticancer agents comprise bevacizumab, pembrolizumab, nivolumab, PDR001, REGN2810 (SAR-439684), BGB-A317, BI 754091, IBI308, INCSHR-1210, JNJ-63723283, JS-001, MEDI0680 (AMP-514), MGA-012, PF-06801591, REGN-2810, TSR-042, atezolizumab, avelumab, CX-072, durvalumab, FAZ053, LY3300054, PD-L1 millamolecule, atezolizumab, durvalumab, avelumab, LY3300054, aminoglutethimide, amsacrine, anastrozole, asparaginase, bcg, beta-hydroxy beta-methylbutyrate, bicalutamide, bleomycin, bortezomib, buserelin, busulfan, campothecin, capecitabine, carfilzomib, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, clodronate, colchicine, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, delanzomib, dienestrol, diethylstilbestrol, disulfiram, docetaxel, doxorubicin, epigallocatechin-3-gallate, epirubicin, epoxomicin, estradiol, estramnustine, etoposide, exemestane, filgrastim, fludarabine, fludrocortisone, fluorouracil, fluoxymesterone, flutamide, gemcitabine, genistein, goserelin, hydroxyurea, idarubicin, ifosfamide, imatinib, interferon, irinotecan, ironotecan, letrozole, leucovorin, leuprolide, levamisole, lomustine, ixazomib, marizomib, mechlorethamine, medroxyprogesterone, megestrol, melphalan, mercaptopurine, mesna, methotrexate, mitomycin, mitotane, mitoxantrone, nilutamide, nocodazole, octreotide, oprozomib, oxaliplatin, paclitaxel, pamidronate, pentostatin, plicamycin, porfimer, procarbazine, raltitrexed, rituximab, streptozocin, suramin, tamoxifen, temozolomide, teniposide, testosterone, thioguanine, thiotepa, titanocene dichloride, topotecan, trastuzumab, tretinoin, vinblastine, vincristine, vindesine, vinorelbine, or a combination thereof, and/or

wherein the one or more cancer therapies comprise surgery, chemotherapy, radiotherapy, immunotherapy, or a combination thereof.