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(54) Title: COMBINATION THERAPY USING C-C CHEMOKINE RECEPTOR 4 (CCR4) ANTAGONISTS AND ONE OR MORE IMMUNE CHECKPOINT INHIBITORS

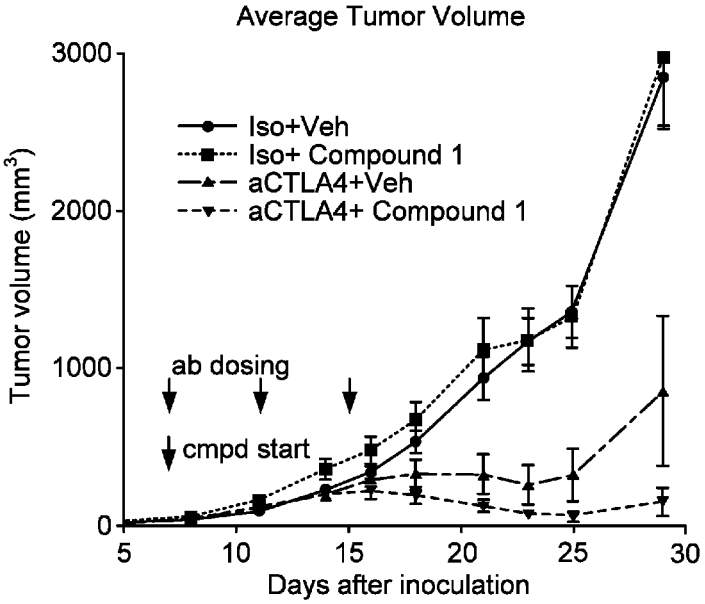


FIG. 6

(57) Abstract: The present disclosure is drawn to the combination therapy of a C-C Chemokine Receptor 4 (CCR4) antagonist and one or more immune checkpoint inhibitors in the treatment of cancer.

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[Continued on next page]

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COMBINATION THERAPY USING C-C CHEMOKINE RECEPTOR 4 (CCR4) ANTAGONISTS AND ONE OR MORE CHECKPOINT INHIBITORS

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority under 35 U.S.C § 119(e) to U.S. Provisional Application Serial Nos. 62/724,412 filed 29 August 2018 and 62/771,853 filed 27 November 2018, the disclosures of each are incorporated herein by reference in their entirety.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0002] NOT APPLICABLE

REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER PROGRAM LISTING APPENDIX SUBMITTED ON A COMPACT DISK

[0003] NOT APPLICABLE

BACKGROUND

[0004] Cancer is a class of diseases in which a group of cells display dysregulated replication and growth. Recent cancer models implicate the immune system, including cellular homing and immune checkpoints, in cancer development and progression. Although great progress has been made in understanding the biological basis of cancer, this disease remains a leading cause of death.

[0005] The CC Chemokine receptor 4, CCR(4), first identified by Power et al. (Power et al. (1995) *J. Biol. Chem.* 270:19495-19500), is a G protein-coupled receptor that binds to chemokines including CCL22, also known as Macrophage-Derived Chemokine (MDC; a CC chemokine reported to be a chemoattractant for the Th2 subset of peripheral blood T cells, dendritic cells, and natural killer (NK) cells), and CCL17, also known as TARC (thymus and activation-regulated chemokine), which is also produced by monocytes and dendritic cells.

[0006] CCR(4) is involved in immuoregulatory processes such as the homing of cells to specific tissues including T lymphocyte homing to the skin and lungs (see, e.g., Campbell et al. (1999) *Nature* 400:776-780, Gonzalo et al. (1999) *J. Immunol.* 163:403- 5 411, Lloyd et al. (2000) *J. Exp. Med.* 191:265-273, Kawasaki et al. (2001) *J. Immunol.* 166:2055-2062). Modulators of CCR4 activity have been described in, for example, WO 2013/082490.

[0007] Cytotoxic T lymphocyte antigen-4 (CTLA-4) is believed to be a key regulator of the adaptive immune responses. In particular, CLTA-4 is understood to play a central role in the maintenance of and repertoire of emergent T cell responses. As such, CTLA-4 is recognized as a possible therapeutic target for the treatment of cancer and inflammation as an immune checkpoint inhibitor. CLTA-4 modulatorys have been described in, for example, WO 2018/035710.

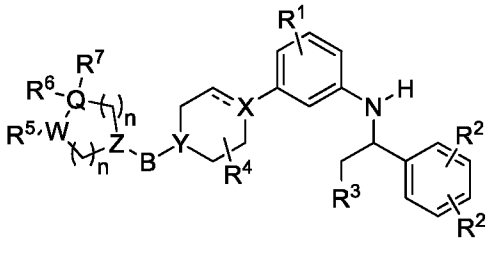
[0008] Programmed death-1 (PD-1) is a transmembrane receptor protein that negatively regulates the function of T cells through interaction with its two native ligands PD-L1 and PD-L2. Like CTLA4, PD-1 is also a central regulator of the immune system, and is also considered an immune checkpoint inhibitor. PD-1/PD-L1 modulators have been described in, for example, WO 2018/005374.

[0009] Given the role of cellular homing and immune checkpoint pathways in cancer development and progression, the need exists for developing combination therapies that can improve cancer treatment.

BRIEF SUMMARY

[0010] The present disclosure is drawn to the combination therapy of a C-C Chemokine Receptor 4 (CCR4) antagonist and one or more checkpoint inhibitors in the treatment of cancer.

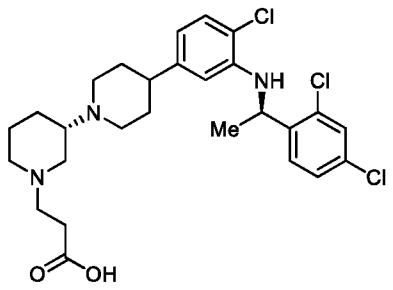
[0011] In some embodiments, the CCR4 receptor antagonist has the Formula I



(I)

where each variable is described below.

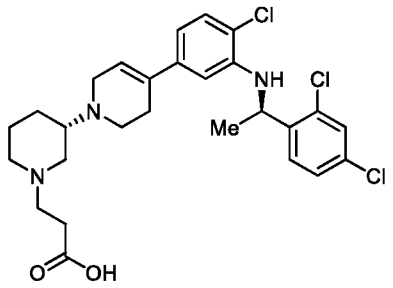
[0012] In some embodiments, the CCR4 antagonist has the formula



(Compound 1)

or a pharmaceutically acceptable salt thereof.

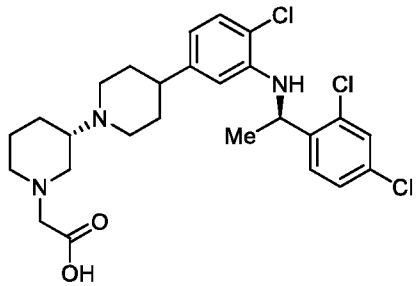
[0013] In some embodiments, the CCR4 antagonist has the formula



(Compound 2)

or a pharmaceutically acceptable salt thereof.

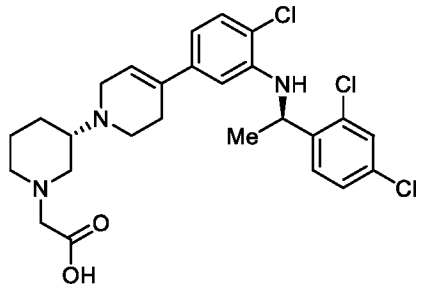
[0014] In some embodiments, the CCR4 antagonist has the formula



(Compound 3)

or a pharmaceutically acceptable salt thereof.

[0015] In some embodiments, the CCR4 antagonist has the formula



(Compound 4)

or a pharmaceutically acceptable salt thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] FIG. 1 illustrates the study design used for the KCM Orthotopic pancreatic tumor model.

[0017] FIG. 2A-C displays the primary tumor + pancreas weight (Panel A), the total tumor + Pancreas weight (Panel B), and the spleen weight (Panel C) of each cohort tested. Combination therapy of an anti-CTLA-4 antibody and Compound 1 reduced tumor weight as compared to antibody or Compound 1 alone.

[0018] FIG. 3A-F reports the relative amounts of suppressive immune cell populations in each cohort tested. Panels A-C report the cells per gram of tissue, while Panels D-F report the percent of CD45+ cells. Panels A & D report T-reg cells; panels B & E report G-MDSC cells; and panels C & F report M-MDSC cells.

[0019] FIG. 4 illustrates the study design used for the CT26 colon cancer tumor model.

[0020] FIG. 5 plots the survival rate of mice during the study from each cohort tested in the CT26 tumor model.

[0021] FIG. 6 plots the average tumor volume in mice from each cohort tested

[0022] FIG. 7A-D plots the individual tumor volume in mice from each cohort tested. Panel A reports the antibody isotype & vehicle group; Panel B reports the antibody isotype and Compound 1 group; Panel C reports the anti-CTLA-4 antibody and vehicle group; and Panel D reports the anti-CTLA-4 antibody and Compound 1 Group.

[0023] FIG. 8A-F plots tumor volume in re-challenged and naïve mice using CT26 colon cancer cells and 4T1 breast cancer cells. Re-challenged mice are those with complete tumor regression previously treated with anti-CTLA-4 (6 mice) or anti-CTLA-4 and Compound 1 (8 mice). Naïve mice are those who have been previously challenged with CT26 colon cancer cells before. Panel A shows that 5/6 mice from the anti-CTLA-4 treatment group were resistant to CT26 tumor re-introduction; Panel B shows that none of the mice from the anti-CTLA-4 treatment group were resistant to 4T1 tumor cells; Panel C shows that 8/8 mice from the anti-CTLA-4/Compound 1 treatment group were resistant to CT26 tumor re-introduction; Panel D shows that 2 of the 8 mice from the anti-CTLA-4/Compound 1 treatment group were resistant to 4T1 tumor cells; Panel E shows that all naïve mice showed tumor growth when first challenged with CT26 cells; and Panel F shows that none of the naïve mice were resistant to 4T1 tumor cells.

[0024] FIG. 9A-C plots flow cytometry results from blood samples obtained from the mice tested in FIG. 8. Panel A shows that before re-challenge mice previously exposed to CT26 cells (and treated CTLA-4 or anti-CTLA-4 and Compound 1) have cytotoxic T cells against CT26 tumor cells, while naïve mice do not. Panels B and C show the number of cytotoxic T cells responsive against CT26 tumor cells before re-challenge and 1 week after re-challenge.

DETAILED DESCRIPTION

I. General

[0025] The present disclosure is drawn to the surprising and unexpected finding that combination therapy using a CCR4 antagonist and one or more immune checkpoint inhibitor significantly improves cancer treatment as compared to the one or more checkpoint inhibitors on their own.

II. Abbreviation and Definitions

[0026] The term "alkyl", by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain hydrocarbon radical, having the number of carbon atoms designated (*i.e.* C_{1-8} means one to eight carbons). Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, n-pentyl, n-hexyl, n-heptyl, n-

octyl, and the like. The term "alkenyl" refers to an unsaturated alkyl group having one or more double bonds. Similarly, the term "alkynyl" refers to an unsaturated alkyl group having one or more triple bonds. Examples of such unsaturated alkyl groups include vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. The term "cycloalkyl" refers to hydrocarbon rings having the indicated number of ring atoms (*e.g.*, C_{3-6}cycloalkyl) and being fully saturated or having no more than one double bond between ring vertices. "Cycloalkyl" is also meant to refer to bicyclic and polycyclic hydrocarbon rings such as, for example, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, etc. The term "heterocycloalkyl" refers to a cycloalkyl group that contain from one to five heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. The heterocycloalkyl may be a monocyclic, a bicyclic or a polycylic ring system. Non limiting examples of heterocycloalkyl groups include pyrrolidine, imidazolidine, pyrazolidine, butyrolactam, valerolactam, imidazolidinone, hydantoin, dioxolane, phthalimide, piperidine, 1,4-dioxane, morpholine, thiomorpholine, thiomorpholine-S-oxide, thiomorpholine-S,S-oxide, piperazine, pyran, pyridone, 3-pyrroline, thiopyran, pyrone, tetrahydrofuran, tetrhydrothiophene, quinuclidine, and the like. A heterocycloalkyl group can be attached to the remainder of the molecule through a ring carbon or a heteroatom. For terms such as cycloalkylalkyl and heterocycloalkylalkyl, it is meant that a cycloalkyl or a heterocycloalkyl group is attached through an alkyl or alkylene linker to the remainder of the molecule. For example, cyclobutylmethyl – is a cyclobutyl ring that is attached to a methylene linker to the remainder of the molecule.

[0027] The term "alkylene" by itself or as part of another substituent means a divalent radical derived from an alkane, as exemplified by $-CH_2CH_2CH_2CH_2-$. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present disclosure. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having four or fewer carbon atoms. Similarly, "alkenylene" and "alkynylene" refer to the unsaturated forms of "alkylene" having double or triple bonds, respectively.

[0028] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N, Si and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any interior position of the heteroalkyl group. The heteroatom Si may be placed at any position of the heteroalkyl group, including the position at which the alkyl group is attached to the remainder of the molecule. Examples include $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2,-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, and $-CH=CH-N(CH_3)-CH_3$. Up to two heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$. Similarly, the terms "heteroalkenyl" and "heteroalkynyl" by itself or in combination with another term, means, unless otherwise stated, an alkenyl group or alkynyl group, respectively, that contains the stated number of carbons and having from one to three heteroatoms selected from the group consisting of O, N, Si and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any interior position of the heteroalkyl group.

[0029] The term "heteroalkylene" by itself or as part of another substituent means a divalent radical, saturated or unsaturated or polyunsaturated, derived from heteroalkyl, as exemplified by $-CH_2-CH_2-S-CH_2CH_2-$ and $-CH_2-S-CH_2-CH_2-NH-CH_2-$, $-O-CH_2-CH=CH-$, $-CH_2-CH=C(H)CH_2-O-CH_2-$ and $-S-CH_2-C\equiv C-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (*e.g.*, alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like).

[0030] The terms "alkoxy," "alkylamino" and "alkylthio" (or thioalkoxy) are used in their conventional sense, and refer to those alkyl groups attached to the remainder of the molecule via an oxygen atom, an amino group, or a sulfur atom, respectively. Additionally, for dialkylamino groups, the alkyl portions can be the same or different and can also be combined to form a 3-7 membered ring with the nitrogen atom to which each is attached. Accordingly, a group

represented as -NR^aR^b is meant to include piperidinyl, pyrrolidinyl, morpholinyl, azetidinyl and the like.

[0031] The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl," are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "C_{1-4} haloalkyl" is mean to include trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0032] The term "aryl" means, unless otherwise stated, a polyunsaturated, typically aromatic, hydrocarbon group which can be a single ring or multiple rings (up to three rings) which are fused together or linked covalently. The term "heteroaryl" refers to aryl groups (or rings) that contain from one to five heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom. Non-limiting examples of aryl groups include phenyl, naphthyl and biphenyl, while non-limiting examples of heteroaryl groups include pyridyl, pyridazinyl, pyrazinyl, pyrimindinyl, triazinyl, quinolinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalaziniyl, benzotriazinyl, purinyl, benzimidazolyl, benzopyrazolyl, benzotriazolyl, benzisoxazolyl, isobenzofuryl, isoindolyl, indolizinyl, benzotriazinyl, thienopyridinyl, thienopyrimidinyl, pyrazolopyrimidinyl, imidazopyridines, benzothiaxolyl, benzofuranyl, benzothienyl, indolyl, quinolyl, isoquinolyl, isothiazolyl, pyrazolyl, indazolyl, pteridinyl, imidazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiadiazolyl, pyrrolyl, thiazolyl, furyl, thienyl and the like. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below.

[0033] For brevity, the term "aryl" when used in combination with other terms (*e.g.*, aryloxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the term "arylalkyl" is meant to include those radicals in which an aryl group is attached to an alkyl group that is attached to the remainder of the molecule (*e.g.*, benzyl, phenethyl, pyridylmethyl and the like).

[0034] The above terms (*e.g.*, "alkyl," "aryl" and "heteroaryl"), in some embodiments, will include both substituted and unsubstituted forms of the indicated radical. Preferred substituents

for each type of radical are provided below. For brevity, the terms aryl and heteroaryl will refer to substituted or unsubstituted versions as provided below, while the term "alkyl" and related aliphatic radicals is meant to refer to unsubstituted version, unless indicated to be substituted.

[0035] Substituents for the alkyl radicals (including those groups often referred to as alkylene, alkenyl, alkynyl and cycloalkyl) can be a variety of groups selected from: -halogen, -OR', -NR'R", -SR', -SiR'R"R"', -OC(O)R', -C(O)R', -CO_2R', -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R"', -NR"$C(O)_2$R', -NH-$C(NH_2)$=NH, -NR'$C(NH_2)$=NH, -NH-$C(NH_2)$=NR', -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", -NR'$S(O)_2$R", -CN and -NO_2 in a number ranging from zero to (2 m'+1), where m' is the total number of carbon atoms in such radical. R', R" and R"' each independently refer to hydrogen, unsubstituted C_{1-8} alkyl, unsubstituted heteroalkyl, unsubstituted aryl, aryl substituted with 1-3 halogens, unsubstituted C_{1-8} alkyl, C_{1-8} alkoxy or C_{1-8} thioalkoxy groups, or unsubstituted aryl-C_{1-4} alkyl groups. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 3-, 4-, 5-, 6-, or 7-membered ring. For example, -NR'R" is meant to include 1-pyrrolidinyl and 4-morpholinyl. The term "acyl" as used by itself or as part of another group refers to an alkyl radical wherein two substitutents on the carbon that is closest to the point of attachment for the radical is replaced with the substitutent =O (e.g., -$C(O)CH_3$, -$C(O)CH_2CH_2$OR' and the like).

[0036] Similarly, substituents for the aryl and heteroaryl groups are varied and are generally selected from: -halogen, -OR', -OC(O)R', -NR'R", -SR', -R', -CN, -NO_2, -CO_2R', -CONR'R", -C(O)R', -OC(O)NR'R", -NR"C(O)R', -NR"$C(O)_2$R', ,-NR'-C(O)NR"R"', -NH-$C(NH_2)$=NH, -NR'$C(NH_2)$=NH, -NH-$C(NH_2)$=NR', -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", -NR'$S(O)_2$R", -N_3, perfluoro(C_1-C_4)alkoxy, and perfluoro(C_1-C_4)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R" and R"' are independently selected from hydrogen, C_{1-8} alkyl, C_{3-6} cycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, unsubstituted aryl and heteroaryl, (unsubstituted aryl)-C_{1-4} alkyl, and unsubstituted aryloxy-C_{1-4} alkyl. Other suitable substituents include each of the above aryl substituents attached to a ring atom by an alkylene tether of from 1-4 carbon atoms.

[0037] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -T-C(O)-$(CH_2)_q$-U-, wherein T and U are independently -NH-, -O-, -CH_2- or a single bond, and q is an integer of from 0 to 2.

Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-$(CH_2)_r$-B-, wherein A and B are independently -CH_2-, -O-, -NH-, -S-, -S(O)-, -$S(O)_2$-, -$S(O)_2$NR'- or a single bond, and r is an integer of from 1 to 3. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -$(CH_2)_s$-X-$(CH_2)_t$-, where s and t are independently integers of from 0 to 3, and X is -O-, -NR'-, -S-, -S(O)-, -$S(O)_2$-, or -$S(O)_2$NR'-. The substituent R' in -NR'- and -$S(O)_2$NR'- is selected from hydrogen or unsubstituted C_{1-6} alkyl.

[0038] As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S) and silicon (Si).

[0039] For the compounds provided herein, a bond that is drawn from a substituent (typically an R group) to the center of an aromatic ring (e.g., benzene, pyridine, and the like) will be understood to refer to a bond providing a connection at any of the available vertices of the aromatic ring. In some embodiments, the depiction will also include connection at a ring which is fused to the aromatic ring. For example, a bond drawn to the center of the benzene portion of an indole, will indicate a bond to any available vertex of the six- or five-membered ring portions of the indole.

[0040] The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present disclosure contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of salts derived from pharmaceutically-acceptable inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc and the like. Salts derived from pharmaceutically-acceptable organic bases include salts of primary, secondary and tertiary amines, including substituted amines, cyclic amines, naturally-occuring amines and the like, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-

ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperadine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like. When compounds of the present disclosure contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge, S.M., et al, "Pharmaceutical Salts", *Journal of Pharmaceutical Science*, **1977**, *66*, 1-19). Certain specific compounds of the present disclosure contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0041] The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present disclosure.

[0042] In addition to salt forms, the present disclosure provides compounds which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present disclosure. Additionally, prodrugs can be converted to the compounds of the present disclosure by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the present disclosure when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

[0043] Certain compounds of the present disclosure can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present disclosure. Certain compounds of the present disclosure may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present disclsure and are intended to be within the scope of the present disclosure.

[0044] Certain compounds of the present disclosure possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers, regioisomers and individual isomers (*e.g.*, separate enantiomers) are all intended to be encompassed within the scope of the present disclosure. When compounds are provided herein with an identified stereochemistry (indicated as R or S, or with dashed or wedge bond designations), those compounds will be understood by one of skill in the art to be substantially free of other isomers (e.g., at least 80%, 90%, 95%, 98%, 99%, and up to 100% free of the other isomer).

[0045] The compounds of the present disclosure may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. Unnatural proportions of an isotope may be defined as ranging from the amount found in nature to an amount consisting of 100% of the atom in question. For example, the compounds may incorporate radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C), or non-radioactive isotopes, such as deuterium (^{2}H) or carbon-13 (^{13}C). Such isotopic variations can provide additional utilities to those described elsewhere within this application. For instance, isotopic variants of the compounds of the disclosure may find additional utility, including but not limited to, as diagnostic and/or imaging reagents, or as cytotoxic/radiotoxic therapeutic agents. Additionally, isotopic variants of the compounds of the disclosure can have altered pharmacokinetic and pharmacodynamic characteristics which can contribute to enhanced safety, tolerability or efficacy during treatment. All isotopic variations of the compounds of the present disclosure, whether radioactive or not, are intended to be encompassed within the scope of the present disclosure.

[0046] As used herein, the term "selective CCR4 antagonist" refers to a highly discriminatory compound that inhibits CCR4 activity with little or no cross reactivity on non-targeted proteins such as CCR1, CCR2, CCR3, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CCR12, CXCR1,

CXCR2, CXCR3, CXCR4, CXCR5, CXCR6, and/or CXCR7. In some embodiments, "selective CCR4 antagonists" have an IC_{50} that is at least 10; 100; 500; 1,000; 2,000; 5,000; or more times lower than for that of proteins such as CCR1, CCR2, CCR3, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CCR12, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CXCR6, and/or CXCR7 when measured in the assays used in Example 3 of this application. In some embodiments, "selective CCR4 antagonists" do not inhibit the activity of CCR1, CCR2, CCR3, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CCR12, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CXCR6, and/or CXCR7 at concentrations of 1 μM or below in assays used in Example 2 of this application. The above-mentioned proteins are considered to be "not inhibited" when they maintain 100%, 99%, 95%, 90%, or 85% of their activity under the referenced conditions with a selective CCR4 antagonist.

III. Combination Therapy using CCR4 Antagonists and One or More Immune Checkpoint Inhibitors

[0047] Provided herein are methods, compositions, and kits that take advantage of the synergistic effect of CCR4 antagonists and immune checkpoint inhibitors in treating cancer. A combination treatment that includes both a CCR4 antagonist and one or more immune checkpoint inhibitors is more effective at treating cancer compared to each treatment on its own.

[0048] Cancer generally includes any of various malignant neoplasms characterized by the proliferation of anaplastic cells that tend to invade surrounding tissue and metastasize to new body sites. Non-limiting examples of different types of cancer suitable for treatment using the compositions of the present disclosure include ovarian cancer, breast cancer, lung cancer (such as non-small-cell lung carcinoma), bladder cancer, thyroid cancer, liver cancer, pleural cancer, pancreatic cancer, cervical cancer, prostate cancer, testicular cancer, colon cancer, anal cancer, colorectal cancer, bile duct cancer, gastrointestinal carcinoid tumors, esophageal cancer, gall bladder cancer, rectal cancer, appendix cancer, small intestine cancer, stomach (gastric) cancer, renal cancer (*i.e.,* renal cell carcinoma), cancer of the central nervous system, skin cancer, choriocarcinomas, head and neck cancers, bone cancer, osteogenic sarcomas, fibrosarcoma, neuroblastoma, glioma, melanoma, leukemia (*e.g.,* acute lymphocytic leukemia, chronic lymphocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, or hairy

cell leukemia), lymphoma (*e.g.*, non-Hodgkin's lymphoma, Hodgkin's lymphoma, B-cell lymphoma, or Burkitt's lymphoma), and multiple myeloma.

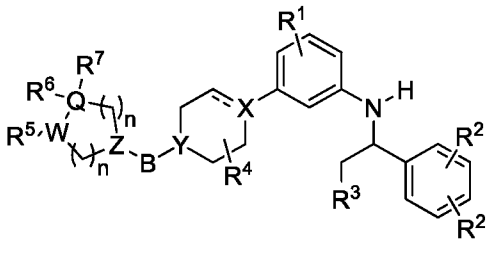
[0049] In some embodiments, the cancer is lung cancer (*e.g.*, non-small-cell lung carcinoma), melanoma, an epithelial cancer (*e.g.*, prostate cancer, ovarian cancer, breast cancer), or a blood cancer (*e.g.*, leukemia, lymphoma, multiple myeloma).

[0050] In some embodiments, the cancer is a solid cancer. In some embodiments, the cancer is pancreatic cancer. In some embodiments, the cancer is colon cancer.

A. CCR4 Antagonists

[0051] CCR4 antagonists are compounds that reduce or inhibit CCR4 activity. There are a number of such compounds known in the art. In some embodiments, the CCR4 antagonists of the present disclosure are selective CCR4 antagonists.

[0052] In some embodiments, the CCR4 antagonists is a small molecule inhibitor of CCR4 having the Formula (I):



(I)

and a pharmaceutically acceptable salt thereof, wherein

R^1 is selected from hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} hydroxyalkyl, C_{3-8} cycloalkyl, halogen, -CN, $-SO_2Me$ and $-C(O)NH_2$;

each R^2 is selected from C_{1-8} alkyl, C_{1-8} haloalkyl, halogen, -CN and C_{1-8} alkoxy; or two R^2 groups attached to adjacent carbon atoms are optionally connected to form a 5 or 6 member ring (aliphatic or aromatic, cycloalkyl or heterocycloalkyl);

R^3 is selected from hydrogen, methyl and C_{1-4} haloalkyl;

R^4 is selected from hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl and C_{1-8} hydroxyalkyl;

each of the subscripts n is independently an integer from 0 to 3;

B is a bond or C(O);

Q is a selected from C, CH, N, O, S, S(O), and SO_2;

W, X, Y, and Z are independently selected from C, CH and N, but Q and W are not both N;

R^5 and R^6 are absent or are independently selected from H, -OH, C_{1-8} alkyl, C_{1-8} hydroxyalkyl, C_{1-4} alkoxy-C_{1-4} alkyl, -C(O)NR^aR^b, C_{1-8} alkylene-C(O)NR^aR^b, -NH-C_{1-4} alkylene-C(O)NR^aR^b, -C(O)-C_{1-4} alkylene-NR^aR^b, -CO_2H and acid isosteres, C_{1-8} alkylene-CO_2H and acid isosteres, -N(R^a)C(O)NR^aR^b, C_{1-8} alkylene-N(R^a)C(O)NR^aR^b, -NR^aR^b, C_{1-8} alkylene-NR^aR^b, C_{1-8} alkoxy, -C(O)OR^a, C_{1-8} alkylene-C(O)OR^a, -CN, -C(O)R^a, -SO_2R^a and -N(R^a)C(O)R^b;

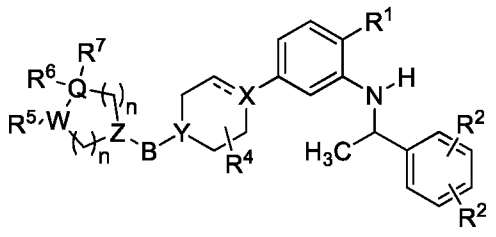
wherein

each R^a and R^b are independently selected from hydrogen, C_{1-8} alkyl, C_{1-8} hydroxyalkyl, C_{1-8} haloalkyl, and C_{1-8} alkoxy; and

R^7 is absent or is selected from H, C_{1-8} alkyl and C_{1-8} haloalkyl.

[0053] In one group of embodiments, the compounds provided herein are those wherein X and Y are not both N. In another group of embodiments, R^3 is H, and each R^2 is independently selected from C_{1-8} alkyl, C_{1-8} haloalkyl, halogen and -CN.

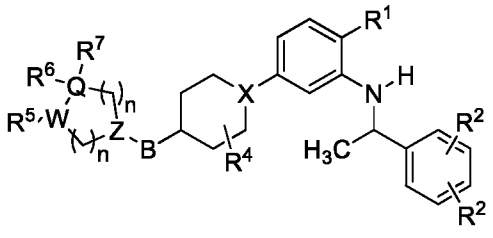
[0054] In another group of embodiments, the compounds provided herein have the formula (Ia):



(Ia)

wherein each of R^1, R^2, R^4, R^5, R^6, R^7, X, Y, Z, W, Q, B and the subscripts n, are as described for formula I. In selected embodiments, X is C or CH.

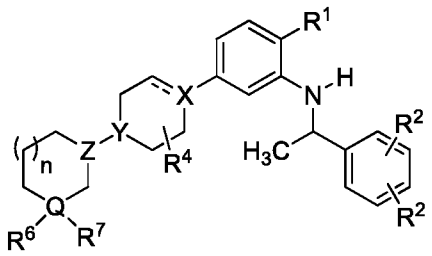
[0055] In another group of embodiments, the compounds provided herein have the formula (Ib):



(Ib)

wherein each R^2 is selected from C_{1-8} alkyl, C_{1-8} haloalkyl, halogen and –CN, and each of R^1, R^4, R^5, R^6, R^7, X, Z, W, Q, B and the subscripts n, are as described for formula I.

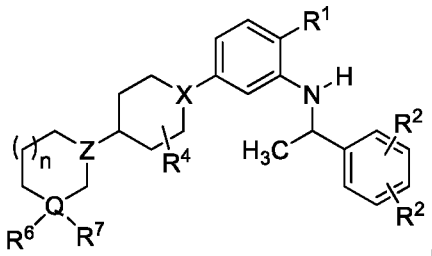
[0056] In another group of embodiments, the compounds provided herein have the formula (Ic):



(Ic)

wherein each R^2 is selected from C_{1-8} alkyl, C_{1-8} haloalkyl, halogen and –CN; the subscript n is 0 or 1; and each of R^1, R^4, R^6, R^7, X, Y, Z, and Q, are as described for formula I. In selected embodiments, n is 1, and R^4 is hydrogen or methyl.

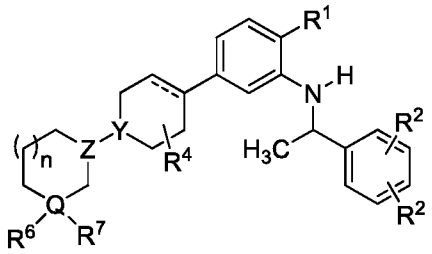
[0057] In another group of embodiments, the compounds provided herein have the formula (Id):



(Id)

wherein each R^2 is a member selected from C_{1-8} alkyl, C_{1-8} haloalkyl, halogen and –CN; the subscript n is 0 or 1, and each of R^1, R^4, R^6, R^7, X, Z, and Q, are as described for formula I. In selected embodiments, n is 1, and R^4 is hydrogen or methyl.

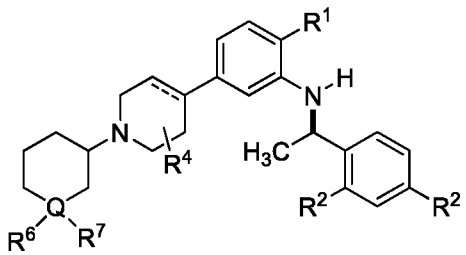
[0058] In another group of embodiments, the compounds provided herein have the formula (Ie):



(Ie)

wherein each R^2 is selected from C_{1-8} alkyl, C_{1-8} haloalkyl, halogen and –CN; the subscript n is 0 or 1; and each of R^1, R^4, R^6, R^7, Y, Z, and Q, are as described for formula I. In selected embodiments, n is 1, and R^4 is hydrogen or methyl.

[0059] In another group of embodiments, the compounds provided herein have the formula (If):



(If)

wherein each R^2 is selected from C_{1-8} alkyl, C_{1-8} haloalkyl, halogen and –CN; and each of R^1, R^4, R^6, R^7, and Q, are as described for formula I. In selected embodiments, R^4 is hydrogen or methyl.

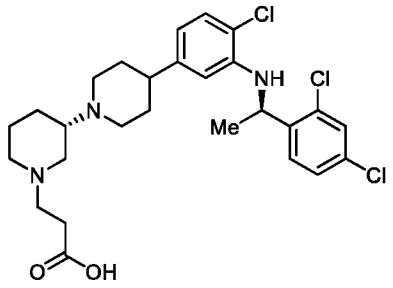
[0060] In still other embodiments, compounds are provided having formulae (I), (Ia), and (Ib), including specific embodiments provided above, wherein B is C(O). Still further, compounds are provided wherein the ring having Z as a ring vertex is selected from pyrrolidine and piperidine. In selected embodiments, compounds are provided wherein the ring having Z as a ring vertex is selected from pyrrolidin-2-yl and piperidin-2-yl, and at least one of R^5, R^6 and R^7 is other than hydrogen

[0061] In yet other embodiments, compounds are provided having formulae (I), (Ia), and (Ib), including specific embodiments provided above, wherein B is a bond. In related embodiments, B is a bond and the ring having Z as a ring vertex is selected from pyrrolidine, piperidine and cyclohexane. In specific embodiments, B is a bond and the ring having Z as a ring vertex is selected from pyrrolidin-1-yl, pyrrolidin-2-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl and cyclohexane. In still other embodiments, B is a bond and the ring having Z as a ring vertex is

selected from the group consisting of pyrrolidin-1-yl, pyrrolidin-2-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl and cyclohexane; and at least one of R^5, R^6 and R^7 is other than hydrogen.

[0062] In one group of embodiments, Z is CH or N.

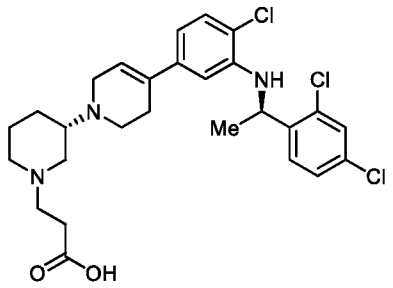
[0063] In some embodiments, the CCR4 antagonist has the formula



(Compound 1)

or a pharmaceutically acceptable salt thereof.

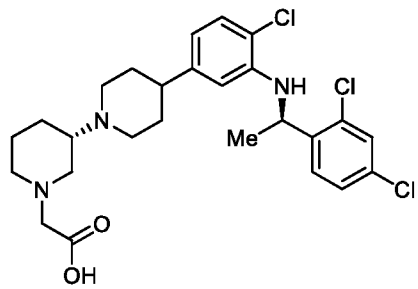
[0064] In some embodiments, the CCR4 antagonist has the formula



(Compound 2)

or a pharmaceutically acceptable salt thereof.

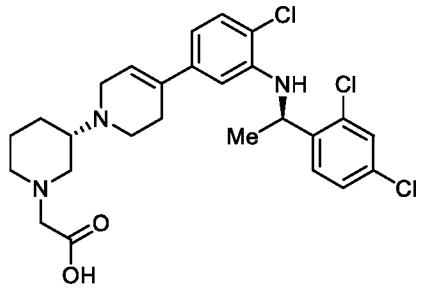
[0065] In some embodiments, the CCR4 antagonist has the formula



(Compound 3)

or a pharmaceutically acceptable salt thereof.

[0066] In some embodiments, the CCR4 antagonist has the formula



(Compound 4)

or a pharmaceutically acceptable salt thereof.

[0067] In some embodiments, the CCR4 antagonist is selected from the compounds or pharmaceutical compositions disclosed in WO 2013/082490 filed by ChemoCentryx. The contents of which is incorporated herein for all purposes.

B. Immune Checkpoint Inhibitors

[0068] Immune checkpoints are signaling proteins that stimulate or inhibit an immune response. Compositions that target immune checkpoints modulate these proteins to alter an individuals natural immune response. This targeted approach is useful because particular cancer cells can circumvent these checkpoints to evade an otherwise natural immune response. Two particular immune checkpoints are programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4).

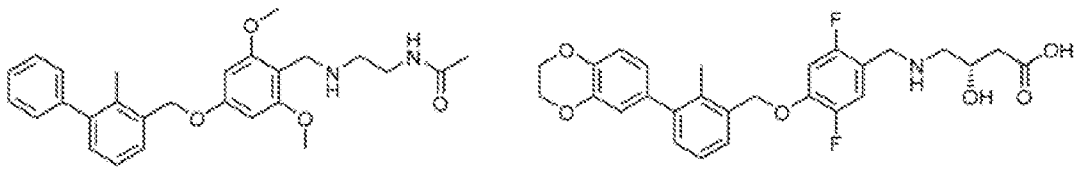
i. PD-1 inhibitors

[0069] Programmed cell death protein-1 (PD-1) is an immune checkpoint protein most commonly found on T cells. Normally, PD-1 binds to its natural ligands PD-L1 and PD-L2, expressed on the surface of different cells. When associated its natural ligand, the T cells is considered to be in the "off" position. Notably, number of cancer cells express unusually high levels of PD-L1, meaning that T cell activity and associated anticancer immune response is aberrantly suppressed. Critically, the use of PD-1 inhibitors that blocks the interaction with it's natural ligands stimulates an immune response to help fight the cancer.

[0070] PD-1 inhibitors of the present disclosure include small molecules and antibodies.

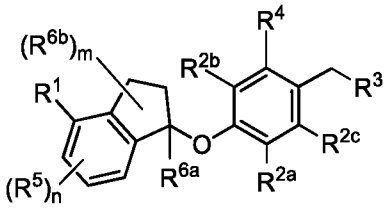
[0071] In some embodiments, the PD-1 inhibitor is a small molecule PD-1/PD-L1 inhibitor.

[0072] In some embodiments, the small molecule PD-1/PD-L1 inhibitor has the formula:



or .

[0073] In some embodiments, the small molecule PD-1/PD-L1 inhibitor is a compound having the Formula (II)



(II)

or a pharmaceutically acceptable salt thereof; wherein:

R^1 is selected from the group consisting of halogen, C_{5-8} cycloalkyl, C_{6-10} aryl and thienyl, wherein the C_{6-10} aryl and thienyl are optionally substituted with 1 to 5 R^x substituents;

each R^x is independently selected from the group consisting of halogen, -CN, -R^c, -CO_2R^a, -$CONR^aR^b$, -$C(O)R^a$, -$OC(O)NR^aR^b$, -$NR^bC(O)R^a$, -$NR^bC(O)_2R^c$, -NR^a-$C(O)NR^aR^b$, -NR^aR^b, -OR^a, -O-X^1-OR^a, -O- X^1-CO_2R^a, -O-X^1-$CONR^aR^b$, -X^1-OR^a, -X^1-NR^aR^b, - X^1-CO_2R^a, -X^1-$CONR^aR^b$, -SF_5, and -$S(O)_2NR^aR^b$, wherein each X^1 is a C_{1-4} alkylene; each R^a and R^b is independently selected from hydrogen, C_{1-8} alkyl, and C_{1-8} haloalkyl, or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O or S, wherein the five or six-membered ring is optionally substituted with oxo; each R^c is independently selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl and C_{1-8} haloalkyl; and optionally when two R^x substituents are on adjacent atoms, they are combined to form a fused five, six or seven-membered carbocyclic or heterocyclic ring optionally substituted with from 1 to 3 substituents independently selected from halo, oxo, C_{1-8} haloalkyl and C_{1-8} alkyl;

each R^{2a}, R^{2b} and R^{2c} is independently selected from the group consisting of H, halogen, -CN, -R^d, -CO_2R^e, -$CONR^eR^f$, -$C(O)R^e$, -$OC(O)NR^eR^f$, -$NR^fC(O)R^e$, -$NR^fC(O)_2R^d$,

$-NR^e-C(O)NR^eR^f$, $-NR^eR^f$, $-OR^e$, $-O-X^2-OR^e$, $-O-X^2-NR^eR^f$, $-O-X^2-CO_2R^e$, $-O-X^2-CONR^eR^f$, $-X^2-OR^e$, $-X^2-NR^eR^f$, $-X^2-CO_2R^e$, $-X^2-CONR^eR^f$, $-SF_5$, $-S(O)_2NR^eR^f$, C_{6-10} aryl and C_{5-10} heteroaryl, wherein each X^2 is a C_{1-4} alkylene; each R^e and R^f is independently selected from hydrogen, C_{1-8} alkyl, and C_{1-8} haloalkyl, or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O and S, and optionally substituted with oxo; each R^d is independently selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, and C_{1-8} haloalkyl;

R^3 is selected from the group consisting of $-NR^gR^h$ and C_{4-12} heterocyclyl, wherein the C_{4-12} heterocyclyl is optionally substituted with 1 to 6 R^y;

each R^y is independently selected from the group consisting of halogen, -CN, $-R^i$, $-CO_2R^j$, $-CONR^jR^k$, $-CONHC_{1-6}$ alkyl-OH, $-C(O)R^j$, $-OC(O)NR^jR^k$, $-NR^jC(O)R^k$, $-NR^jC(O)_2R^k$, CONOH, PO_3H_2, $-NR^j-C_{1-6}$ alkyl-$C(O)_2R^k$, $-NR^jC(O)NR^jR^k$, $-NR^jR^k$, $-OR^j$, $-S(O)_2NR^jR^k$, $-O-C_{1-6}$alkyl-OR^j, $-O-C_{1-6}$ alkyl-NR^jR^k, $-O-C_{1-6}$ alkyl-CO_2R^j, $-O-C_{1-6}$ alkyl-$CONR^jR^k$, $-C_{1-6}$ alkyl-OR^j, - C_{1-6} alkyl-NR^jR^k, $-C_{1-6}$ alkyl-CO_2R^j, $-C_{1-6}$ alkyl-$CONR^jR^k$, and SF_5,

wherein the C_{1-6} alkyl portion of R^y is optionally further substituted with OH, SO_2NH_2, $CONH_2$, CONOH, PO_3H_2, COO-C_{1-8}alkyl or CO_2H, wherein each R^j and R^k is independently selected from hydrogen, C_{1-8} alkyl optionally substituted with 1 to 2 substituents selected from OH, SO_2NH_2, $CONH_2$, CONOH, PO_3H_2, COO-C_{1-8}alkyl or CO_2H, and C_{1-8} haloalkyl optionally substituted with 1 to 2 substituents selected from OH, SO_2NH_2, $CONH_2$, CONOH, PO_3H_2, COO-C_{1-8}alkyl or CO_2H, or when attached to the same nitrogen atom R^j and R^k can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O or S, and optionally substituted with oxo; each R^i is independently selected from the group consisting of –OH, C_{1-8} alkyl, C_{2-8} alkenyl, and C_{1-8} haloalkyl each of which may be optionally substituted with OH, SO_2NH_2, $CONH_2$, CONOH, PO_3H_2, COO-C_{1-8}alkyl or CO_2H;

R^g is selected from the group consisting of H, C_{1-8} haloalkyl and C_{1-8} alkyl;

R^h is selected from -C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkyl-COOH, C_{1-8} alkyl-OH, C_{1-8} alkyl-$CONH_2$, C_{1-8} alkyl-SO_2NH_2, C_{1-8} alkyl-PO_3H_2, C_{1-8} alkyl-CONOH, C_{1-8} alkyl-$NR^{h1}R^{h2}$, -

$C(O)$-C_{1-8}alkyl, -$C(O)$-C_{1-8}alkyl-OH, -$C(O)$-C_{1-8}alkyl-COOH, C_{3-10} cycloalkyl,-C_{3-10} cycloalkyl-COOH, -C_{3-10} cycloalkyl-OH, C_{4-8} heterocyclyl, -C_{4-8} heterocyclyl-COOH, -C_{4-8} heterocyclyl-OH, -C_{1-8} alkyl-C_{4-8} heterocyclyl, -C_{1-8} alkyl-C_{3-10} cycloalkyl, C_{5-10} heteroaryl, -C_{1-8}alkyl-C_{5-10} heteroaryl, C_{10} carbocyclyl, -C_{1-8} alkyl-C_{6-10} aryl, -C_{1-8} alkyl-$(C=O)$-C_{6-10} aryl, -C_{1-8} alkyl-NH$(C=O)$-C_{1-8} alkenyl , -C_{1-8} alkyl-NH$(C=O)$-C_{1-8} alkyl, -C_{1-8} alkyl-NH$(C=O)$-C_{1-8} alkynyl, -C_{1-8} alkyl-$(C=O)$-NH-C_{1-8} alkyl-COOH, and -C_{1-8} alkyl-$(C=O)$-NH-C_{1-8} alkyl-OH optionally substituted with CO_2H; or

R^h combined with the N to which it is attached is a mono-, di- or tri-peptide comprising 1-3 natural amino acids and 0-2 non-natural amino acids, wherein

the non-natural aminoacids have an alpha carbon substituent selected from the group consisting of C_{2-4} hydroxyalkyl, C_{1-3} alkyl-guanidinyl, and C_{1-4} alkyl-heteroaryl,

the alpha carbon of each natural or non-natural amino acids are optionally further substituted with a methyl group, and

the terminal moiety of the mono-, di-, or tri-peptide is selected from the group consisting of C(O)OH, C(O)O-C_{1-6} alkyl, and PO_3H_2, wherein

R^{h1} and R^{h2} are each independently selected from the group consisting of H, C_{1-6} alkyl, and C_{1-4} hydroxyalkyl;

the C_{1-8} alkyl portions of R^h are optionally further substituted with from 1 to 3 substituents independently selected from OH, COOH, SO_2NH_2, $CONH_2$, CONOH, COO-C_{1-8} alkyl, PO_3H_2 and C_{5-6} heteroaryl optionally substituted with 1 to 2 C_{1-3} alkyl substituents,

the C_{10} carbocyclyl, C_{5-10} heteroaryl and the C_{6-10} aryl portions of R^h are optionally substituted with 1 to 3 substituents independently selected from OH, $B(OH)_2$, COOH, SO_2NH_2, $CONH_2$, CONOH, PO_3H_2, COO-C_{1-8}alkyl, C_{1-4}alkyl, C_{1-4}alkyl-OH, C_{1-4}alkyl-SO_2NH_2, C_{1-4}alkyl $CONH_2$, C_{1-4}alkyl-CONOH, C_{1-4}alkyl- PO_3H_2, C_{1-4}alkyl-COOH, and phenyl and

the C_{4-8} heterocyclyl and C_{3-10} cycloalkyl portions of R^h are optionally substituted with 1 to 4 R^w substituents;

each R^w substituent is independently selected from C_{1-4} alkyl, C_{1-4} alkyl-OH, C_{1-4} alkyl-COOH, C_{1-4} alkyl-SO_2NH_2, C_{1-4} alkyl $CONH_2$, C_{1-4} alkyl- CONOH, C_{1-4} alkyl-PO_3H, OH, COO-C_{1-8} alkyl, COOH, SO_2NH_2, $CONH_2$, CONOH, PO_3H_2 and oxo;

R^4 is selected from the group consisting of O-C_{1-8} alkyl, O-C_{1-8} haloalkyl, O-C_{1-8} alkyl-R^z, C_{6-10} aryl, C_{5-10} heteroaryl , -O-C_{1-4} alkyl-C_{6-10}aryl and -O-C_{1-4} alkyl-C_{5-10} heteroaryl, wherein the C_{6-10} aryl and the C_{5-10} heteroaryl are optionally substituted with 1 to 5 R^z;

each R^z is independently selected from the group consisting of halogen, -CN, -R^m, -CO_2R^n, -$CONR^nR^p$, -$C(O)R^n$, -$OC(O)NR^nR^p$, -$NR^nC(O)R^p$, -$NR^nC(O)_2R^m$, -NR^n-$C(O)NR^nR^p$, -NR^nR^p, -OR^n, -O-X^3-OR^n , -O-X^3-NR^nR^p, -O- X^3-CO_2R^n, -O-X^3-$CONR^nR^p$, -X^3-OR^n, -X^3-NR^nR^p, - X^3-CO_2R^n, -X^3-$CONR^nR^p$, -SF_5, -$S(O)_2R^nR^p$, -$S(O)_2NR^nR^p$, and three to seven-membered carbocyclic or four to seven-membered heterocyclic ring wherein the three to seven-membered carbocyclic or four to seven-membered heterocyclic ring is optionally substituted with 1 to 5 R^t, wherein each R^t is independently selected from the group consisting of C_{1-8} alkyl, C_{1-8}haloalkyl, -CO_2R^n, -$CONR^nR^p$, -$C(O)R^n$, -$OC(O)NR^nR^p$, -$NR^nC(O)R^p$, -$NR^nC(O)_2R^m$, -NR^n-$C(O)NR^nR^p$, -NR^nR^p, -OR^n, -O-X^3-OR^n , -O-X^3-NR^nR^p, -O- X^3-CO_2R^n, -O-X^3-$CONR^nR^p$, -X^3-OR^n, -X^3-NR^nR^p, - X^3-CO_2R^n, -X^3-$CONR^nR^p$, -SF_5, and -$S(O)_2NR^nR^p$;

wherein each X^3 is a C_{1-4} alkylene; each R^n and R^p is independently selected from hydrogen, C_{1-8} alkyl, and C_{1-8} haloalkyl, or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O or S, and optionally substituted with oxo; each R^m is independently selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, and C_{1-8} haloalkyl; and optionally when two R^z substituents are on adjacent atoms, they are combined to form a fused five or six-membered carbocyclic or heterocyclic ring optionally substituted with oxo;

n is 0, 1, 2 or 3;

each R^5 is independently selected from the group consisting of halogen, -CN, -R^q, -CO_2R^r, -$CONR^rR^s$, -$C(O)R^r$, -$OC(O)NR^rR^s$, -$NR^rC(O)R^s$, -$NR^rC(O)_2R^q$, -NR^r-$C(O)NR^rR^s$, -NR^rR^s, -OR^r, -O-X^4-OR^r , -O-X^4-NR^rR^s, -O- X^4-CO_2R^r, -O-X^4-$CONR^rR^s$, -X^4-OR^r, -X^4-NR^rR^s, -X^4-CO_2R^r, -X^4-$CONR^rR^s$, -SF_5, -$S(O)_2NR^rR^s$, wherein each X^4 is a C_{1-4} alkylene; each R^r and R^s is independently selected from hydrogen, C_{1-8} alkyl, and C_{1-8} haloalkyl, or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as

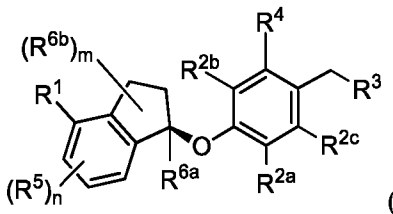
ring members selected from N, O or S, and optionally substituted with oxo; each R^q is independently selected from the group consisting of C_{1-8} alkyl, and C_{1-8} haloalkyl;

R^{6a} is selected from the group consisting of H, C_{1-4} alkyl and C_{1-4} haloalkyl;

each R^{6b} is independently selected from the group consisting of F, C_{1-4} alkyl, O-R^u, C_{1-4} haloalkyl, NR^uR^v, wherein each R^u and R^v is independently selected from hydrogen, C_{1-8} alkyl, and C_{1-8} haloalkyl, or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O or S, and optionally substituted with oxo; and

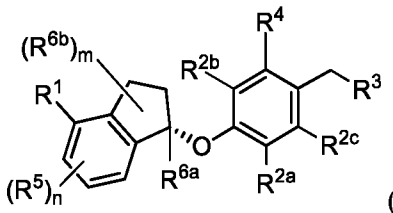
m is 0, 1, 2, 3 or 4.

[0074] In some embodiments, the compound, or a pharmaceutically acceptable salt thereof has the formula (IIa)



(IIa) .

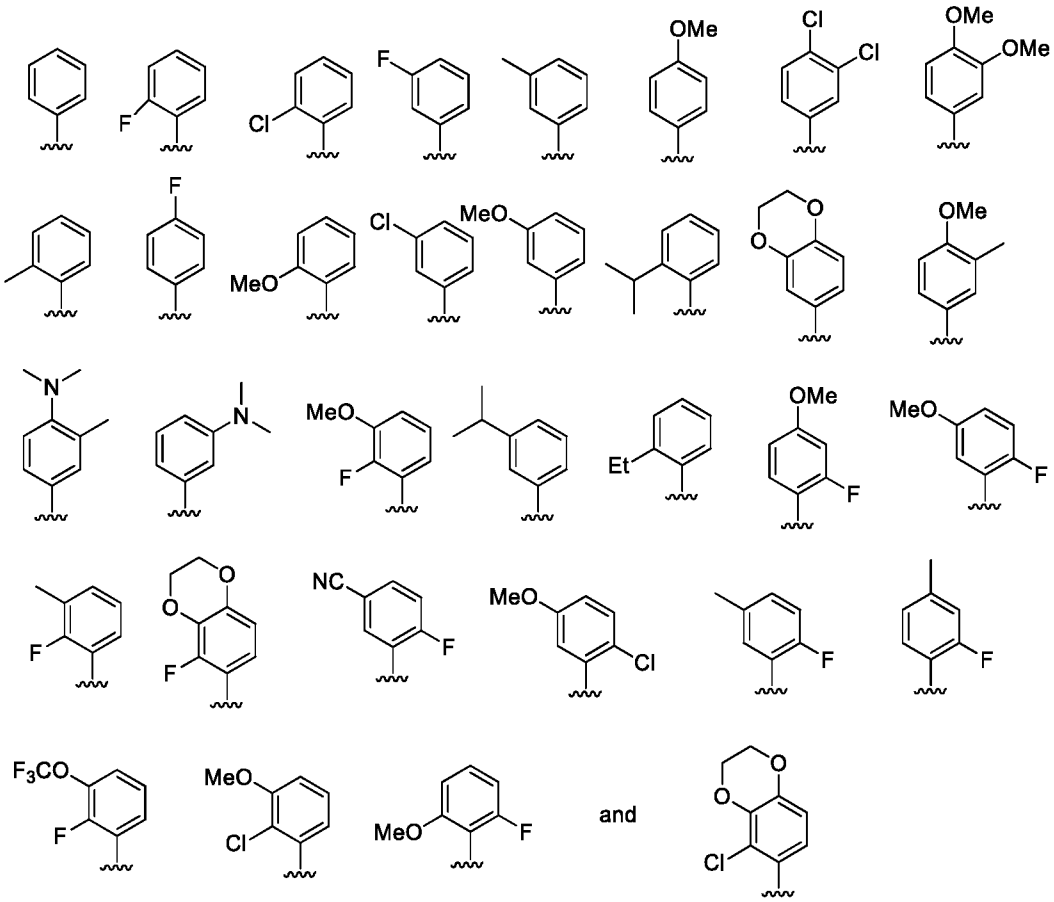
[0075] In some embodiments, the compound, or a pharmaceutically acceptable salt thereof having the formula (IIb)



(IIb) .

[0076] In some embodiments, R^1 is selected from the group consisting of phenyl and thienyl, wherein the phenyl and thienyl are optionally substituted with 1 to 5 R^x substituents. In some embodiments, R^1 is phenyl optionally substituted with 1 or 2 R^x wherein each R^x is independently selected from halogen, C_{1-8} alkyl, O-C_{1-8} alkyl, O-C_{1-8} haloalkyl, -NR^aR^b, and CN, and optionally when two R^x substituents are on adjacent atoms, they are combined to form a fused six-membered heterocyclic ring optionally substituted with from 1 to 3 substituents independently selected from oxo, C_{1-8} haloalkyl and C_{1-8} alkyl. In some embodiments, R^1 is

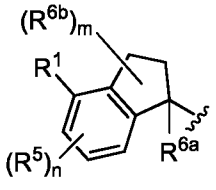
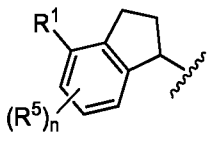
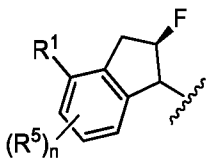
phenyl optionally substituted with F. In some embodiments, R^1 is selected from the group consisting of:

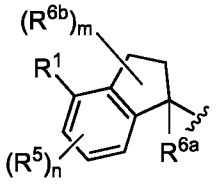
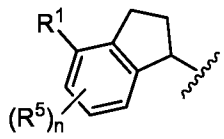


[0077] In some embodiments, each R^{2a}, R^{2b} and R^{2c} is independently selected from the group consisting of H, halogen, -CN, -R^d, -NR^eR^f, -OR^e, -X^2-OR^e, -X^2-NR^eR^f, wherein X^2 is C_{1-4} alkylene; each R^e and R^f is independently selected from hydrogen, C_{1-8} alkyl, and C_{1-8} haloalkyl, or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O or S, and optionally substituted with oxo; each R^d is independently selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, and C_{1-8} haloalkyl. In some embodiments, R^{2b} and R^{2c} are both H and R^{2a} is selected from the group consisting of halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-3} haloalkyl, -CN, -OMe and OEt. In some embodiments, R^{2b} and R^{2c} are both H and R^{2a} is halogen. In some embodiments, R^{2b} and R^{2c} are both H and R^{2a} is Cl.

[0078] In some embodiments, n is 0, 1 or 2 and each R^5 is independently selected from the group consisting of halogen, -CN, $-R^q$, $-NR^rR^s$, and $-OR^r$, wherein each R^r and R^s is independently selected from hydrogen, C_{1-8} alkyl and C_{1-8} haloalkyl and each R^q is independently selected from the group consisting of C_{1-8} alkyl and C_{1-8} haloalkyl. In some embodiments, n is 0.

[0079] In some embodiments, R^{6a} is H. In some embodiments, m is 0. In some embodiments, m is 1 and R^{6b} is selected from the group consisting of F, C_{1-4} alkyl, $O-R^u$, C_{1-4} haloalkyl and NR^uR^v, wherein each R^u and R^v is independently selected from hydrogen, C_{1-8} alkyl, and C_{1-8} haloalkyl. In some embodiments, m is 1 and R^{6b} is F.

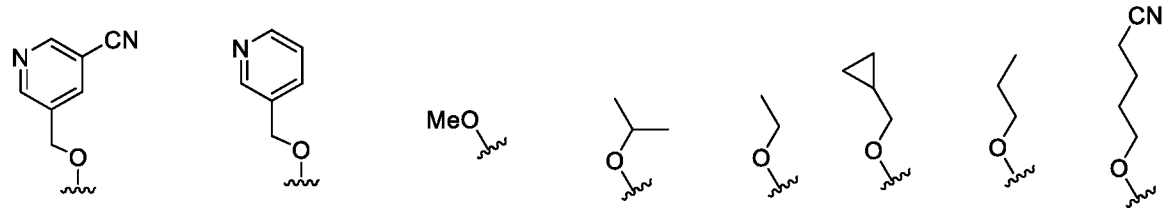
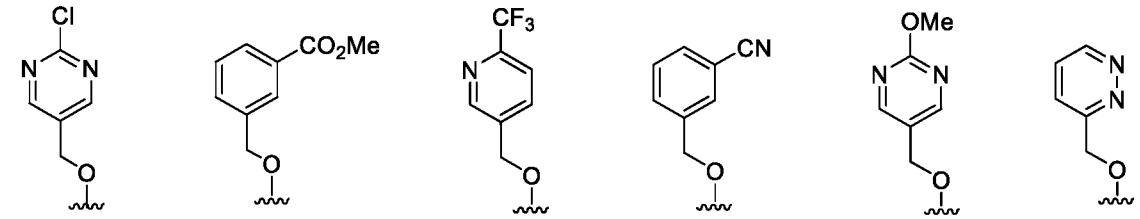
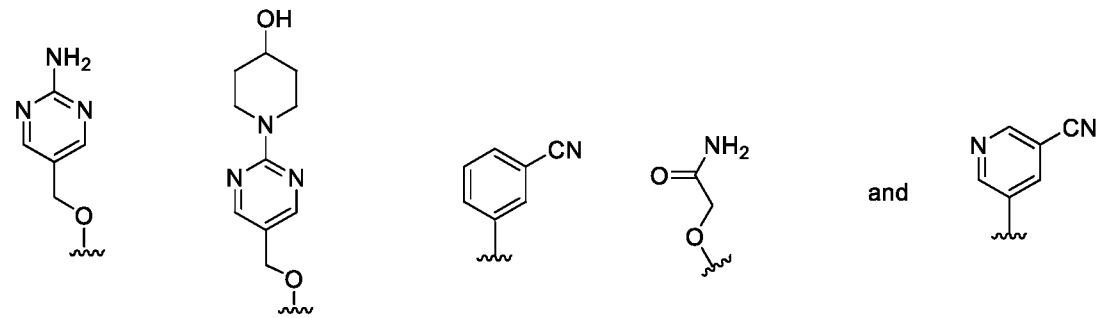
[0080] In some embodiments,  is  or .

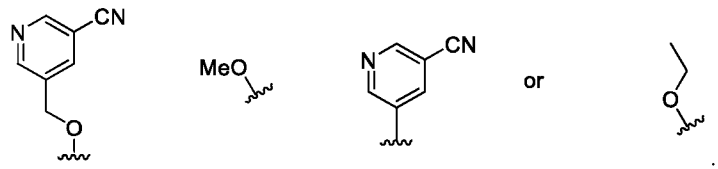
[0081] In some embodiments,  is .

[0082] In some embodiments, R^4 is selected from the group consisting of $O-C_{1-4}$ alkyl, $O-C_{1-6}$ alkyl-R^z, C_{6-10} aryl, C_{5-10} heteroaryl , $-O-C_{1-4}$ alkyl-C_{6-10}aryl and $-O-C_{1-4}$ alkyl-C_{5-10} heteroaryl, wherein the C_{6-10} aryl and the C_{5-10} heteroaryl are optionally substituted with 1 to 2 R^z, wherein each R^z is independently selected from the group consisting of halogen, -CN, $-R^m$, $-CO_2R^n$, $-CONR^nR^p$, $-C(O)R^n$, $-OC(O)NR^nR^p$, $-NR^nC(O)R^p$, $-NR^nC(O)_2R^m$, $-NR^n-C(O)NR^nR^p$, $-NR^nR^p$, $-OR^n$, $-S(O)_2NR^nR^p$, three to seven-membered carbocyclic ring and four to seven-membered heterocyclic ring wherein the three to seven-membered carbocyclic or four to seven-membered heterocyclic ring is optionally substituted with 1 to 2 R^t, wherein each R^t is independently selected from the group consisting of C_{1-8} alkyl, C_{1-8}haloalkyl, $-CO_2R^n$, $-CONR^nR^p$, $-C(O)R^n$, $-OC(O)NR^nR^p$, $-NR^nC(O)R^p$, $-NR^nC(O)_2R^m$, $-NR^n-C(O)NR^nR^p$, $-NR^nR^p$, $-OR^n$, and $-S(O)_2NR^nR^p$. In some embodiments, R^4 is selected from the group consisting of $O-C_{1-4}$ alkyl, $O-C_{1-6}$ alkyl-CN, phenyl, pyridinyl , $-O-C_{1-2}$ alkyl-pyridinyl, $-O-C_{1-2}$ alkyl-pyrimidinyl, $-O-C_{1-2}$ alkyl- pyridazinyl, and $-O-C_{1-2}$ alkyl-phenyl, wherein the pyridinyl, phenyl, pyrimidinyl and pyridazinyl is optionally substituted with 1 to 2 R^z, wherein each R^z is independently selected

from the group consisting of halogen, -CN, $-CO_2R^n$, $-NR^nR^p$, $-OR^n$, and piperidinyl optionally substituted with OH.

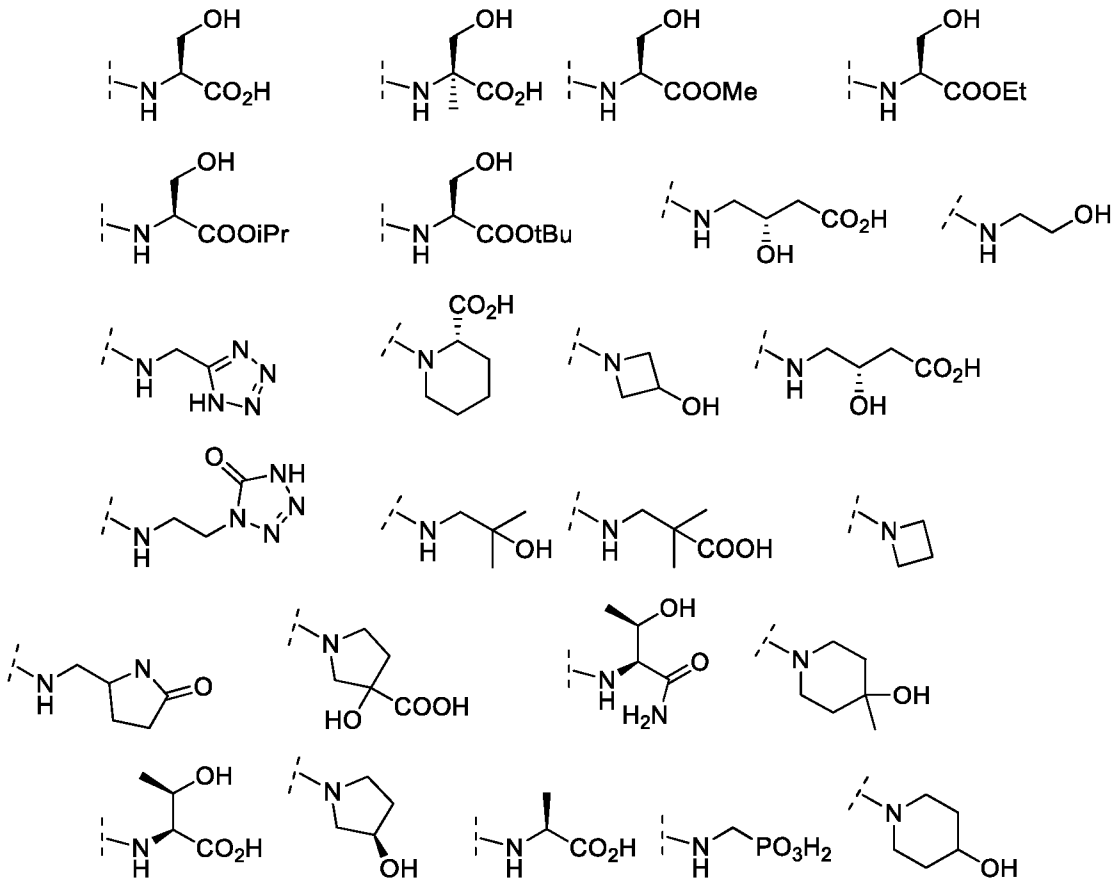
[0083] In some embodiments, R^4 is selected from the group consisting of:

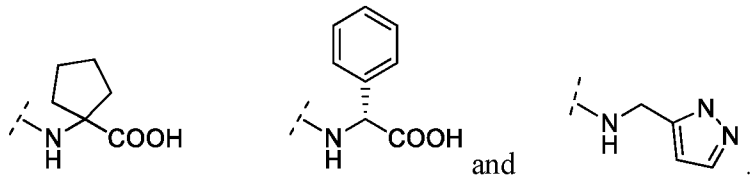




[0084] In some embodiments, R^4 is .

[0085] In some embodiments, R^3 is selected from the group consisting of NR^gR^h and C_{4-6} heterocyclyl wherein the C_{4-6} heterocyclyl is optionally substituted with 1 to 3 R^y, wherein R^g is selected from the group consisting of H, C_{1-8} haloalkyl and C_{1-8} alkyl, and wherein R^h is $-C_{1-8}$ alkyl substituted with from 1 to 3 substituents independently selected from OH, COOH, SO_2NH_2, $CONH_2$, CONOH, $COO-C_{1-8}$ alkyl, C_{5-6} heteroaryl, C_{5-6} heterocyclyl and PO_3H_2, wherein the C_{5-6} heteroaryl and the C_{5-6} heterocyclyl are optionally substituted with 1 to 3

substituents independently selected from OH, $B(OH)_2$, COOH, SO_2NH_2, $CONH_2$, CONOH, PO_3H_2, COO-C_{1-8}alkyl, C_{1-4}alkyl, C_{1-4}alkyl-OH, C_{1-4}alkyl-SO_2NH_2, C_{1-4}alkyl $CONH_2$, C_{1-4}alkyl-CONOH, C_{1-4}alkyl- PO_3H_2, and C_{1-4}alkyl-COOH and wherein the C_{5-6} heterocyclyl is additionally optionally substituted with oxo. In some embodiments, R^3 is selected from the group consisting of azetidinyl, pyrrolidinyl and piperidinyl, wherein the azetidinyl, pyrrolidinyl or piperidinyl is linked through the nitrogen atom and wherein the azetidinyl, pyrrolidinyl or piperidinyl is optionally substituted with 1 to 3 R^y, wherein each R^y is independently selected from the group consisting of -CO_2H, CONOH, PO_3H_2, OH, SO_2NH_2, $CONH_2$, and COO-C_{1-8}alkyl. In some embodiments, R^3 is NHR^h, wherein R^h is -C_{1-8} alkyl substituted with from 1 to 2 substituents independently selected from OH, COOH, $CONH_2$, PO_3H_2, tetrazolyl, tetrazolonyl, and pyrazolyl. In some embodiments, R^3 is selected from the group consisting of:





[0086] In some embodiments, R^3 is $-NR^gR^h$. In some embodiments, R^h combined with the N to which it is attached is a mono-, di- or tri-peptide comprising 1-3 natural amino acids and 0-2 non-natural amino acids, wherein

the non-natural aminoacids have an alpha carbon substituent selected from the group consisting of C_{2-4} hydroxyalkyl, C_{1-3} alkyl-guanidinyl, and C_{1-4} alkly-heteroaryl,

the alpha carbon of each natural or non-natural amino acids are optionally further substituted with a methyl group, and

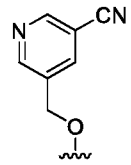
the terminal moiety of the mono-, di-, or tri-peptide is selected from the group consisting of C(O)OH, C(O)O-C_{1-6} alkyl, and PO_3H_2.

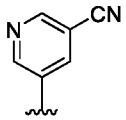
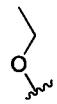
[0087] In some embodiments, each natural amino acid of R^h is independently selected from the group consisting of serine, alanine, glycine, lysine, argining, threonine, phenylalanine, tyrosine, asparatate, asparagine, histidine, and leucine.

[0088] In some embodiments, R^1 is phenyl optionally substituted with 1 to 3 R^x, R^{6a} is H, R^4 is selected from the group consisting of O-C_{1-4} alkyl, O-C_{1-6} alkyl-CN, phenyl, pyridinyl , -O-C_{1-2} alkyl-pyridinyl, -O-C_{1-2} alkyl-pyrimidinyl, -O-C_{1-2} alkyl- pyridazinyl, and -O-C_{1-2} alkyl-phenyl, wherein the pyridinyl, phenyl, pyrimidinyl and pyridazinyl is optionally substituted with 1 to 2 R^z, wherein each R^z is independently selected from the group consisting of halogen, -CN, $-CO_2R^n$, $-NR^nR^p$, $-OR^n$, and piperidinyl optionally substituted with OH, and R^3 is selected from the group consisting of NR^gR^h and C_{4-6} heterocyclyl wherein the C_{4-6} heterocyclyl is optionally substituted with 1 to 3 R^y, wherein R^g is selected from the group consisting of H, C_{1-8} haloalkyl and C_{1-8} alkyl, and wherein R^h is -C_{1-8} alkyl substituted with from 1 to 3 substituents independently selected from OH, COOH, SO_2NH_2, $CONH_2$, CONOH, COO-C_{1-8} alkyl, C_{5-6} heteroaryl, C_{5-6} heterocyclyl and PO_3H_2, wherein the C_{5-6} heteroaryl and the C_{5-6} heterocyclyl are optionally substituted with 1 to 3 substituents independently selected from OH, $B(OH)_2$, COOH, SO_2NH_2, $CONH_2$, CONOH, PO_3H_2, COO-C_{1-8}alkyl, C_{1-4}alkyl, C_{1-4}alkyl-OH, C_{1-4}alkyl-SO_2NH_2,

C_{1-4}alkyl $CONH_2$, C_{1-4}alkyl-CONOH, C_{1-4}alkyl- PO_3H_2, and C_{1-4}alkyl-COOH and wherein the C_{5-6} heterocyclyl is additionally optionally substituted with oxo.

[0089] In some embodiments, R^1 is phenyl optionally substituted with 1 or 2 R^x wherein each R^x is independently selected from halogen, C_{1-8} alkyl, O-C_{1-8} alkyl, O-C_{1-8} haloalkyl, -NR^aR^b, and CN, wherein R^{2b} and R^{2c} are both H, R^{2a} is selected from the group consisting of halogen, C_{1-4} alkyl, C_{1-3} haloalkyl, -CN, -OMe and OEt, R^{6a} is H, m is 0, n is 0, R^4 is




or

, and R^3 is selected from the group consisting of NHR^h, azetidinyl, pyrrolidinyl and piperidinyl, wherein the azetidinyl, pyrrolidinyl or piperidinyl is linked through the nitrogen atom and wherein the azetidinyl, pyrrolidinyl or piperidinyl is optionally substituted with 1 to 3 R^y, wherein each R^y is independently selected from the group consisting of CO_2H, CONOH, PO_3H_2, OH, SO_2NH_2, $CONH_2$, and COO-C_{1-8}alkyl, and wherein R^h is C_{1-8} alkyl substituted with from 1 to 2 substituents independently selected from OH, COOH, $CONH_2$, PO_3H_2, tetrazolyl, tetrazolonyl, and pyrazolyl. In some embodiment, R^{2a} is halogen.

[0090] In some embodiments, the small molecule PD-1/PD-L1 inhibitor is selected from the compounds or pharmaceutical compositions disclosed in WO 2018/005374 filed by ChemoCentryx on June 26, 2017. The contents of which is incorporated herein for all purposes.

[0091] In some embodiments, the PD-1 inhibitor is an antibody. In some embodiments, the PD-1 inhibitor antibody is selected from Nivolumab, Pembrolizumab, and Pidilizumab. In some embodiments the PD-1 inhibitor antibody is Nivolumab. In some embodiments the PD-1 inhibitor antibody is Pembrolizumab. In some embodiments the PD-1 inhibitor antibody is Pidilizumab.

[0092] The PD-1 inhibitors of the present disclosure can be prepared using known methods in the art. For example, human monoclonal antibodies of this disclosure can be prepared using SCID mice into which human immune cells have been reconstituted such that a human antibody response can be generated upon immunization. Such mice are described in, for example, U.S. Pat. Nos. 5,476,996 and 5,698,767 to Wilson et al. The PD-1 inhibitors of the present disclosure

can be formulated to retard the degradation of the compound or antibody or to minimize the immunogenicity of the antibody. A variety of techniques are known in the art to achieve this purposes.

ii. CTLA-4 Inhibitors

[0093] Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is an immune checkpoint protein most commonly expressed by activated T cells. Like PD-1, CTLA-4 acts as a negative regulator of T-cell immune function. By providing inhibitors of CTLA-4, the negative regulation is reduced and the antitumor activity of T cells is increased.

[0094] In some embodiments, the CTLA-4 inhibitor is an antibody. In some embodiments, the CLTA-4 inhibitor antibody has a binding affinity of about 10^8 M^{-1} or greater. In some embodiments, the CLTA-4 inhibitor antibody has a binding affinity of about 10^9 M^{-1} or greater. In some embodiments, the CTLA-4 inhibitor antibody inhibits the binding of human CTLA-4 to B7-1 or to B7-2.

[0095] In some embodiments, the CTLA-4 inhibitor antibody is selected from Ipilimumab, Tremelimumab, AGEN1884, and AGEN2041. In some embodiments, the CTLA-4 inhibitor antibody is Ipilimumab. In some embodiments, the CTLA-4 inhibitor antibody is Tremelimumab. In some embodiments, the CTLA-4 inhibitor antibody is AGEN1884. In some embodiments, the CTLA-4 inhibitor antibody is AGEN2041.

[0096] In some embodiments, the CTLA-4 inhibitor is selected from the compounds or pharmaceutical compositions disclosed in WO/2009/100140 or WO 2017/194265. The contents of each is incorporated herein for all purposes.

[0097] The CTLA-4 inhibitors of the present disclosure can be prepared using known methods in the art. For example, human monoclonal antibodies of this disclosure can be prepared using SCID mice into which human immune cells have been reconstituted such that a human antibody response can be generated upon immunization. Such mice are described in, for example, U.S. Pat. Nos. 5,476,996 and 5,698,767 to Wilson et al. The CTLA-4 inhibitors of the present disclosure can also be formulated to retard the degradation of the compound or antibody or to

minimize the immunogenicity of the antibody. A variety of techniques are known in the art to achieve this purposes.

IV. Methods of Administration of Combination Therapy

[0098] In another aspect, the present disclosure provides a combination therapy for the treatment of cancer. The combination therapy includes a therapeutically effective amount of a CCR4 antagonist and a therapeutically effective amount of one or more immune checkpoint inhibitors. In some embodiments, the one or more immune checkpoint inhibitors is a PD-1 inhibitor. In some embodiments, the one or more immune checkpoint inhibitors is a CTLA-4 inhibitor. In some embodiments, the one or more immune checkpoint inhibitors are a PD-1 inhibitor and a CTLA-4 inhibitor. The combination of therapeutic agents act synergistically to affect the treatment or prevention of cancer.

[0099] The term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a cell, tissue, system, or animal, such as a human, that is being sought by the researcher, veterinarian, medical doctor or other treatment provider.

[0100] Depending on the disease status and the subject's condition, the compounds, antibodies, and formulations of the present disclosure may be administered by oral, parenteral (*e.g.*, intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical routes of administration. In addition, the compounds and antibodies may be formulated, alone or together, in suitable dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each rouse of administration. The present disclosure also contemplates administration of the compounds and antibodies of the present disclosure in a depot formulation.

[0101] It will be understood, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, hereditary characteristics, general health, sex, diet, mode and

time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

[0102] Combination therapy includes co-administration of the CCR4 antagonist and the one or more immune checkpoint inhibitors, sequential administration of the CCR4 antagonist and the one or more checkpoint inhibitors, administration of a composition containing the CCR4 antagonist and the one or more checkpoint inhibitors, or simultaneous administration of separate compositions such that one composition contains the CCR4 antagonist and one or more compositions contain the one or more checkpoint inhibitors. In embodiments where two immune checkpoint inhibitors are administered, it is understood that each immune checkpoint inhibitor can be formulated separately or formulated in a single dosage unit.

[0103] Co-administration includes administering the CCR4 antagonist of the present disclosure within 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, or 24 hours of the one or more immune checkpoint inhibitors of the present disclosure. Co-administration also includes administering simultaneously, approximately simultaneously (*e.g.*, within about 1, 5, 10, 15, 20, or 30 minutes of each other), or sequentially in any order. Moreover, the CCR4 antagonist and one or more checkpoint inhibitors can each be administered once a day, or two, three, or more times per day so as to provide the preferred dosage level per day.

V. Kits

[0104] In some aspects, provided herein are kits containing a CCR4 antagonist and one or more immune check-point inhibitors that are useful for treating a cancer. A kit can contain a pharmaceutical composition containing a CCR4 antagonist compound, *e.g.*, a small molecule inhibitor of CCR4 and one or more pharmaceutical composition containing immune checkpoint inhibitors, e.g., an anti-PD-1 inhibitor and/or an anti-CTLA-4 inhibitor. In some instances, the kit includes written materials *e.g.*, instructions for use of the compound, antibody or pharmaceutical compositions thereof. Without limitation, the kit may include buffers, diluents, filters, needles, syringes, and package inserts with instructions for performing any methods disclosed herein.

VI. Examples

Example 1: C-C Chemokine Receptor 4 (CCR4) Antagonism Enhances the Effectiveness of Checkpoint Inhibition in Mouse Tumor Models (Summary)

[0105] Chemokines and their receptors influence many of the hallmark processes in cancer: they act not only on infiltrating leukocytes, but also on fibroblasts, endothelial cells and directly on some types of tumor cells. C-C Chemokine receptor 4 (CCR4) and its ligands have been found to be highly expressed in multiple types of human tumors, and are associated with poor prognosis. CCR4 antagonism has been demonstrated to reduce tumor growth in various mouse tumor models. Here we assess small molecule inhibition of CCR4 as a therapeutic agent to potentiate the effects of checkpoint inhibitors in the CT26 and KCM tumor models.

Methods

[0106] The subcutaneous CT26 colon cancer model and the orthotopic KCM pancreatic cancer model were used to assess the effects of a CCR4 inhibitor, Compound 1, in combination with anti-CTLA-4 antibody (BioXcell: anti-mouse CTLA-4 (Clone: 9H10), raised in Syrian Hamster, purified with protein G). CT26 cells were implanted into the flanks of 9 week female Balb/c mice. Mice were randomized into study groups based on the tumor sizes on day 6, and dosing of both Compound 1 and anti-CTLA-4 started on day 7. For the orthotopic pancreatic cancer model, KCM cells were implanted directly into the pancreas, and dosing of Compound 1 and anti-CTLA-4 also began on day 7. Compound 1 was dosed orally twice daily at 30mg/kg, and anti-CTLA-4 was dosed IP **on days 7, 11 and 15 at 100μg/mouse.**

Results

[0107] Blockade of CCR4 appreciably enhanced the therapeutic effects of anti-CTLA-4 in both models. Combined anti-CTLA-4/CCR4 inhibitor significantly decreased tumor size and increased the proportion of long-term survivors in the CT26 model. The anti-tumor response was CT26-specific; long term survivors were resistant to re-inoculation with CT26 cells (without further dosing of either drug), but 4T1 breast tumors grew well upon challenge of CT26 survivors. Mice with tumor regression exhibited a high proportion of CD8 T cells that recognized a CT26-specific neoantigen, as illustrated by AH1 peptide-MHC tetramer staining.

[0108] Although long term survival has not yet been examined the KCM model, Compound 1 alone significantly reduced tumor burden in 3 independent studies. Anti-CTLA-4 alone provided substantial inhibition of tumor growth in this model, which was further enhanced by Compound 1.

Example 2: Compound 1 is a Highly Potent and Selective CCR4 Inhibitor

[0109] The selectivity of Compound 1 was tested by determining the IC_{50} value against a diverse panel of receptors, enzymes, and ion channels. Compound 1 was found to be highly specific for CCR4. *See*, Table 1.

Table 1: Compound 1 Selectivity

Receptor	Buffer IC_{50} (nM)	Receptor	Buffer IC_{50} (nM)
CCR1	>10,000	CCR10	>10,000
CCR2	>10,000	CCR12	>10,000
CCR4	2	CXCR1	>10,000
CCR5	>10,000	CXCR2	>10,000
CCR6	>10,000	CXCR3	>10,000
CCR7	>10,000	CXCR4	>10,000
CCR8	>10,000	CXCR6	>10,000
CCR9	>10,000	CXCR7	>10,000
		Duffy	>10,000

[0110] The binding activity of Compound 1 in humans and mice is reported in Table 2.

Table 2: Cross Species Activity

Species	Cells	Binding IC_{50} (nM)	Chemotaxis A_2 (nM)	
		Buffer	Buffer	100% serum
		^{125}I-CCL17	CCL22	CCL22
Human	CEM	23	2	20
	Lymphocytes	37	10	20
Mouse	mCCR4-Baf3		4	60
	mCCR4-293	27		

Example 3: Combination therapy using a KCM Orthotopic Pancreatic Tumor Model

[0111] As briefly described in Example 1, above, a KCM pancreatic cancer model was used to assess the effectiveness of a CCR4 inhibitor in combination with an anti-CTLA-4 antibody. The study design is shown in FIG. 1. The mice were broken into 4 groups (n = 12 each group): isotype antibody + Vehicle; Isotype Antibody + Compound 1; anti-CTLA-4 + Vehicle; anti-CTLA-4 + Compound 1. The mice used were 7-8 week old C57BL/6 female mice. Anti-CTLA-4 (BioXcell: anti-mouse CTLA-4 (Clone: 9H10), raised in Syrian Hamster, purified with protein G) and isotype matched control antibody were injected i.p. at 100 μg/mice on day 7, 11, and 16. Compound 1 (40mg/kg) and vehicle dose p.i. twice daily (bid). KCM cells in matrigel were injected into the pancreas.

[0112] After completion of the study, the tumor/pancreases weight for each group was measured. The results are shown in FIG. A-C. As displayed in this figure, Compound 1 alone or in combination with anti-CTLA-4 reduced tumor burden in the KCM tumor model. In this model, most mice develop a secondary tumor on the abdominal wall near the incision sites. These secondary tumors were dissected and the weights were included in the total tumor plus pancreas weights. Primary tumors were weighed together with pancreas as they cannot be surgically separated. Spleen weights were also reduced by Compound 1 treatment. Adequate compound levels were confirmed by measuring plasma compound concentrations at trough on day 12.

[0113] Changes in suppressive immune cell populations were also measured at the completion of this study. On day 25 after KCM cell inoculation, primary tumor (together with pancreas) and secondary tumor were dissected, minced and digested with collagenase D for immune cell analysis by flow cytometry. Pancreas from sham-operated mice were processed and analyzed. Results looking at changes in T-regulatory cells, G-MDSC, and M-MDSC from the process material are shown in FIG. 3A-F. These cell populations are shown as cell number per gram of tissue (Panels A-C) or as percentage of CD45+ cells (Panels D-F). While no changes were observed on T regulatory (CD4+/FoxP3+) cells, both monocytic and granulocytic myeloid-derived suppressor cells (mMDSC - CD11b+/Ly6G-/Ly6C-high, gMDSC - CD11b+/Ly6G+/Ly6C-low) showed a trend of decrease with a-CTLA-4/Compound 1 treatment vs. a-CTLA-4 treatment alone.

Example 4: Combination Therapy using a CT26 Colon Cancer Model

[0114] As briefly described in Example 1, above, a CT26 colon cancer model was used to asses the effectiveness of a CCR4 inhibitor in combination with an anti-CTLA-4 antibody. The study design is shown in FIG. 4. The mice were broken into 4 groups (n = 12 each group): isotype antibody + Vehicle; Isotype Antibody + Compound 1; anti-CTLA-4 + Vehicle; anti-CTLA-4 + Compound 1. The mice used were 7-8 week old C57BL/6 female mice. Anti-CTLA-4 (BioXcell: anti-mouse CTLA-4 (Clone: 9H10), raised in Syrian Hamster, purified with protein G) and isotype matched control antibody were injected i.p. at 100 μg/mice on day 7, 11, and 16. Compound 1 (40mg/kg) and vehicle dose p.i. twice daily (bid). At the beginning of the study, CT25 cells were injected subcutaneously (s.c.).

[0115] Tumor volume and percent survival were monitored throughout the study. The survival rate is plotted in FIG. 5, and the average tumor volume is plotted in FIG. 6. As seen in FIG. 6, the combination of Compound 1 with an anti-CTLA-4 reduced tumor growth and improved survivial. Individual tumor sizes of each treatment group are shown in FIG. 7A-D. Note how particular mice in the aCTLA-4 + Vehicle group (Panel C) have tumors that are completely unresponsive to aCTLA-4 treatment, while the combination on aCTLA+Compound 1 shows that all tumors are responsive to treatment (Panel D).

[0116] Three months after the last dosing, mice with complete tumor regression previously treated with a-CTLA-4 (6 mice) or a-CTLA-4/Compound 1 (8 mice) were re-challenged with

CT26 tumor cells s.c. on left flank, and these mice were also injected with 4T1 mouse breast cancer cells s.c on the right flank. The results are shown in FIG. 8A-F. As seen in this figure, 1 of 6 mice previously treated with a-CTLA-4 (Panel A), while none of the 8 mice previously treated with a-CTLA-4/Compound 1, developed CT26 tumors (Panel B). All 6 mice previously treated with a-CTLA-4 developed 4T1 tumors (Panel D), while 2 of 8 previously treated with a-CTLA-4/Compound 1 did not develop 4T1 tumors (Panel E). All 5 naïve mice developed both CT26 and 4T1 tumors (Panels C and F).

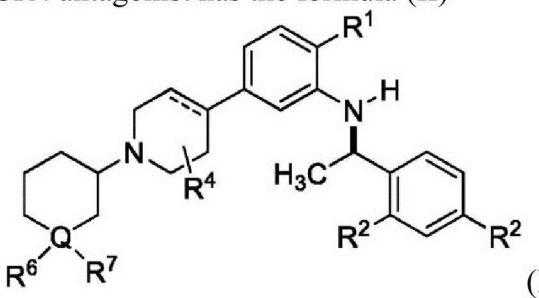
[0117] Blood cells from mice in FIG. 8 were stained with fluorescence-labeled AH1 peptide, both before and 7 days after CT26 re-challenge. AH1 is the immunodominant peptide for cytotoxic T cell response against CT26 tumor cells, and it labels CT26 antigen-reactive CD8+ T cells. Flow cytometry analysis of these samples are shown in FIG. 9A-C. These CT26 antigen-reactive CD8+ T cells are largely absent from the peripheral blood of naive mice, but are abundant in majority of surviving CT26 mice even 3 months after last dosing (Panel A and B). Re-challenge with CT26 cells further increased the number of these cells in the surviving mice from previous treatments, but had minimal effects in naïve mice (Panel C).

[0118] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, one of skill in the art will appreciate that certain changes and modifications may be practiced within the scope of the appended claims. In addition, each reference provided herein is incorporated by reference in its entirety to the same extent as if each reference was individually incorporated by reference. Where a conflict exists between the instant application and a reference provided herein, the instant application shall dominate.

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Claims

1. A method of treating cancer, said method comprising administering a therapeutically effective amount of a C-C Chemokine Receptor 4 (CCR4) antagonist and a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor to a mammal in need thereof, wherein the CCR4 antagonist has the formula (If)



(If)

or a pharmaceutically acceptable salt thereof, wherein

R^1 is selected from hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} hydroxyalkyl, C_{3-8} cycloalkyl, halogen, -CN, $-SO_2Me$ and $-C(O)NH_2$;

each R^2 is selected from C_{1-8} alkyl, C_{1-8} haloalkyl, halogen and –CN;

R^4 is hydrogen;

Q is selected from C, CH, and N;

R^6 is selected from H, -OH, C_{1-8} alkyl, C_{1-8} hydroxyalkyl, C_{1-4} alkoxy-C_{1-4} alkyl, $-C(O)NR^aR^b$, C_{1-8} alkylene-$C(O)NR^aR^b$, -NH-C_{1-4} alkylene-$C(O)NR^aR^b$, -C(O)-C_{1-4} alkylene-NR^aR^b, $-CO_2H$, C_{1-8} alkylene-CO_2H, $-N(R^a)C(O)NR^aR^b$, C_{1-8} alkylene-$N(R^a)C(O)NR^aR^b$, $-NR^aR^b$, C_{1-8} alkylene-NR^aR^b, C_{1-8} alkoxy, $-C(O)OR^a$, C_{1-8} alkylene-$C(O)OR^a$, -CN, $-C(O)R^a$, $-SO_2R^a$ and $-N(R^a)C(O)R^b$;

wherein

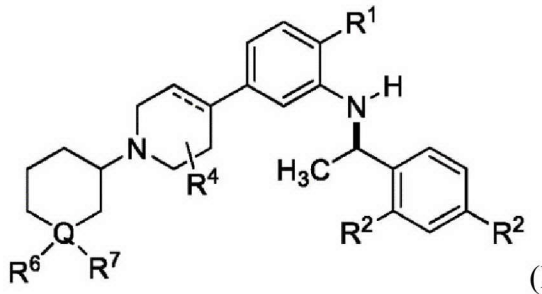
each R^a and R^b are independently selected from hydrogen, C_{1-8} alkyl, C_{1-8} hydroxyalkyl, C_{1-8} haloalkyl, and C_{1-8} alkoxy; and

R^7 is absent or is selected from H, C_{1-8} alkyl and C_{1-8} haloalkyl.

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2. Use of a C-C Chemokine Receptor 4 (CCR4) antagonist for the manufacture of a medicament for treating cancer in a mammal in need thereof, wherein the CCR4 antagonist is administered to the mammal in combination with a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor;

wherein the CCR4 antagonist has the formula (If)



(If)

or a pharmaceutically acceptable salt thereof, wherein

R^1 is selected from hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} hydroxyalkyl, C_{3-8} cycloalkyl, halogen, -CN, $-SO_2Me$ and $-C(O)NH_2$;

each R^2 is selected from C_{1-8} alkyl, C_{1-8} haloalkyl, halogen and –CN;

R^4 is hydrogen;

Q is selected from C, CH, and N;

R^6 is selected from H, -OH, C_{1-8} alkyl, C_{1-8} hydroxyalkyl, C_{1-4} alkoxy-C_{1-4} alkyl, $-C(O)NR^aR^b$, C_{1-8} alkylene-$C(O)NR^aR^b$, -NH-C_{1-4} alkylene-$C(O)NR^aR^b$, -C(O)-C_{1-4} alkylene-NR^aR^b, $-CO_2H$, C_{1-8} alkylene-CO_2H, $-N(R^a)C(O)NR^aR^b$, C_{1-8} alkylene-$N(R^a)C(O)NR^aR^b$, $-NR^aR^b$, C_{1-8} alkylene-NR^aR^b, C_{1-8} alkoxy, $-C(O)OR^a$, C_{1-8} alkylene-$C(O)OR^a$, -CN, $-C(O)R^a$, $-SO_2R^a$ and $-N(R^a)C(O)R^b$;

wherein

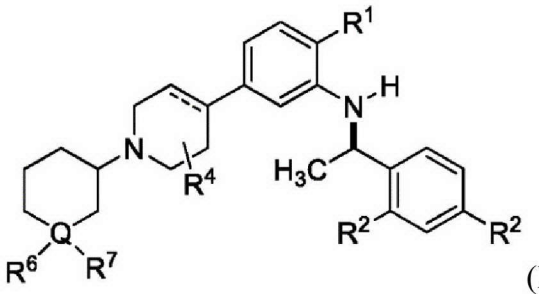
each R^a and R^b are independently selected from hydrogen, C_{1-8} alkyl, C_{1-8} hydroxyalkyl, C_{1-8} haloalkyl, and C_{1-8} alkoxy; and

R^7 is absent or is selected from H, C_{1-8} alkyl and C_{1-8} haloalkyl.

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3. Use of a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor for the manufacture of a medicament for treating cancer in a mammal, wherein the CTLA-4 inhibitor is administered to the mammal in combination with a C-C Chemokine Receptor 4 (CCR4) antagonist;

wherein the CCR4 antagonist has the formula (If)



(If)

or a pharmaceutically acceptable salt thereof, wherein

R^1 is selected from hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} hydroxyalkyl, C_{3-8} cycloalkyl, halogen, -CN, $-SO_2Me$ and $-C(O)NH_2$;

each R^2 is selected from C_{1-8} alkuyl, C_{1-8} haloalkyl, halogen and –CN;

R^4 is hydrogen;

Q is selected from C, CH, and N;

R^6 is selected from H, -OH, C_{1-8} alkyl, C_{1-8} hydroxyalkyl, C_{1-4} alkoxy-C_{1-4} alkyl, $-C(O)NR^aR^b$, C_{1-8} alkylene-$C(O)NR^aR^b$, -NH-C_{1-4} alkylene-$C(O)NR^aR^b$, -C(O)-C_{1-4} alkylene-NR^aR^b, $-CO_2H$, C_{1-8} alkylene-CO_2H, $-N(R^a)C(O)NR^aR^b$, C_{1-8} alkylene-$N(R^a)C(O)NR^aR^b$, $-NR^aR^b$, C_{1-8} alkylene-NR^aR^b, C_{1-8} alkoxy, $-C(O)OR^a$, C_{1-8} alkylene-$C(O)OR^a$, -CN, $-C(O)R^a$, $-SO_2R^a$ and $-N(R^a)C(O)R^b$;

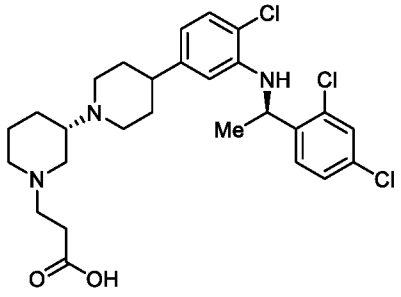
wherein

each R^a and R^b are independently selected from hydrogen, C_{1-8} alkyl, C_{1-8} hydroxyalkyl, C_{1-8} haloalkyl, and C_{1-8} alkoxy; and

R^7 is absent or is selected from H, C_{1-8} alkyl and C_{1-8} haloalkyl.

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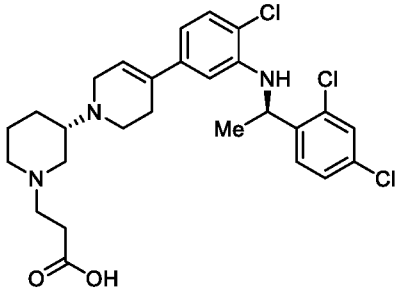
4. The method of claim 1, or use of claim 2 or 3, wherein the CCR4 antagonist has the formula



(Compound 1)

or a pharmaceutically acceptable salt thereof.

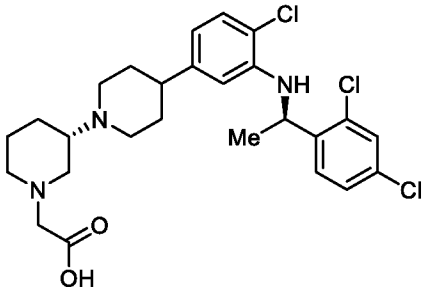
5. The method of claim 1, or use of claim 2 or 3, wherein the CCR4 antagonist has the formula



(Compound 2)

or a pharmaceutically acceptable salt thereof.

6. The method of claim 1, or use of claim 2 or 3, wherein the CCR4 antagonist has the formula

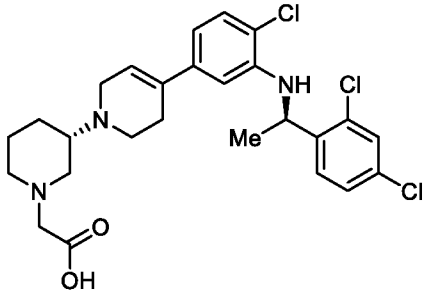


(Compound 3)

or a pharmaceutically acceptable salt thereof.

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7. The method of claim 1, or use of claim 2 or 3, wherein the CCR4 antagonist has the formula



(Compound 4)

or a pharmaceutically acceptable salt thereof.

8. The method of any one of claims 1 and 4 to 7, or use of any one of claims 2 to 7, wherein said CTLA-4 inhibitor is an anti- CTLA-4 antibody,

9. The method or use of claim 8, wherein said anti- CTLA-4 antibody is selected from the group consisting of Ipilimumab, Tremelimumab, AGEN1884, and AGEN2041.

10. The method or use of claim 8, wherein said anti-CLTA-4 antibody is Ipilimumab.

11. The method or use of claim 8, wherein said anti-CLTA-4 antibody is Tremelimumab.

12. The method or use of claim 8, wherein said anti-CLTA-4 antibody is AGEN1884.

13. The method or use of claim 8, wherein said anti-CLTA-4 antibody is AGEN2041.

14. The method of any one of claims 1 and 4 to 13, or use of any one of claims 2 to 13, wherein said cancer is colon cancer.

15. The method of any one of claims 1 and 4 to 13, or use of any one of claims 2 to 13, wherein said cancer is pancreatic cancer.

ChemoCentryx, Inc.

Patent Attorneys for the Applicant/Nominated Person
SPRUSON & FERGUSON

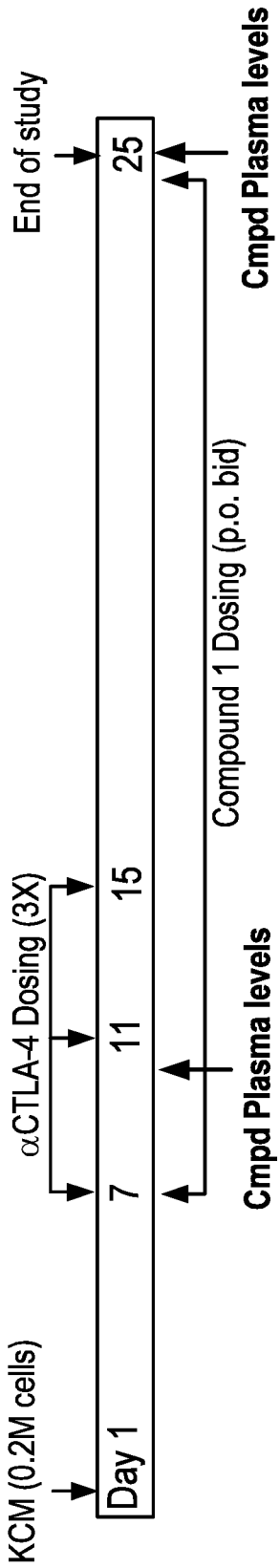

KCM (0.2M cells)
Day 1
αCTLA-4 Dosing (3X)
7
11
15
End of study
25
Compound 1 Dosing (p.o. bid)
Cmpd Plasma levels
Cmpd Plasma levels

FIG. 1

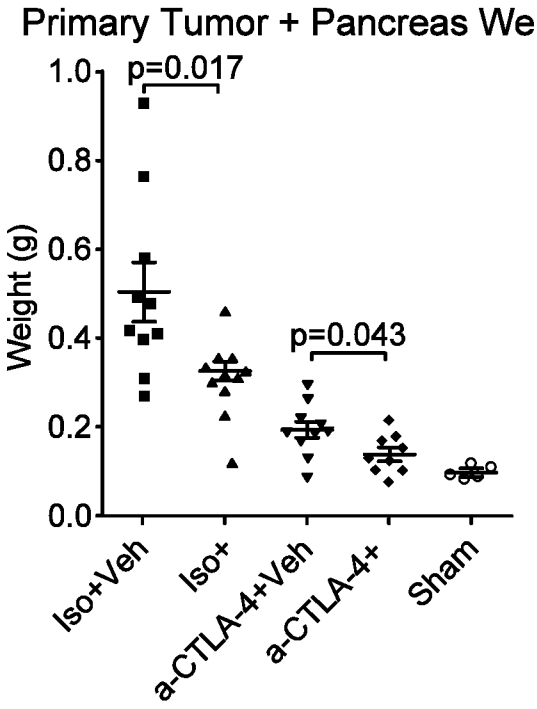


FIG. 2A

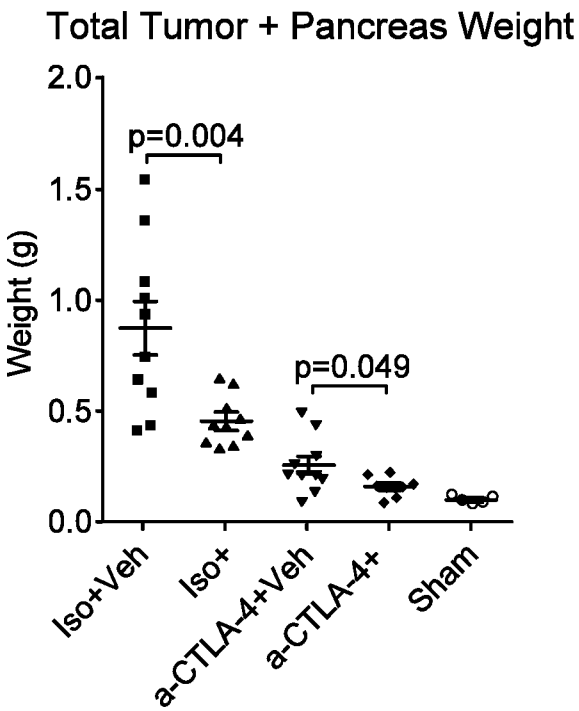


FIG. 2B

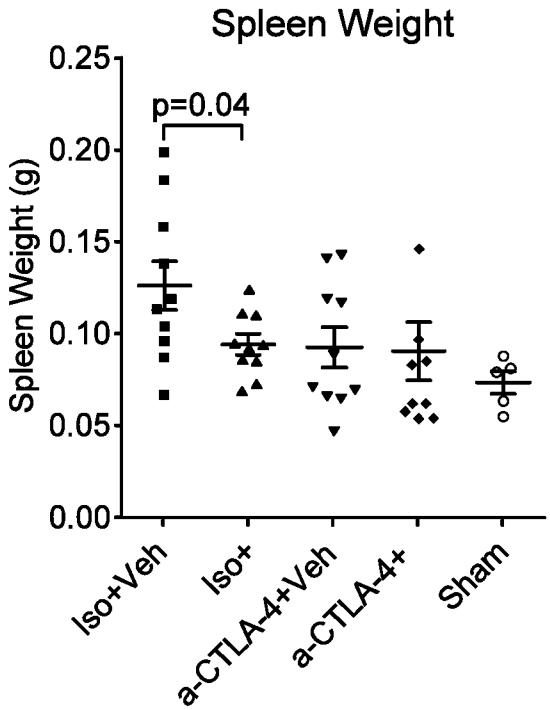


FIG. 2C

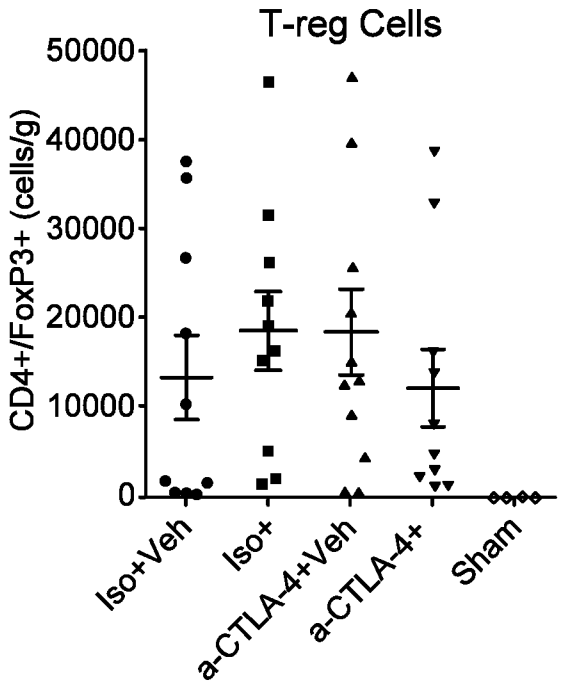


FIG. 3A

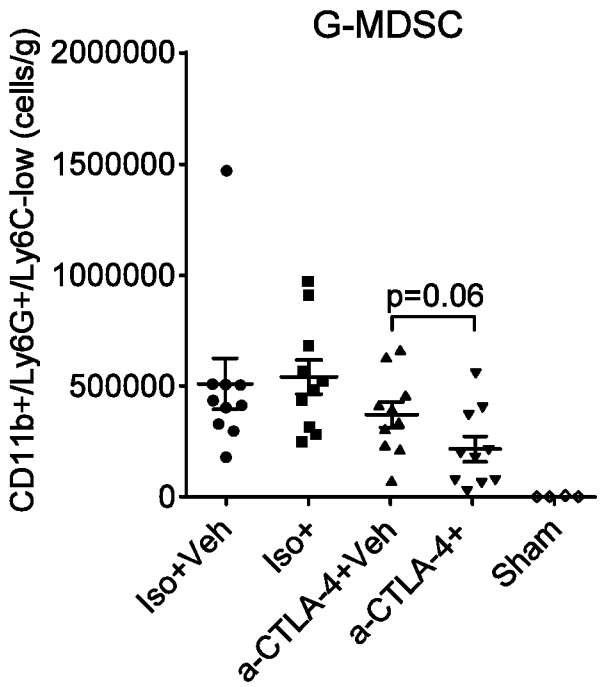


FIG. 3B

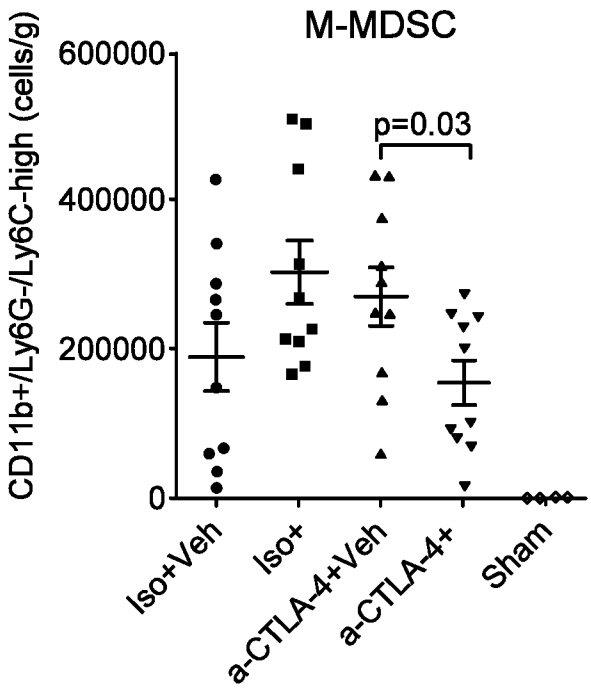


FIG. 3C

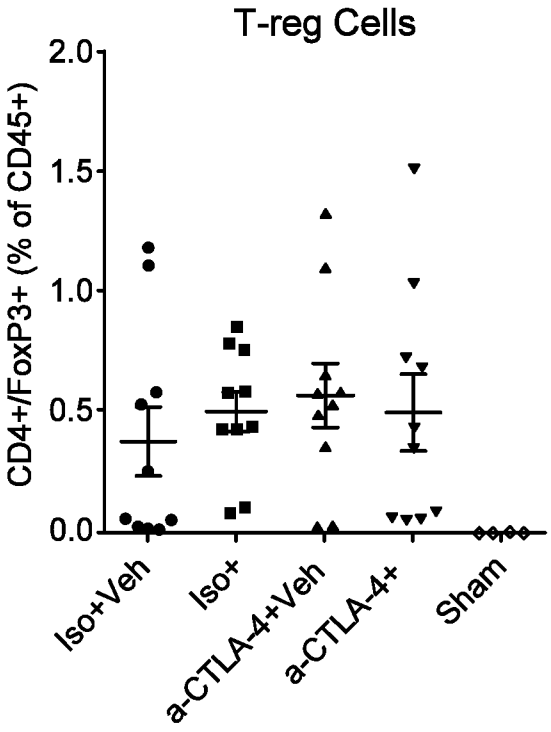


FIG. 3D

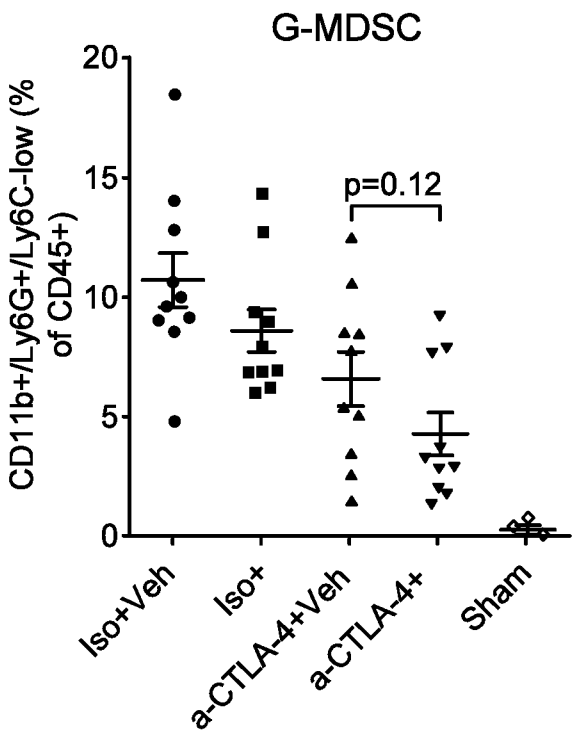


FIG. 3E

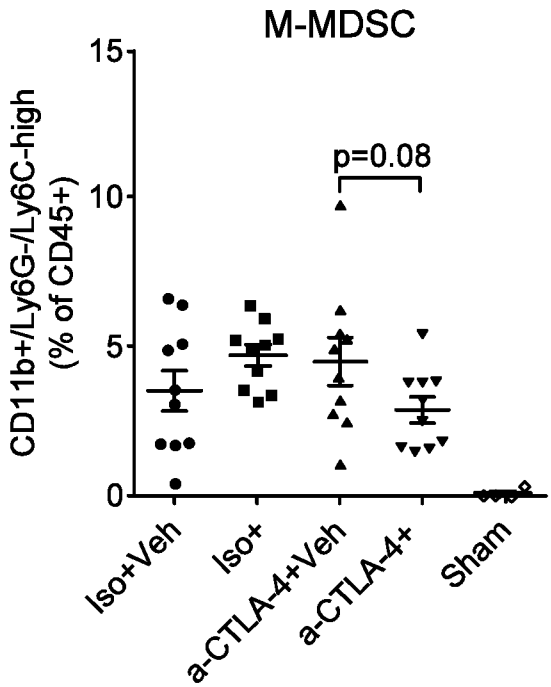


FIG. 3F

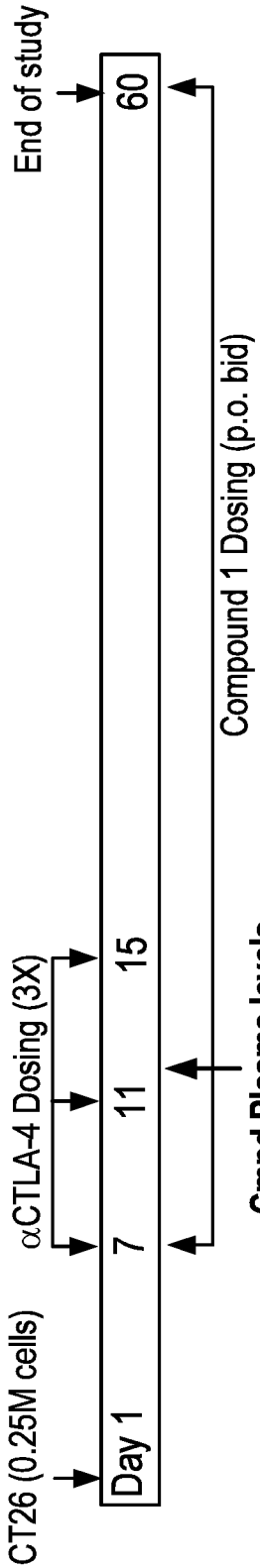

End of study
60
Compound 1 Dosing (p.o. bid)
Cmpd Plasma levels
αCTLA-4 Dosing (3X)
15
11
7
Day 1
CT26 (0.25M cells)

FIG. 4

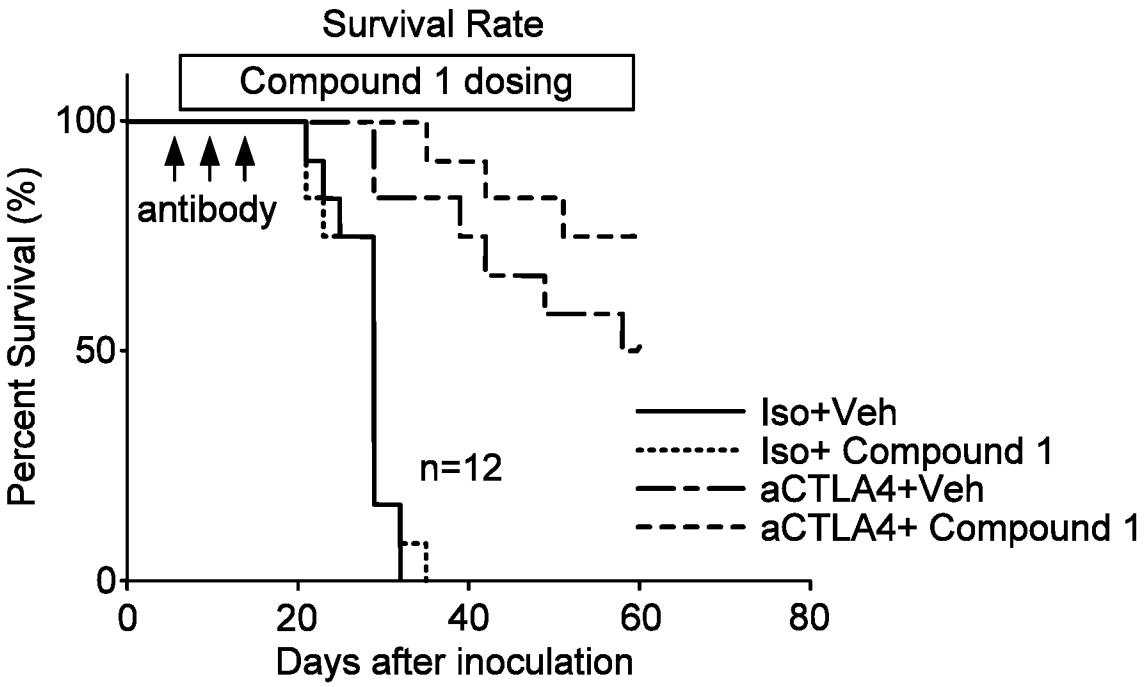

Survival Rate
Compound 1 dosing
100
50
0
antibody
n=12
Percent Survival (%)
0
20
40
60
80
Days after inoculation
Iso+Veh
Iso+ Compound 1
aCTLA4+Veh
aCTLA4+ Compound 1

FIG. 5

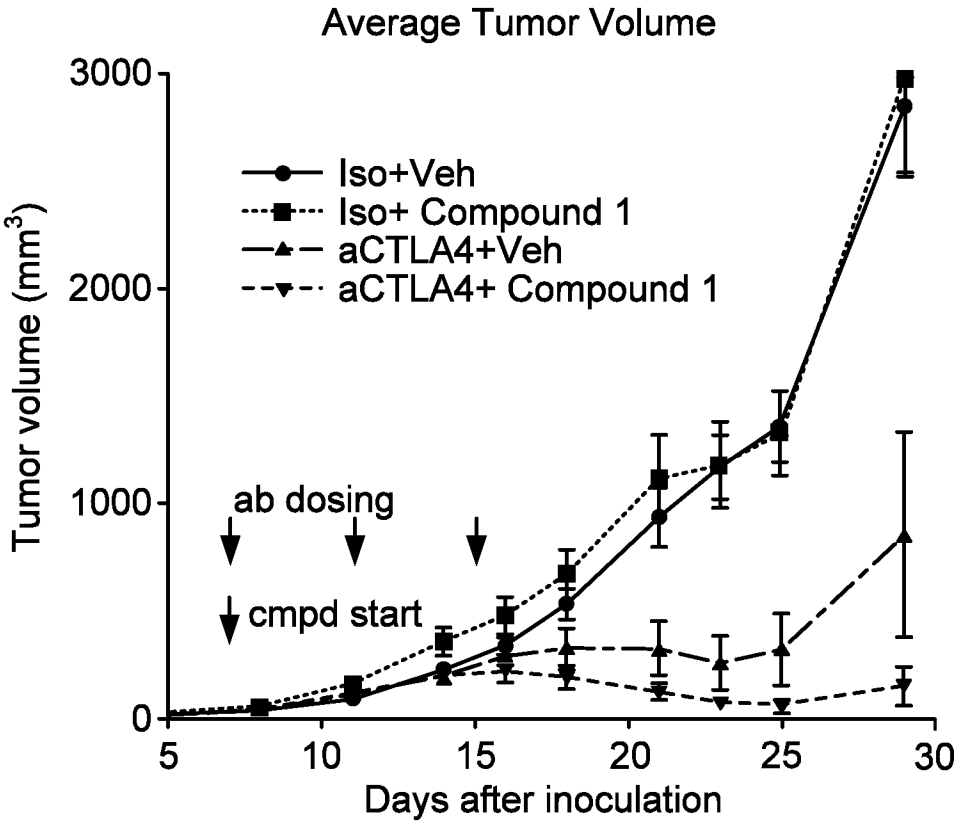

Average Tumor Volume
3000
2000
1000
0
Tumor volume (mm3)
Iso+Veh
Iso+ Compound 1
aCTLA4+Veh
aCTLA4+ Compound 1
ab dosing
cmpd start
5
10
15
20
25
30
Days after inoculation

FIG. 6

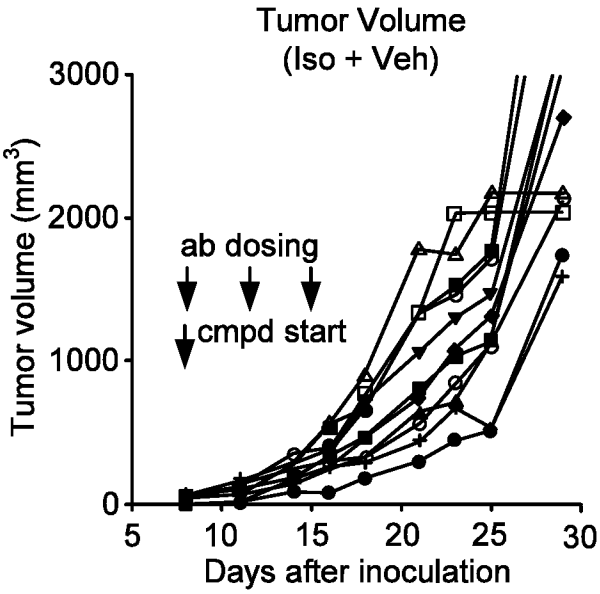


FIG. 7A

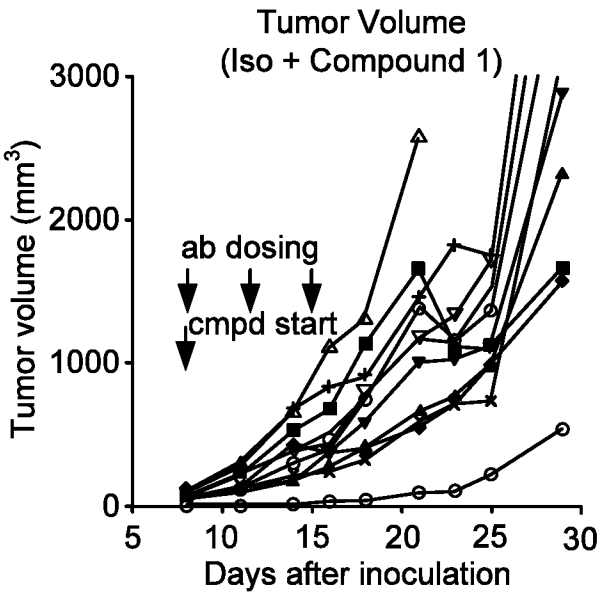


FIG. 7B

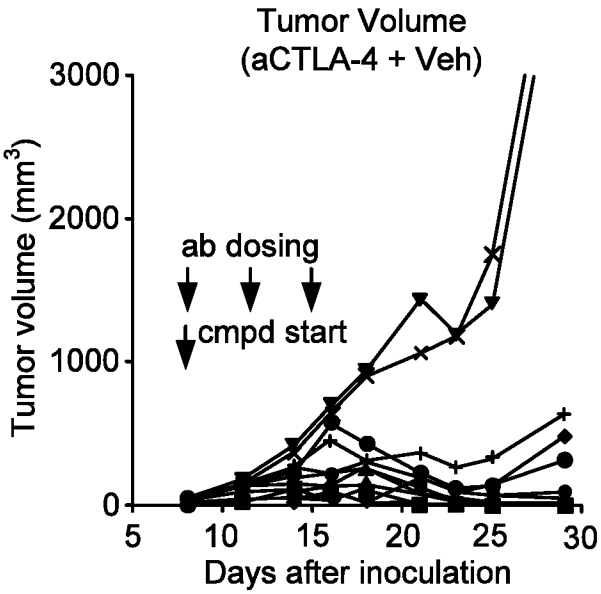


FIG. 7C

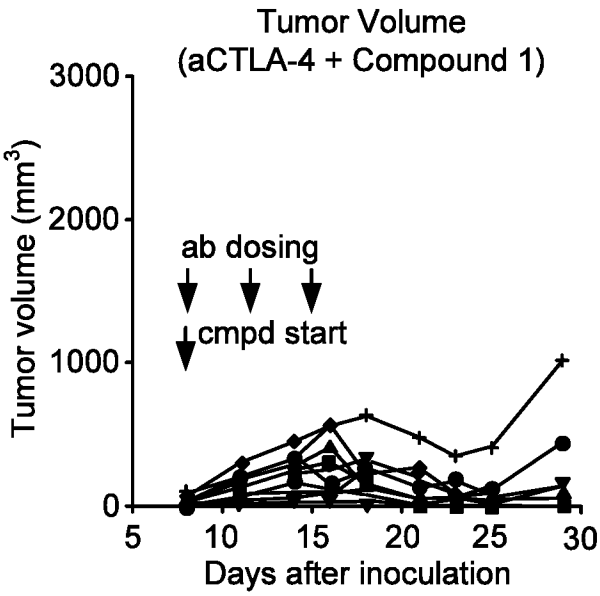


FIG. 7D

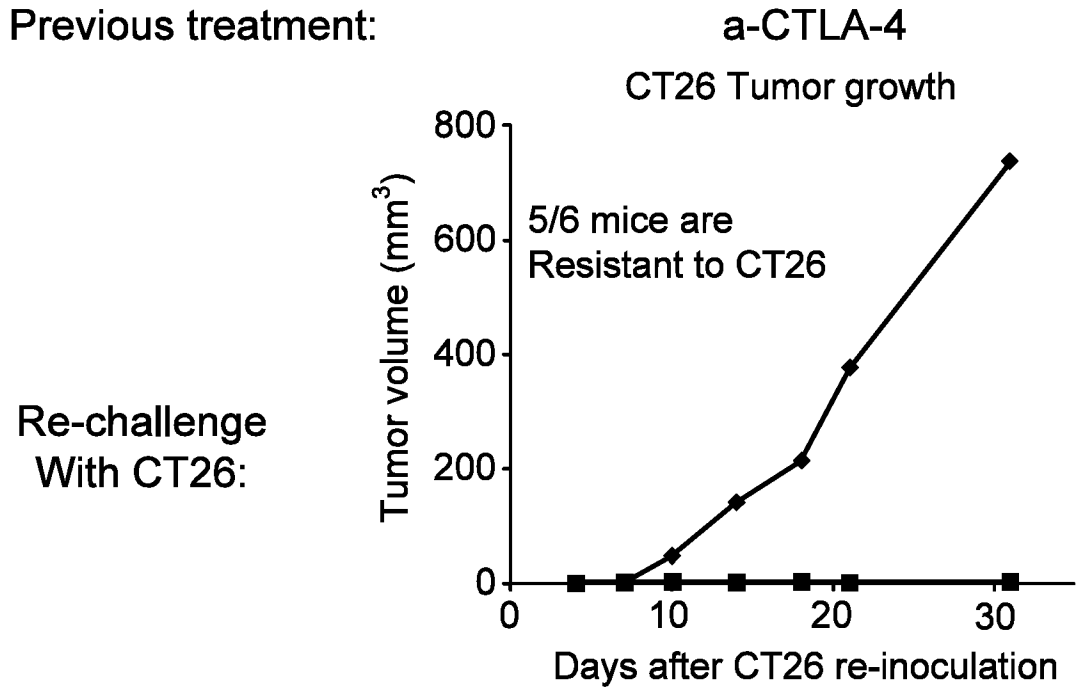

Previous treatment:
a-CTLA-4
CT26 Tumor growth
Re-challenge
With CT26:
Tumor volume (mm3)
800
600
400
200
0
5/6 mice are
Resistant to CT26
0
10
20
30
Days after CT26 re-inoculation

FIG. 8A

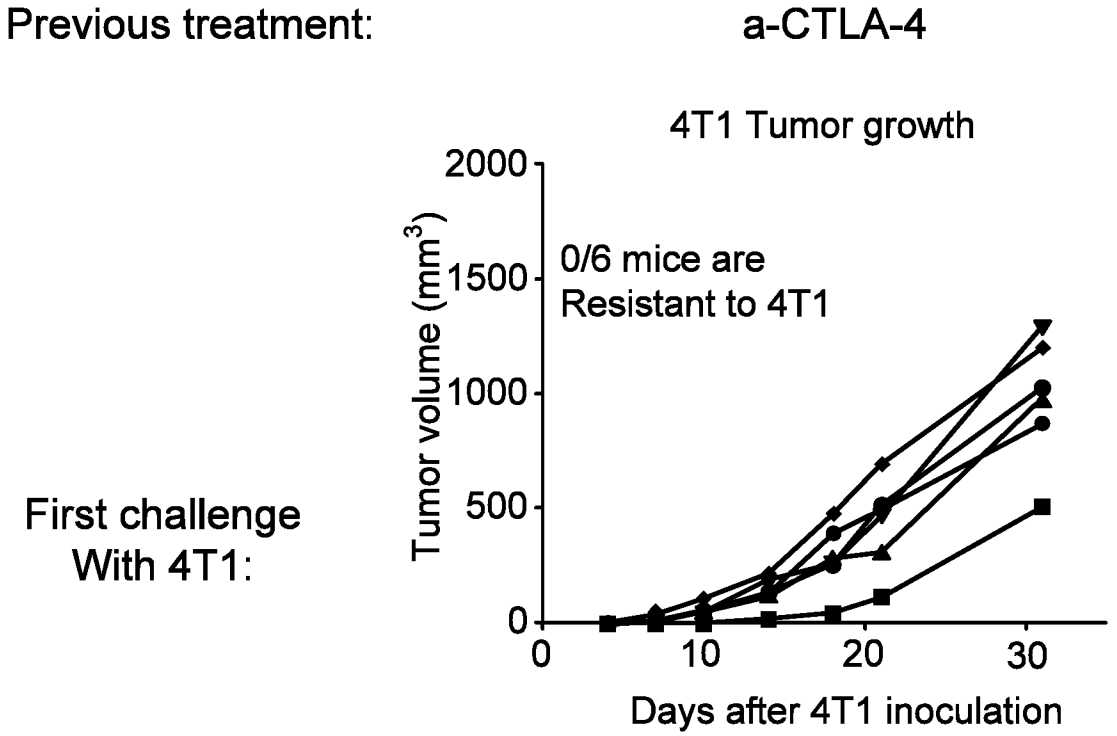

Previous treatment:
a-CTLA-4
4T1 Tumor growth
First challenge
With 4T1:
Tumor volume (mm3)
2000
1500
1000
500
0
0/6 mice are
Resistant to 4T1
0
10
20
30
Days after 4T1 inoculation

FIG. 8B

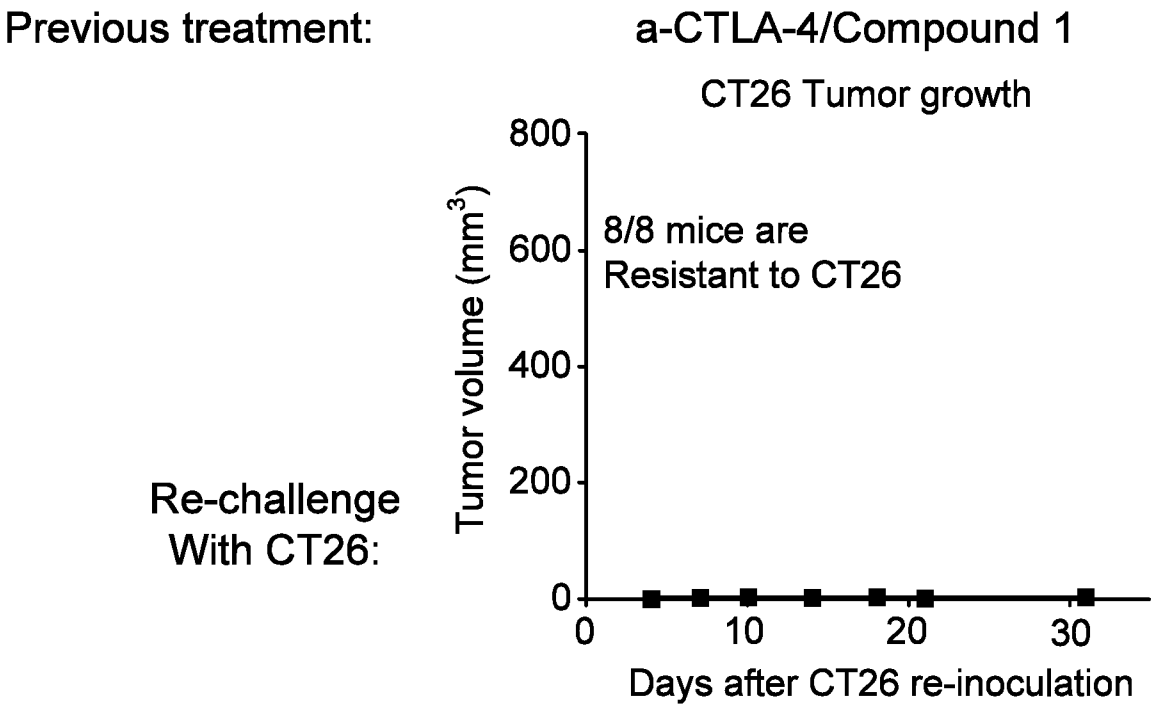

Previous treatment:
a-CTLA-4/Compound 1
CT26 Tumor growth
Re-challenge
With CT26:
Tumor volume (mm3)
800
600
400
200
0
8/8 mice are
Resistant to CT26
0
10
20
30
Days after CT26 re-inoculation

FIG. 8C

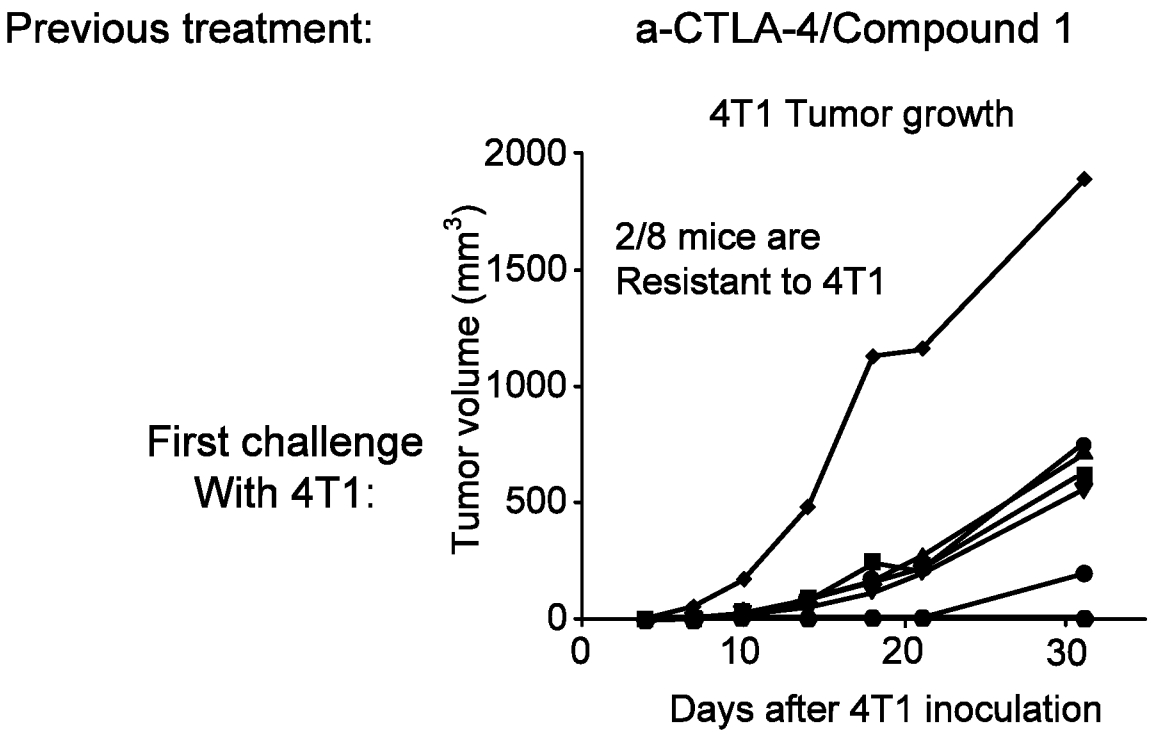

Previous treatment:
a-CTLA-4/Compound 1
4T1 Tumor growth
First challenge
With 4T1:
Tumor volume (mm3)
2000
1500
1000
500
0
2/8 mice are
Resistant to 4T1
0
10
20
30
Days after 4T1 inoculation

FIG. 8D

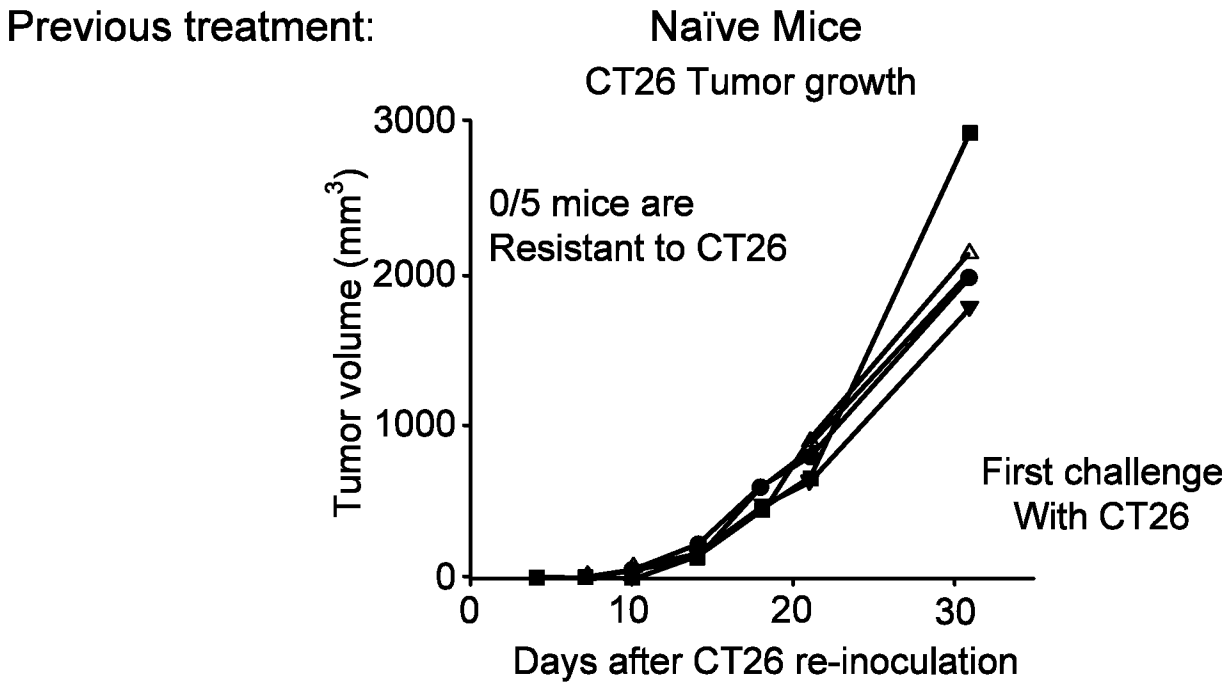

Previous treatment:
Naïve Mice
CT26 Tumor growth
3000
2000
1000
0
Tumor volume (mm3)
0/5 mice are
Resistant to CT26
First challenge
With CT26
0
10
20
30
Days after CT26 re-inoculation

FIG. 8E

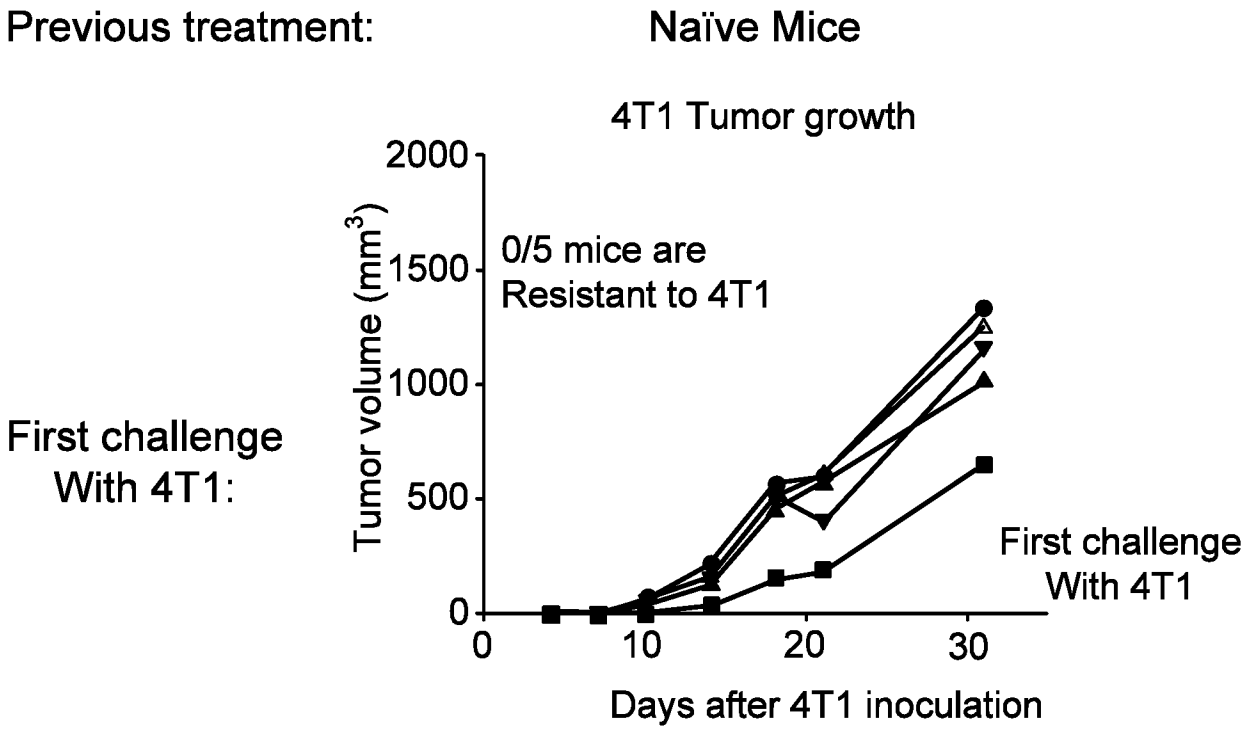

Previous treatment:
Naïve Mice
4T1 Tumor growth
First challenge
With 4T1:
2000
1500
1000
500
0
Tumor volume (mm3)
0/5 mice are
Resistant to 4T1
First challenge
With 4T1
0
10
20
30
Days after 4T1 inoculation

FIG. 8F

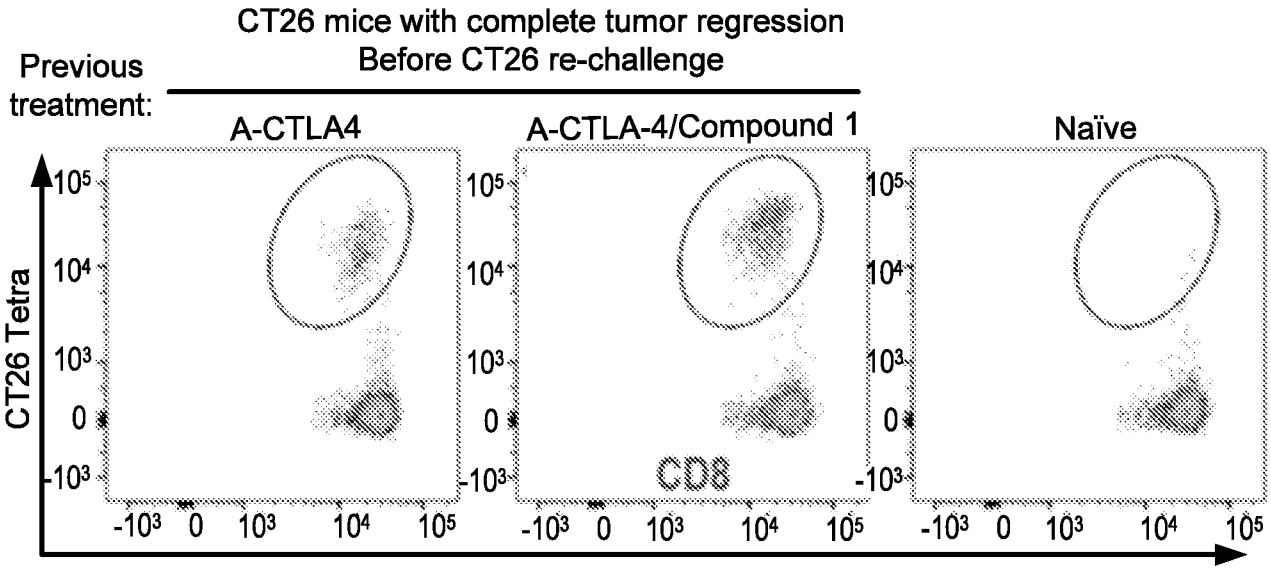


FIG. 9A

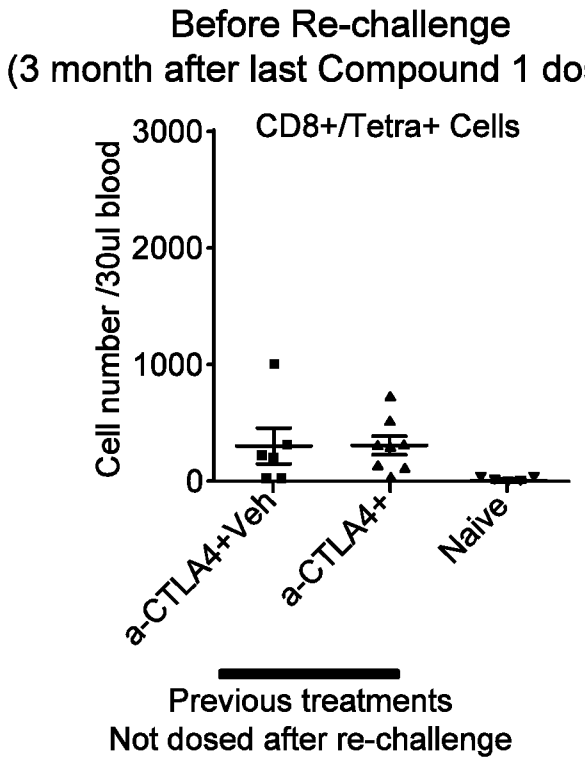


FIG. 9B

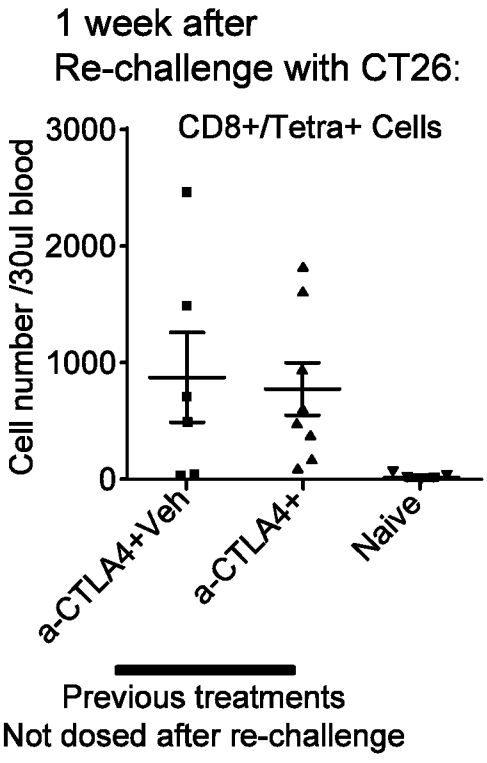


FIG. 9C