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(54) **TREATMENT OF DISEASES BY CONCURRENTLY ELICITING REMYELINATION EFFECTS AND IMMUNOMODULATORY EFFECTS USING SELECTIVE RXR AGONISTS**

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(57) **ABSTRACT**

The present specification provides RXR agonists with both remyelination promotion and immunomodulatory activities, compositions comprising such RXR agonists, and methods using such compounds and compositions to treat a demyelination-related disorder by both promoting remyelination of neurons and modulating the immune system.

21 Claims, 12 Drawing Sheets

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FIG. 1A
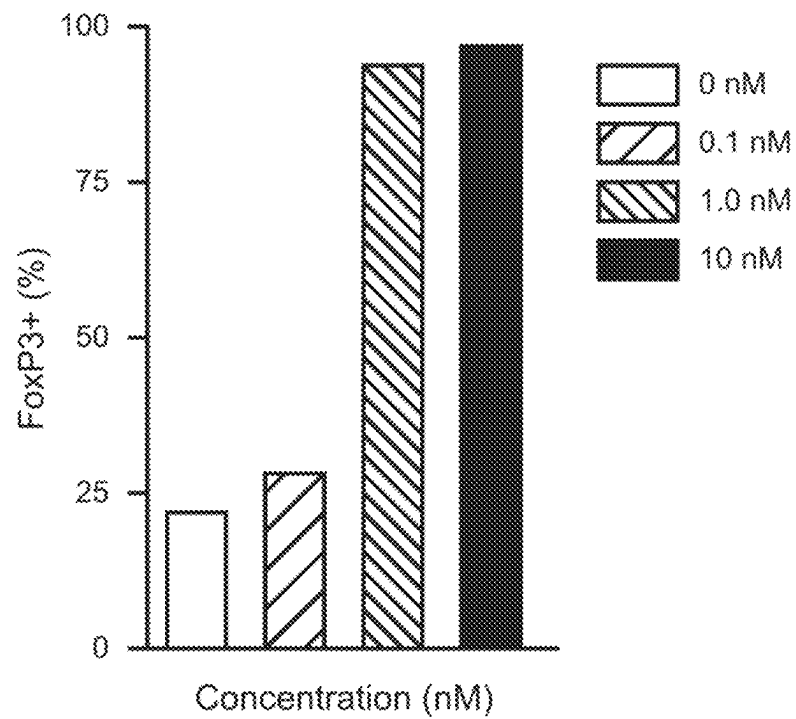
FIG. 1B
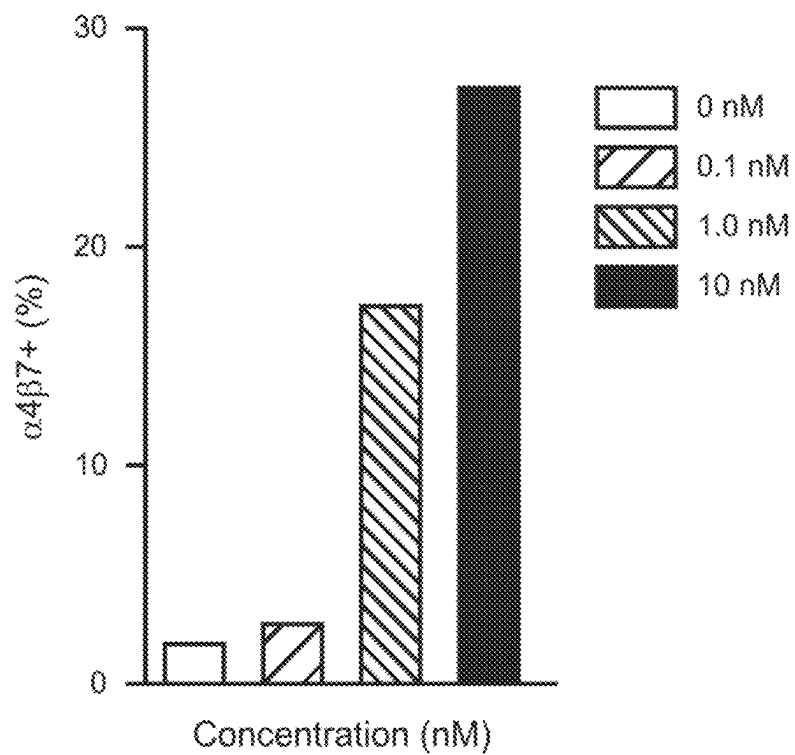
FIG. 2A
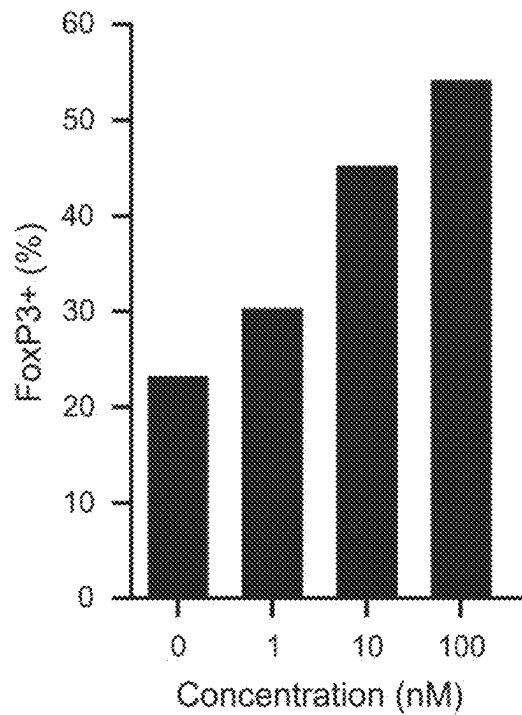
FIG. 2B
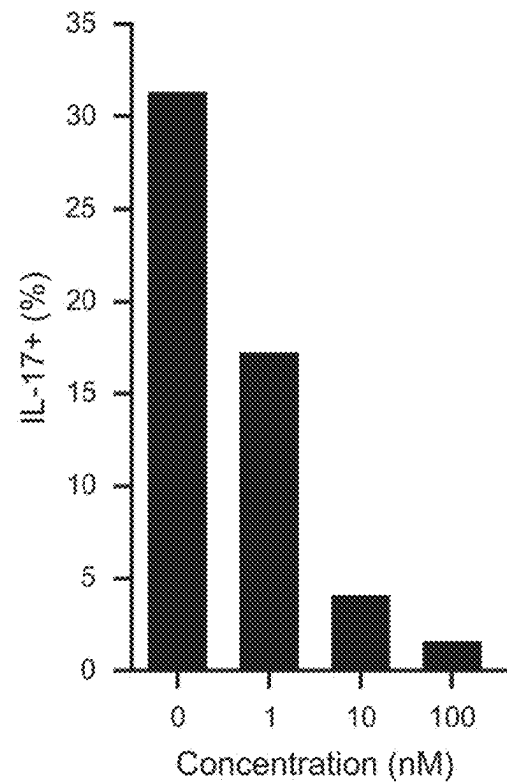
FIG. 3
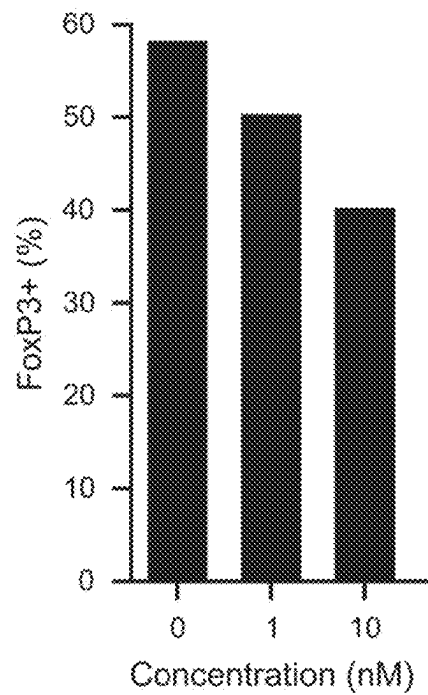
FIG. 4
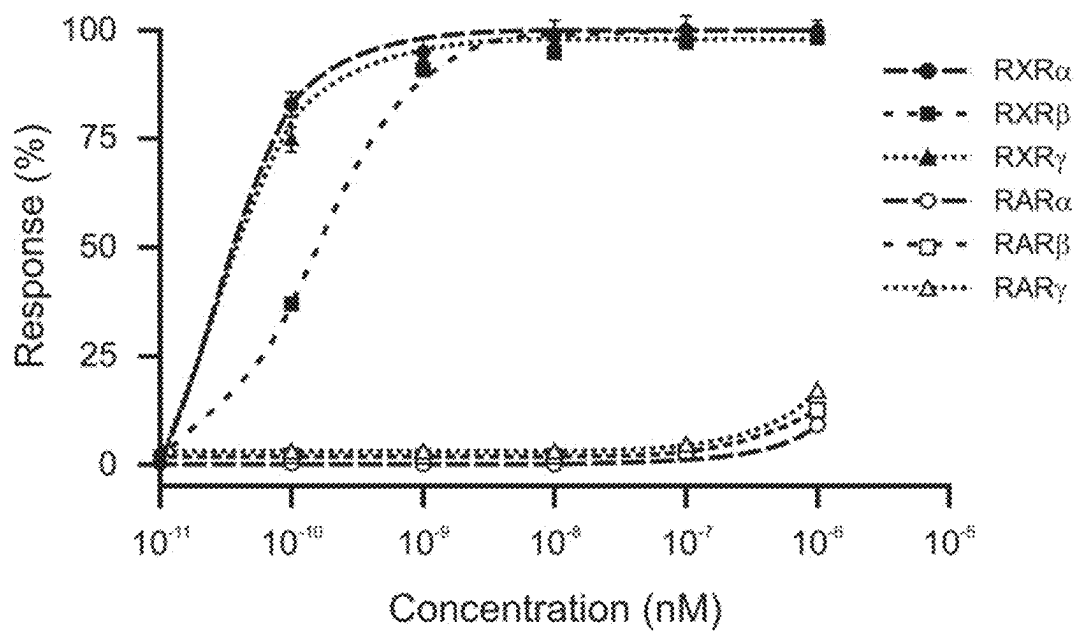
FIG. 5
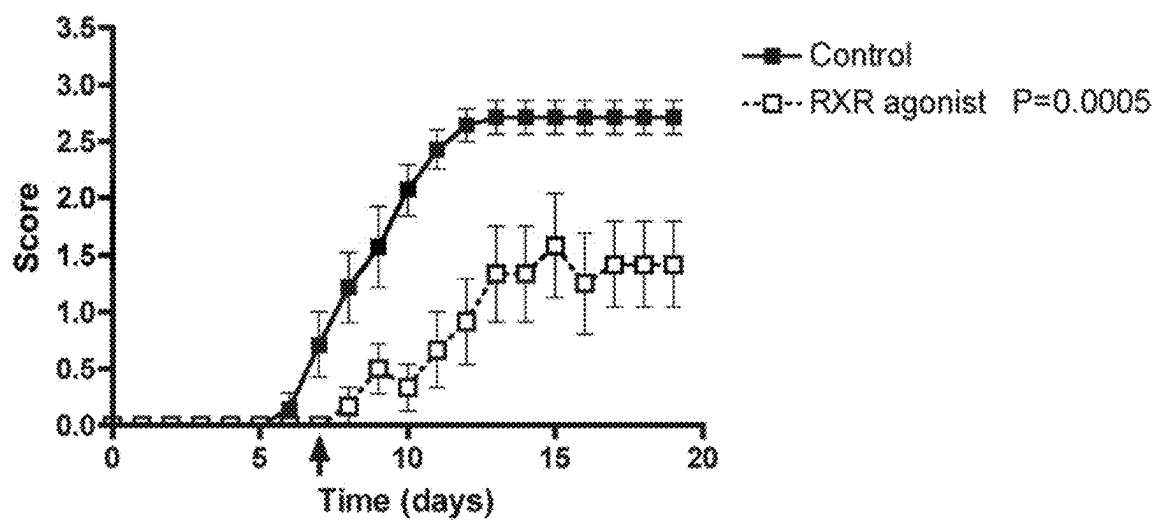
FIG. 6A
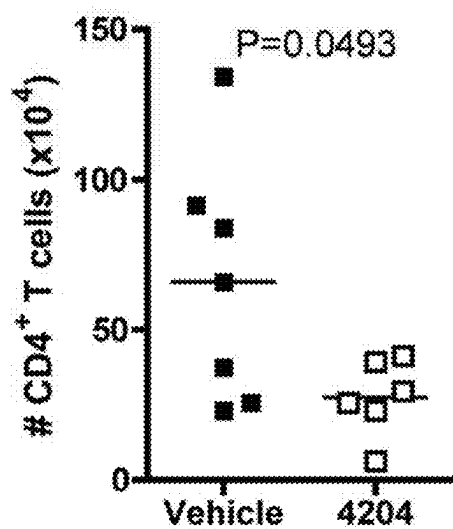
FIG. 6B
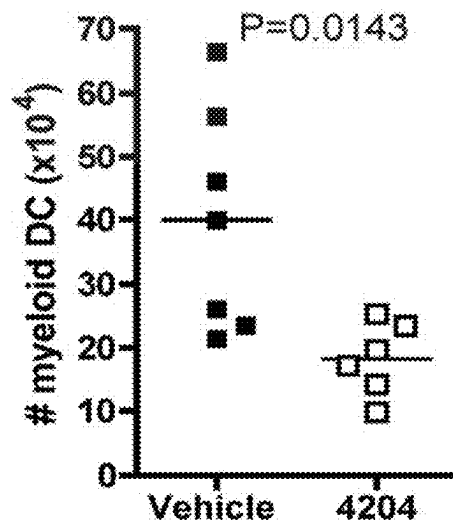
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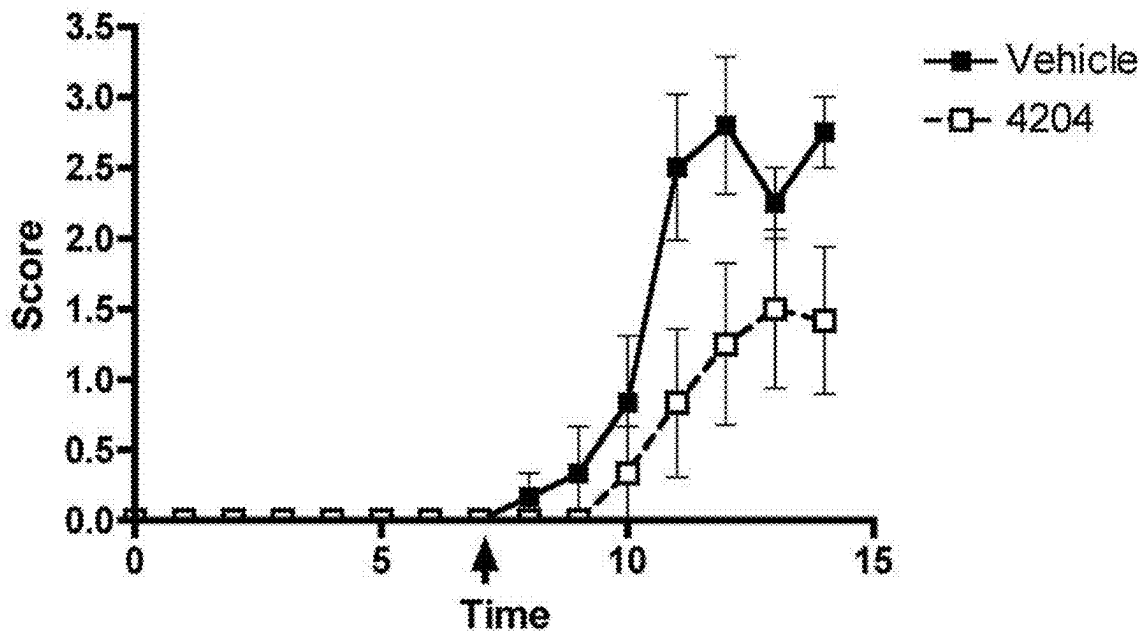
FIG. 8A
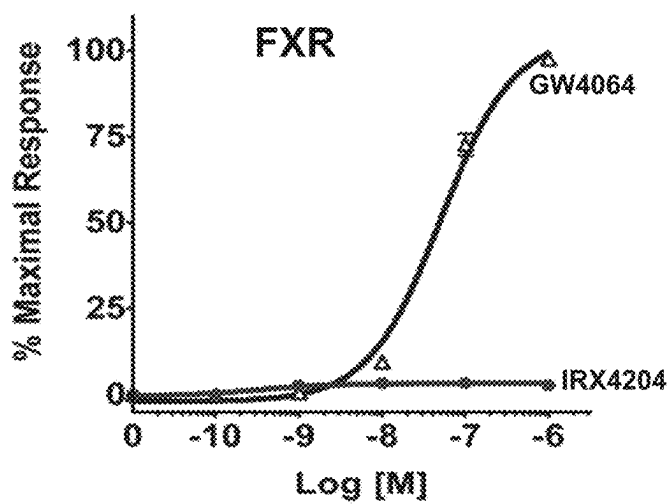
FIG. 8B
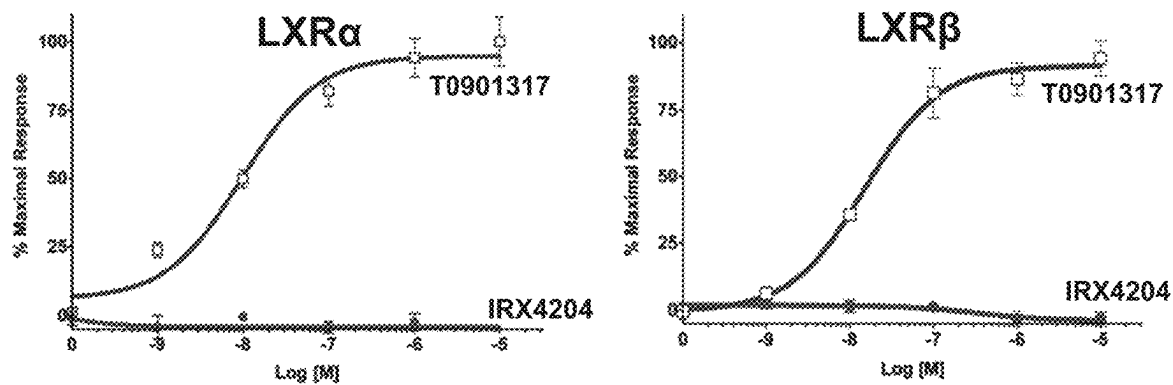
FIG. 8C

FIG. 8D

FIG. 9

FIG. 10
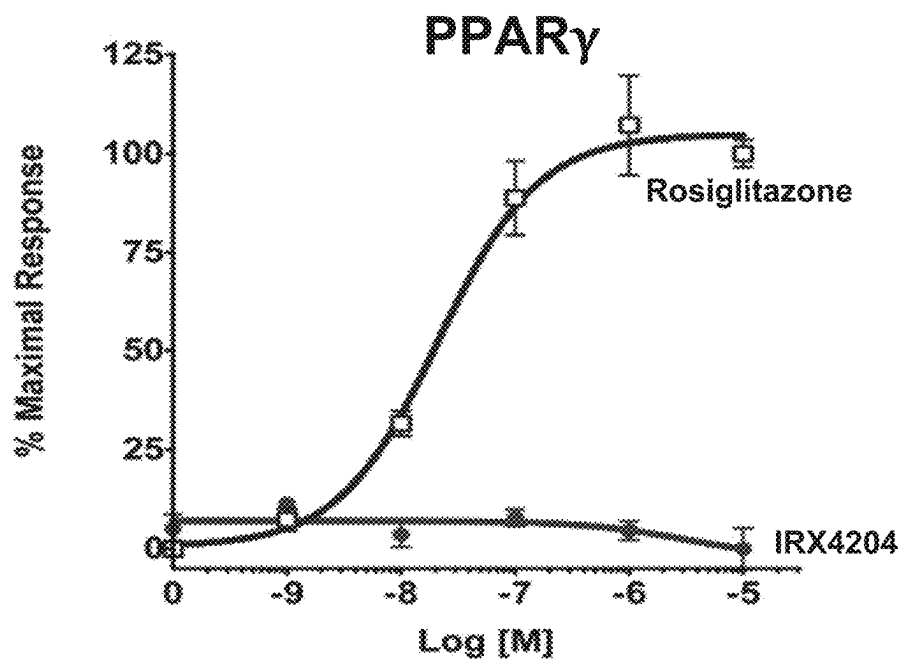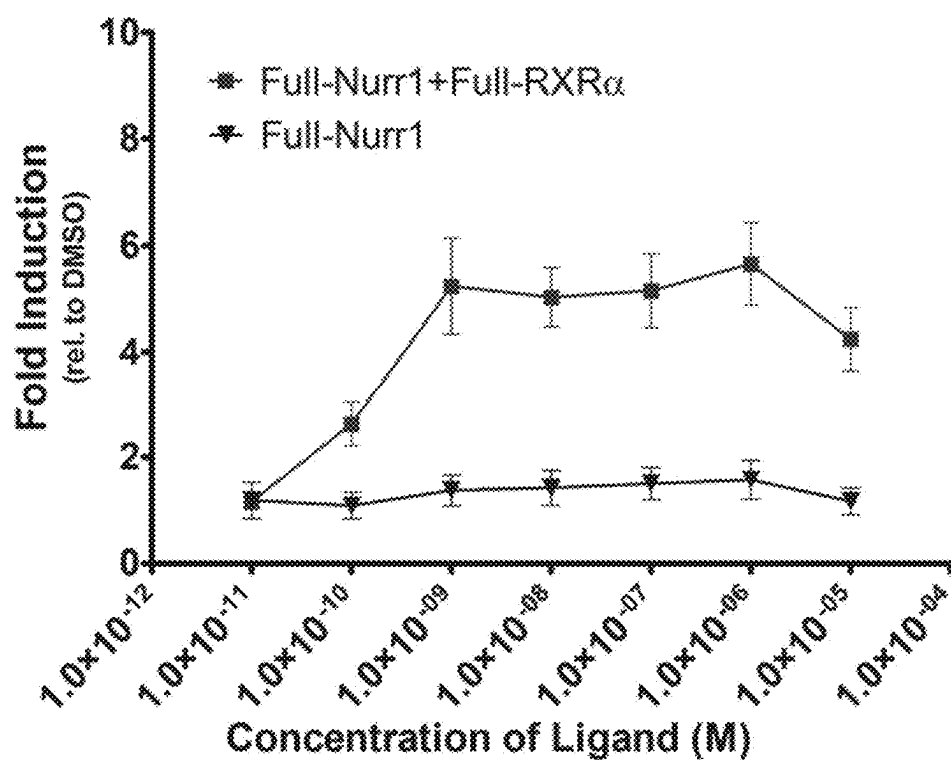
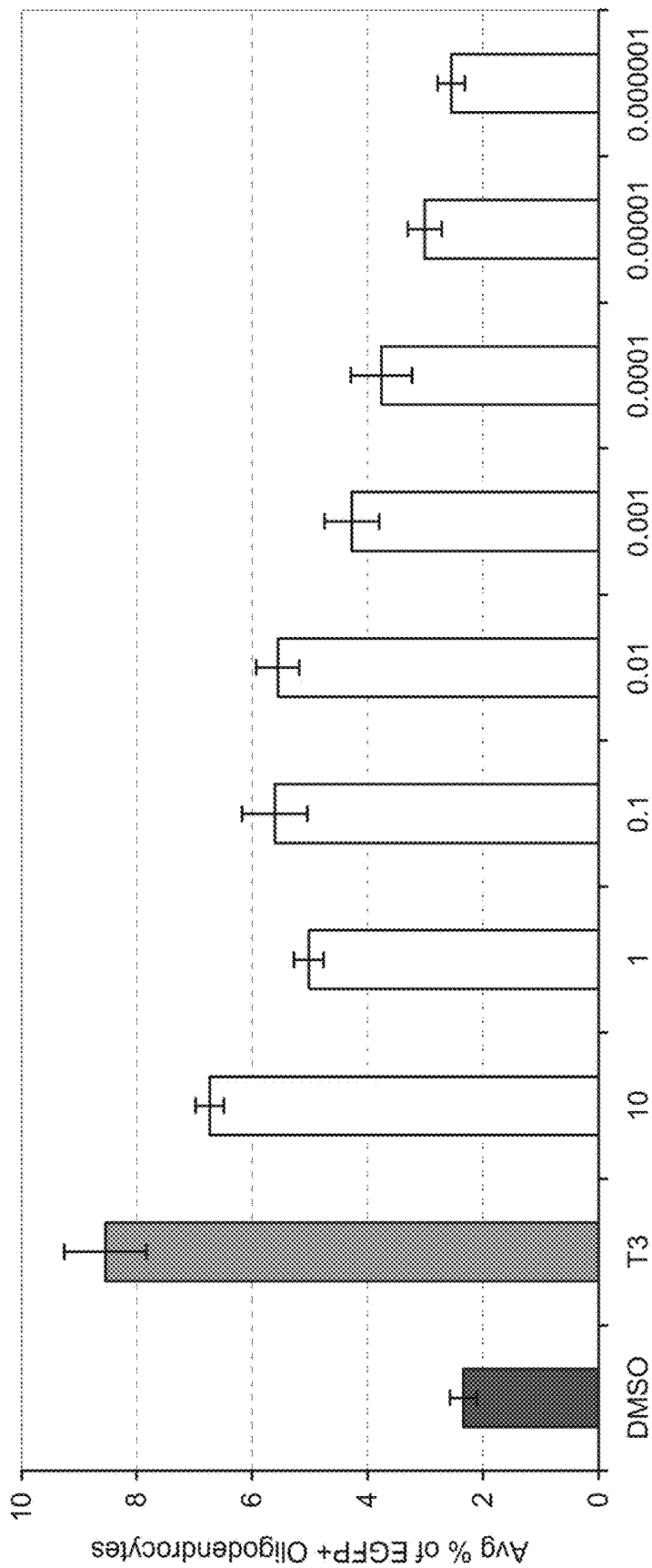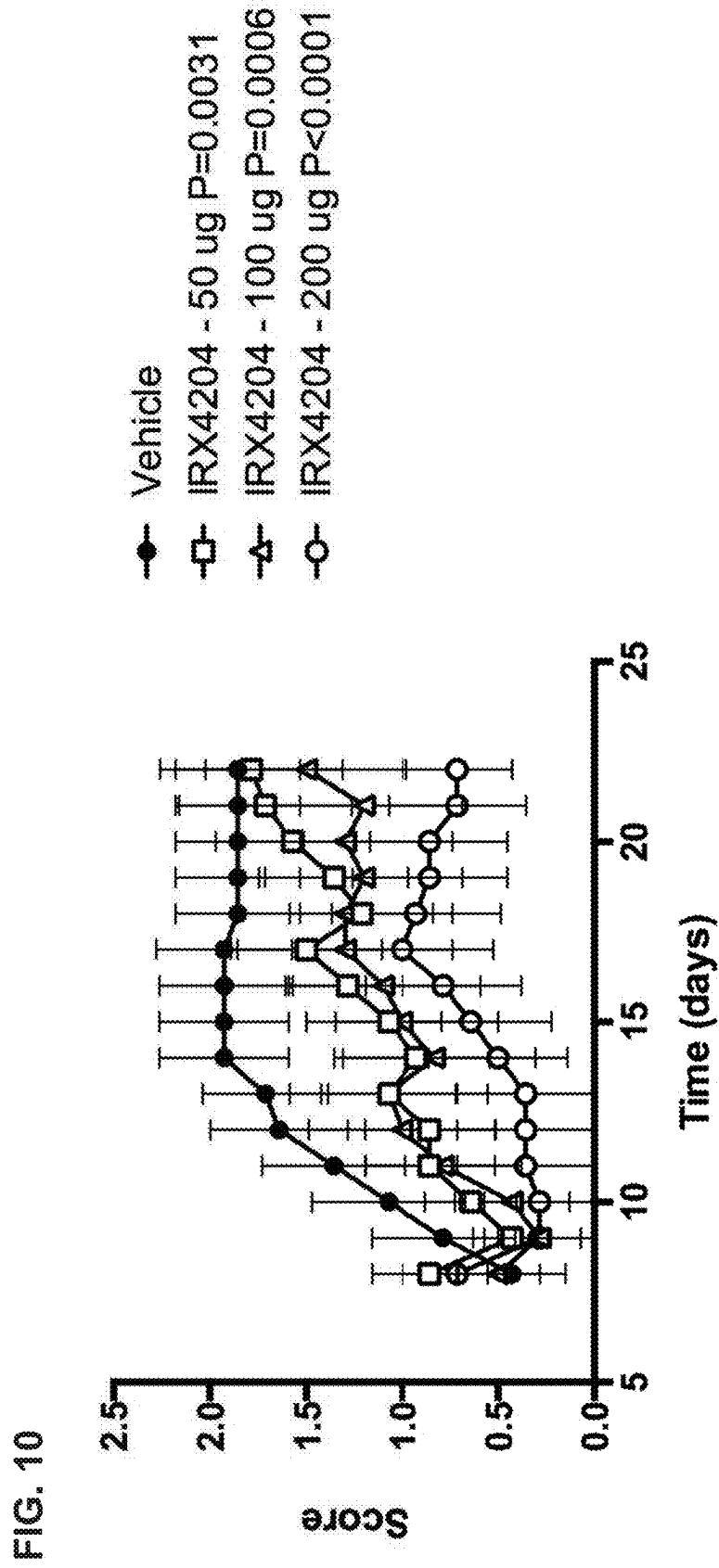FIG. 11A

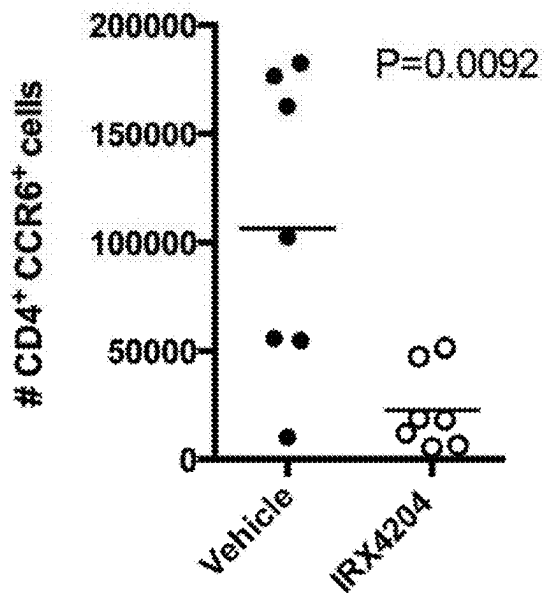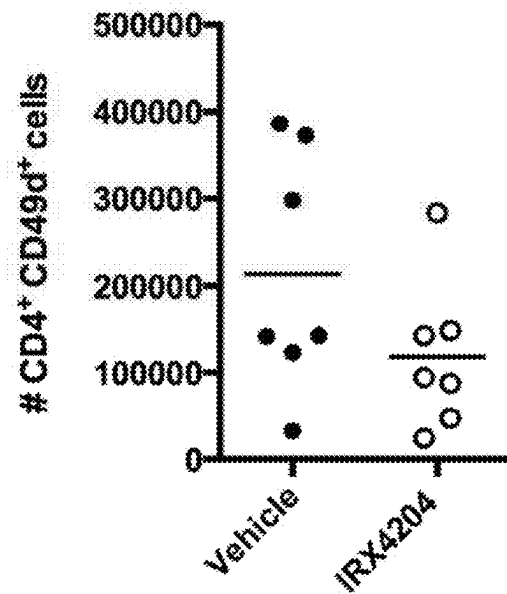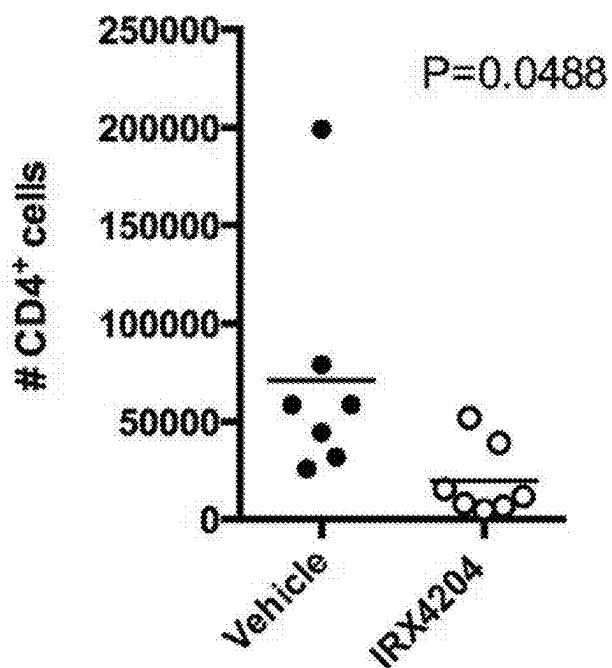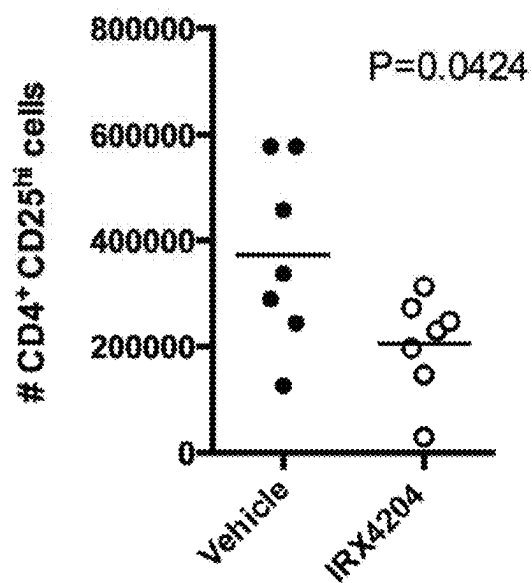
FIG. 11B

FIG. 13

FIG. 12A

FIG.12B

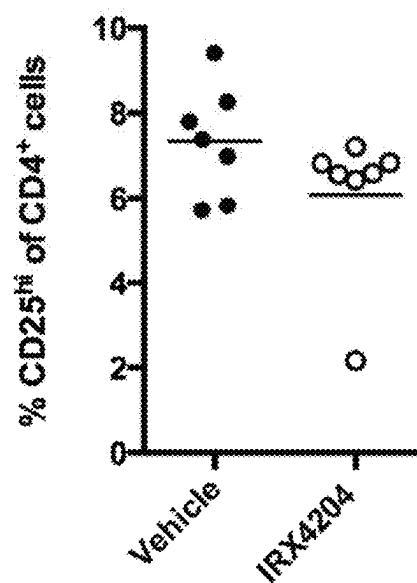FIG. 12C
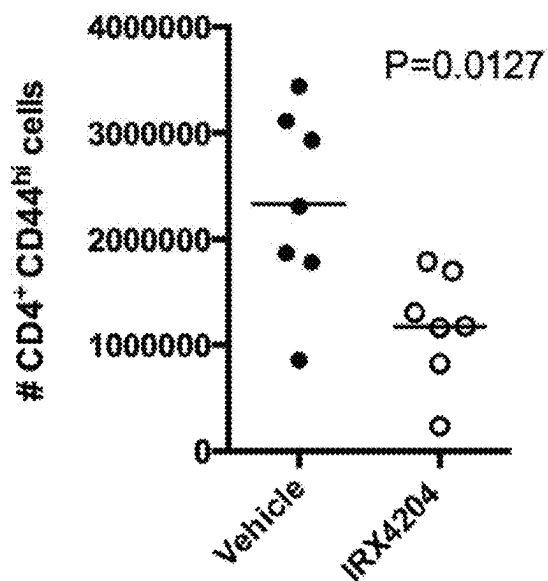
FIG. 12D
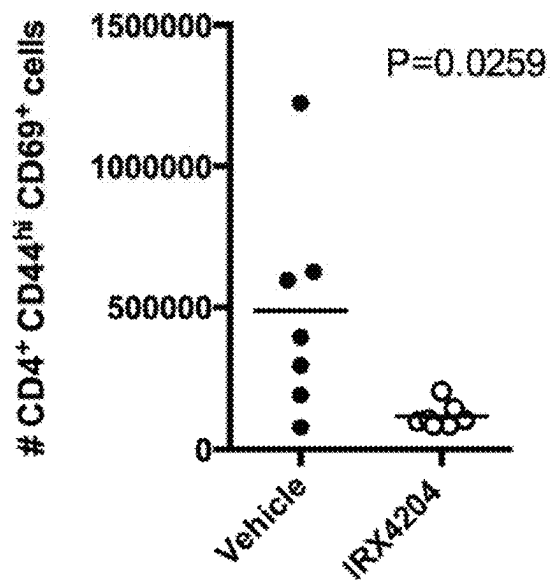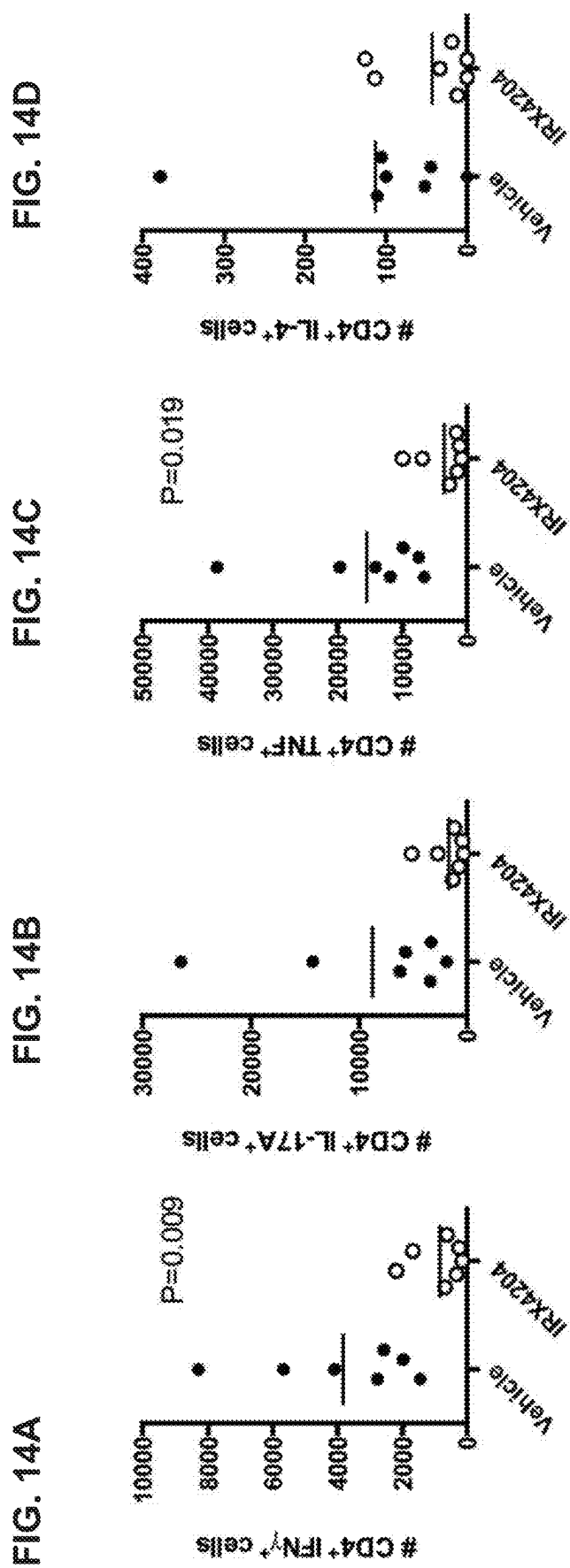
FIG. 14A

CD4⁺ IFNγ⁺ cells

P=0.009

FIG. 14B

CD4⁺ IL-17A⁺ cells

FIG. 14C

CD4⁺ TNF⁺ cells

P=0.019

FIG. 14D

CD4⁺ IL-4⁺ cells

FIG. 15A

CD4+ IL-17A+ IFNγ+ cells

FIG. 15B

CD4+ IL-17A+ IFNγ+ cells

FIG. 15C

P=0.0047

CD4+ IFNγ+ IL-17A+ cells
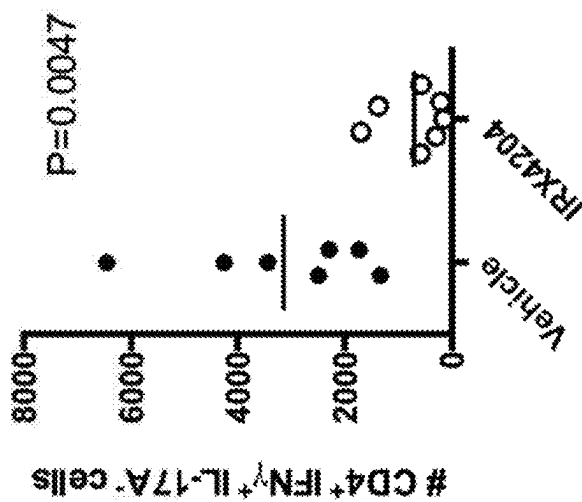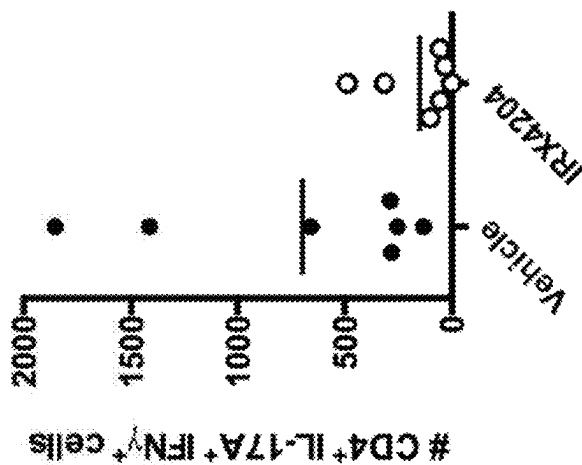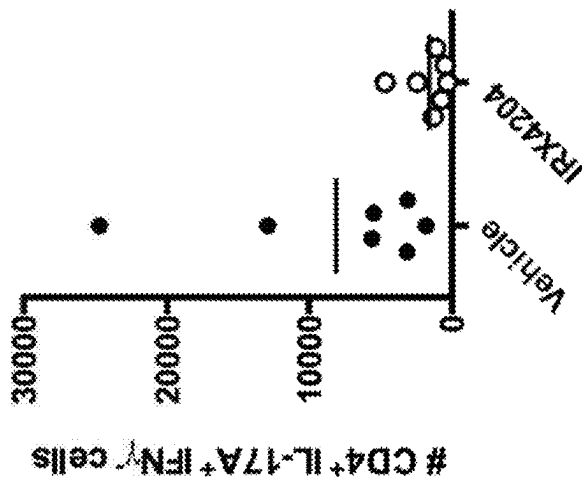
TREATMENT OF DISEASES BY CONCURRENTLY ELICITING REMYELINATION EFFECTS AND IMMUNOMODULATORY EFFECTS USING SELECTIVE RXR AGONISTS

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application is a continuation of U.S. patent application Ser. No. 16/736,705, filed Jan. 7, 2020, which is a continuation of U.S. patent application Ser. No. 14/507,730, filed Oct. 6, 2014, now U.S. Pat. No. 10,653,650, which claims the benefit of U.S. Provisional Patent Application 61/887,529, filed Oct. 7, 2013 and is a continuation-in-part of U.S. patent application Ser. No. 13/714,051 filed Dec. 13, 2012, which claims the benefit of U.S. Provisional Patent Application 61/570,182, filed Dec. 13, 2011, all of which are hereby incorporated by reference in their entirety.

GOVERNMENT SUPPORT

This invention was made with government support under R01-CA062275 and R01-AT005382 awarded by National Institutes of Health (NIH). The government has certain rights in the invention.

FIELD

The present invention is directed to methods of inducing remyelination in demyelination-associated disorders using RXR agonists.

BACKGROUND

Attempts to treat autoimmune disorders have met with limited success. This is due, in part, to the fact that the etiology of autoimmune disorders is a complex response based in part on a combination of factors, including, without limitation, genetic make-up of individual, gender or hormonal status, bacterial or viral infection, metal or chemical toxin exposure, vaccinations or immunizations, stress, trauma, smoking and/or nutritional deficiencies. Therefore, compounds, compositions, and methods that can reduce a symptom associated with an autoimmune disorder, inflammation associated with an autoimmune disorder, and/or a transplant rejection would be highly desirable.

Naïve CD4$^+$ T cells play a central role in immune protection. They do so through their capacity to help B cells make antibodies, to induce macrophages to develop enhanced microbicidal activity, to recruit neutrophils, eosinophils, and basophils to sites of infection and inflammation, and, through their production of cytokines and chemokines, to orchestrate the full panoply of immune responses. Naïve CD4$^+$ T cells are multipotential precursors that differentiate into various T cell subsets, such as, e.g., T helper (Th) cells (also called T effector cells) and T regulatory (Treg) cells. T helper cells are characterized by their distinct functions and include Th1, Th2, and Th17. Th1 cells aid in the clearance of intracellular bacteria and viruses, secrete IFN-γ in response to the cytokine interleukin-12 (IL-12), and require the transcription factors T-box21 (T-bet) and signal transducer and activator of transcription 1 (Stat1) and (Stat4). Th2 cells help control extracellular pathogens, secrete the cytokines IL-4, IL-5 and IL-13, and require transcription factors GATA-binding protein 3 (GATA-3) and Stat6. Th17 cells provide protection against fungi and vari-

ous other extracellular bacteria, secrete the pro-inflammatory cytokine IL-17A, and express the transcription factor retinoic acid orphan receptor gamma (RORγt). Treg cells play a critical role in maintaining self-tolerance as well as in regulating immune responses and express the transcription factor forkhead box P3 (FoxP3). Tregs normally develop in the thymus, but can also differentiate from naïve CD4$^+$ cells stimulated with TGF-β and IL-2. Development and differentiation of Treg cells, as well as expression of FoxP3, require the transcription factor Stat5.

Although several cytokines participate in Th17 cell differentiation, IL-6 and TGF-β are key factors for the generation of Th17 cells from naïve T CD4$^+$ cells. On the other hand, IL-6 inhibits TGF-β-induced Treg cells which suppress adaptive T cell responses and prevent autoimmunity, and are thus important in the maintenance of immune homeostasis. The two T-cell subsets play prominent roles in immune functions: Th17 plays a key role in the pathogenesis of autoimmune diseases and protection against bacterial infections, while Treg functions to restrain excessive helper T-cell responses. Essentially immunosuppressive Tregs cells and pro-inflammatory Th17 cells functionally antagonize each other.

As such, a fine balance between Th17 and Treg cells may be crucial for the stability of immune homeostasis. Once the equilibrium is broken, the destabilization may lead to chronic inflammation and autoimmunity. For example, dysregulation or overproduction of IL-6 leads to autoimmune diseases such as multiple sclerosis (MS) and rheumatoid arthritis (RA), in which Th17 cells are considered to be the primary cause of pathology. Clinical evidence indicates that both defects in Treg function or reduced numbers, as well as Th17 activity are important in several autoimmune diseases, including seronegative arthritis in adults, and childhood arthritis (juvenile idiopathic arthritis). Therefore, an effective approach in the treatment of various autoimmune and inflammatory diseases will be to normalize the balance between Treg and Th17 cell development.

There are two main types of receptors that mediate the effects of derivatives of vitamin A in mammals (and other organisms), the Retinoic Acid Receptors (RARs) and the Retinoid X Receptors (RXRs). Within each type there are three subtypes designated RAR alpha, RAR beta, and RAR gamma for the RAR family and RXR alpha, RXR beta, and RXR gamma for the RXR family. These receptor types are evolutionarily related but are functionally distinct. The ligands that activate the RARs, referred to as retinoids, and the ligands that activate the RXRs, referred to as rexinoids, elicit quite different biological effects. Retinoic acid (RA), the physiological hormone of all three RARs, has been shown to enhance the in vitro differentiation of Treg cells that suppress immunity. RA can also inhibit the differentiation of pro-inflammatory Th17 cells that have been casually implicated in the development of many human autoimmune diseases. Based on this ability to restore a normal Th17/Treg cell ratio by decreasing Th17 cells while simultaneously increasing Treg cells, RAR agonists have been proposed as effective therapeutic compounds for the treatment of inflammatory and autoimmune disorders. However, recent findings have identified retinoid signaling through RARs as being required for the initial development of Th17 cell mediated immune responses and inflammation. These counteracting effects of RAR pan agonists on Th17 cell development bring into question the value of such compounds as anti-inflammatory and immunosuppressive agents.

Although RAR agonists like retinoic acid have been used to treat autoimmune disorders associated with inflammation,

their usefulness in clinical practice has been limited due to unwanted side effects and counter-therapeutic inflammatory effects. Thus, what are needed are compounds and compositions that maintain the ability to inhibit Th17 cell formation and function and to promote Treg cell formation, but not possess any pro-inflammatory activities and other unwanted side effects associated with RAR pan agonists like RA. Such compounds will be of considerable therapeutic value as immunomodulatory agents.

RXRs function as ligand-activated nuclear receptors which regulate the transcription of target genes. RXRs can form RXR homodimers and also can form heterodimers with a range of other nuclear receptors. These RXR heterodimers fall into two broad classes; non-permissive heterodimers with receptors such as RAR, vitamin D receptor (VDR), and thyroid hormone receptor (TR) and permissive heterodimers with receptors such as peroxisome proliferator activator receptor (PPAR), farnesoid X receptor (FXR), and liver X receptor (LXR). The non-permissive RXR heterodimers such as RXR/RAR cannot be activated by RXR ligands but only by ligands to the partner receptor (e.g.: RAR). However, the permissive heterodimers can be activated by both ligands to RXR as well as ligands to the partner receptor (e.g.: PPAR).
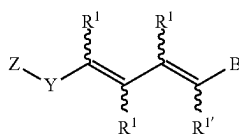
SUMMARY

The present specification discloses compounds, compositions, and methods for treating an individual suffering from an autoimmune disorder, in particular a demyelination-related disorder. This is accomplished by administering a therapeutically effective amount of a RXR agonist or composition comprising such agonist to an individual suffering from an autoimmune disorder, in particular a demyelination-related disorder. As disclosed herein, the disclosed RXR agonists can control the Th17/Treg cell number ratio by elevating Treg cell numbers and suppressing Th17 cell numbers and also promote remyelination. As such, the disclosed RXR agonists would be useful in treating an autoimmune disorder, in particular a demyelination-related disorder.

Thus, disclosed herein is a method of treating a demyelination-related disorder, the method comprising the step of administering to an individual in need thereof a therapeutically effective amount of a RXR agonist with both remyelination promotion and immunomodulatory activities, wherein administration of the RXR agonist treats the demyelination-related disorder in the individual by both promoting remyelination of neurons and modulating the individual's immune system.

In one embodiment, the immunomodulatory activity comprises increasing the number of Treg cells in the individual. In another embodiment, the immunomodulatory activity comprises decreasing the number of Th17 cells in the individual. In yet another embodiment, the immunomodulatory activity comprises increasing the number of Treg cells and decreasing the number of Th17 cells in the individual.
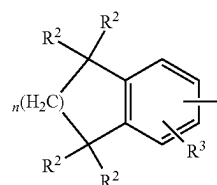
Thus, aspects of the present specification disclose a RXR agonist. Non-limiting examples of a RXR agonist include a compound having the structure of formula I,

(I)

wherein Z is a radical having the structure of Formula II:

(II)

Y is cycloalkyl or cycloalkenyl of 3 to 8 carbons optionally substituted with one or two R^4 groups, or Y is selected from phenyl, pyridyl, thienyl, furyl, pyrrolyl, pyridazinyl, pyrimidiyl, pyrazinyl, thiazolyl, oxazolyl, and imidazolyl, the groups being optionally substituted with one or two R^4 groups, the divalent Y radical being substituted by the Z and —$(CR^1=CR^1=CR^1=CR^1)$— groups on adjacent carbons; R^1 and R^2 independently are H, lower alkyl or fluoroalkyl; R^3 is hydrogen, lower alkyl, Cl or Br; R^4 is lower alkyl, fluoroalkyl or halogen, and B is hydrogen, —COOH or a pharmaceutically acceptable salt thereof, —$COOR^8$, —$CONR^9R^{10}$, —CH_2OH, —CH_2OR^{11}, —CH_2OCOR^{11}, —CHO, —$CH(OR^{12})_2$, —$CHOR^{13}O$, —$OCOR^7$, —CR7 $(OR^{12})_2$, —$CR^7OR^{13}O$, or tri-lower alkylsilyl, where R^7 is an alkyl, cycloalkyl or alkenyl group, containing 1 to 5 carbons, R^8 is an alkyl group of 1 to 10 carbons, a cycloalkyl group of 5 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or R^8 is phenyl or lower alkylphenyl, R^9 and R^{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R^{11} is lower alkyl, phenyl or lower alkylphenyl, R^{12} is lower alkyl, R^{13} is divalent alkyl radical of 2-5 carbons; and n is 1 or 2.

In another embodiment, the demyelination-related disorder is a central nervous system disorder and the central nervous system disorder is multiple sclerosis, neuromyelitis optica, acute disseminated encephalomyelitis, Marburg multiple sclerosis, diffuse myelinoclastic sclerosis (Schilder's disease), Balo concentric sclerosis, solitary sclerosis, optic neuritis, transverse myelitis, amyotrophic lateral sclerosis, leukodystrophy (multiple variants, e.g. adrenoleukodystrophy, adrenomyeloneuropathy), Parkinson's disease, Alzheimer's disease, progressive supranuclear palsy, stroke, traumatic brain injury, radiation induced neuroinflammation, radiation-induced central nervous system inflammation, radiation somnolence syndrome, Devic's disease, inflammatory demyelinating diseases, a CNS neuropathies like those produced by vitamin B12 deficiency, central pontine myelinolysis, myelopathies like Tabes dorsalis (syphilitic myelopathy), leukoencephalopathies like progressive multifocal leukoencephalopathy, or leukodystrophies.

In another embodiment, the demyelination-related disorder is a peripheral nervous system disorder such as Guillain-Barré Syndrome, acute inflammatory demyelinating polyneuropathy, chronic inflammatory demyelinating polyneuropathy, demyelinating diabetic neuropathy, progressive inflammatory neuropathy, drug- or toxin-induced neuropathy, such as chemotherapy-induced neuropathy or organophosphate-induced neuropathy, anti-MAG peripheral neuropathy, Charcot-Marie-Tooth Disease, or copper deficiency.

In another embodiment, the therapeutically effective amount is about 0.001 mg/kg/day to about 100 mg/kg/day, or about 0.1 mg/kg/day to about 10 mg/kg/day. In yet

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another embodiment, the therapeutically effective amount is about 0.01 mg/m²/day to about 100 mg/m²/day or about 15 mg/m²/day to about 60 mg/m²/day.

In certain embodiments, the RXR agonist is administered by nasal administration.

In another embodiment, treatment with the RXR agonist reduces at least one symptom of the demyelination-related disorder, wherein at least one symptom reduced is inflammation, fatigue, dizziness, malaise, elevated fever and high body temperature, extreme sensitivity to cold in the hands and feet, weakness and stiffness in muscles and joints, weight changes, digestive or gastrointestinal problems, low or high blood pressure, irritability, anxiety, or depression, blurred or double vision, ataxia, clonus, dysarthria, fatigue, clumsiness, hand paralysis, hemiparesis, genital anesthesia, incoordination, paresthesias, ocular paralysis, impaired muscle coordination, weakness (muscle), loss of sensation, impaired vision, neurological symptoms, unsteady gait, spastic paraparesis, incontinence, hearing problems, or speech problems.

Also disclosed herein is a method of treating multiple sclerosis, the method comprising the step of administering to an individual in need thereof a therapeutically effective amount of a RXR agonist, wherein the RXR agonist is 3,7-dimethyl-6(S),7(S)-methano,7-[1,1,4,4-tetramethyl-1,2, 3,4-tetrahydronaphth-7-yl]2(E),4(E) heptadienoic acid; and wherein administration of the RXR agonist reduces a symptom associated with the multiple sclerosis, thereby treating the individual.

Also disclosed herein is a method of treating radiation-induced central nervous system (CNS) inflammation, the method comprising the step of administering to an individual in need thereof a therapeutically effective amount of a RXR agonist, wherein the RXR agonist is 3,7-di methyl-6(S),7(S)-methano, 7-[1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphth-7-yl]2(E),4(E) heptadienoic acid; and wherein administration of the RXR agonist reduces a symptom associated with the radiation-induced CNS inflammation, thereby treating the individual.

Also disclosed herein is a method of treating a CNS demyelination-related disorder, the method comprising the step of administering to an individual in need thereof a therapeutically effective amount of a RXR agonist, wherein the RXR agonist is 3,7-dimethyl-6(S),7(S)-methano,7-[1,1, 4,4-tetramethyl-1,2,3,4-tetrahydronaphth-7-yl]2(E),4(E) heptadienoic acid; and wherein administration of the RXR agonist reduces a symptom associated with the CNS demyelination-related disorder, thereby treating the individual and wherein the RXR agonists is delivered directly to the CNS of the individual by intrathecal administration, epidural administration, cranial injection or implant, or nasal administration.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1A-B shows that RXR agonists regulate Foxp3 (FIG. 1A) and α4β7 (FIG. 1B) expression.

FIG. 2A-B shows that RXR agonists increase Treg differentiation under Th17 conditions (FIG. 2A) and inhibit Th17 differentiation under Th17 conditions (FIG. 2B).

FIG. 3 shows the effects of RAR signaling inhibition on RXR agonist inducement of Treg differentiation.

FIG. 4 shows RXR agonist activation of transcription from RXRα, RXRβ, RXRγ, RARα, RARβ, and RARγ using transactivation assays.

FIG. 5 shows that RXR agonists attenuate experimental autoimmune encephalomyelitis (EAE) in C57BL/6 mice.

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FIG. 6A-B shows that RXR agonists reduce leukocyte infiltration into the central nervous system. FIG. 6A depicts the number of CD4⁺ cells and FIG. 6B depicts the number of CD11c⁺ CD11b⁺ cells (myeloid DC) in mice treated with the RXR agonist IRX4204 (4204) verses the vehicle control.

FIG. 7 shows RXR agonists attenuate EAE in SJL mice.

FIG. 8A-D shows that IRX4204 selectively activates RXR-Nurr1 heterodimers. Transactivation assay of IRX4204 (194204, Formula XXIX) for farnesoid X receptor FXR (FIG. 8A); for liver X receptors LXRα and LXRβ (FIG. 8B); for peroxisome proliferator-activated receptor PPARγ (FIG. 8C); and for Nurr1 receptor in the presence or absence of RXR (FIG. 8D).

FIG. 9 shows the percentage of green fluorescent protein (EGFP) positive oligodendrocytes after culture of oligodendrocyte precursor cells derived from embryonic mouse brains with various concentrations of IRX4204.

FIG. 10 depicts effects of RXR agonist IRX4204 on EAE in mice,

FIG. 11A-B depicts expression of CCR6 (FIG. 11A) and CD49d (FIG. 11B) on splenocytes from EAE mice treated with 200 μg/day of IRX4204 or control.

FIG. 12A-D depicts quantification (FIG. 12A) and frequency (FIG. 12B) of CD4⁺ CD25hi cells, total number of effector and memory CD4 T cells (FIG. 12C), and total number of activated CD4 T cells (FIG. 12D) in splenocytes from EAE mice treated with 200 μg/day of IRX4204 or control.

FIG. 13 depicts the total number of infiltrating CD4 T cells in the CNS of EAE mice treated with 200 μg/day of IRX4204 or control.

FIG. 14A-D depicts restimulation of the infiltrating lymphocytes of FIG. 13 to determine expression of interferon gamma (IFNγ) (FIG. 14A), IL-17A (FIG. 14B), tumor necrosis factor (TNF) (FIG. 14C), and IL-4 (FIG. 14D).

FIG. 15A-C depicts the quantification of co-expression of IFNγ and IL-17A by CD4 T cells of FIG. 13 expressing IL-17A and not IFNγ (FIG. 15A), IL-17A and IFNγ (FIG. 15B), IFNγ and not IL-17A (FIG. 15C).

DETAILED DESCRIPTION

Many diseases of the central nervous system (CNS) are associated with demyelination of axons and neurons. Such disorders of demyelination may be autoimmune diseases or disorders of other etiologies. Multiple Sclerosis (MS) is an example of an autoimmune disorder which is also associated with demyelination. Accordingly, an optimal drug for the treatment of MS would address the autoimmune aspect of the disease while concurrently enhancing remyelination. MS is currently treated by several immunomodulatory drugs that provide clinical benefit by modulating patient immune responses and producing anti-inflammatory effects. These drugs delay disease progression but do not reverse disease pathology or restore neurological function by restoring myelination of damaged neurons. IRX4204 (194204, Formula XXIX), a Retinoid X Receptor (RXR) ligand that has an unique mechanism of action in being a selective activator of RXR homodimers and RXR-Nurr1 heterodimers, simultaneously provides immunomodulatory activities and also promotes remyelination. IRX4204 promotes the differentiation of suppressive Treg cells while simultaneously inhibiting the differentiation of pro-inflammatory Th17 cells thereby favorably affecting the aberrantly skewed Th17/Treg cell ratio which underlies human autoimmune diseases such as MS. Thus, by virtue of its effects on Th17/Treg cell ratios, IRX4204 will have clinical benefits similar to current

standard of care treatments in MS. IRX4204 can additionally promote remyelination of demyelinated CNS neurons. Accordingly, IRX4204, and other RXR ligands of the same receptor activating profile, compounds that provide both immunomodulatory activity and promote remyelination, will not only delay disease progression in MS but also effect neural repair by regenerating healthy axons and neurons. IRX4204 is expected to be an optimal drug for the treatment of MS and other autoimmune diseases which are also associated with demyelination.

The RARs and RXRs and their cognate ligands function by distinct mechanisms. The RARs always form heterodimers with RXRs and these RAR/RXR heterodimers bind to specific response elements in the promoter regions of target genes. The binding of RAR agonists to the RAR receptor of the heterodimer results in activation of transcription of target genes leading to retinoid effects. On the other hand, RXR agonists do not activate RAR/RXR heterodimers. RXR heterodimer complexes like RAR/RXR, can be referred to as non-permissive RXR heterodimers as activation of transcription due to ligand-binding occurs only at the non-RXR protein (e.g., RAR); activation of transcription due to ligand binding does not occur at the RXR. RXRs also interact with nuclear receptors other than RARs and RXR agonists may elicit some of its biological effects by binding to such RXR/receptor complexes. These RXR/receptor complexes can be referred to as permissive RXR heterodimers as activation of transcription due to ligand-binding could occur at the RXR, the other receptor, or both receptors. Examples of permissive RXR heterodimers include, without limitation, peroxisome proliferator activated receptor/RXR (PPAR/RXR), farnesyl X receptor/RXR (FXR/RXR), nuclear receptor related-1 protein (Nurr1/RXR) and liver X receptor/RXR (LXR/RXR). Alternately, RXRs may form RXR/RXR homodimers which can be activated by RXR agonists leading to rexinoid effects. Also, RXRs interact with proteins other than nuclear receptors and ligand binding to an RXR within such protein complexes can also lead to rexinoid effects. Due to these differences in mechanisms of action, RXR agonists and RAR agonists elicit distinct biological outcomes and even in the instances where they mediate similar biological effects, they do so by different mechanisms. Moreover, the unwanted side effects of retinoids, such as pro-inflammatory responses or mucocutaneous toxicity, are mediated by activation of one or more of the RAR receptor subtypes. Stated another way, biological effects mediated via RXR pathways would not induce pro-inflammatory responses, and thus, would not result in unwanted side effects.

As disclosed herein, RXR agonists inhibit Th17 cell formation and promote Treg cell formation by mechanisms that do not involve RARs. As such, a selective RXR agonist that does not activate RARs would be a more effective agent in the treatment of an autoimmune disorder, in particular a demyelination-related disorder. In support of this, the present specification discloses that RXR agonists have cell differentiating effects in that they can regulate the Th17/Treg cell number ratio by elevating Treg cell numbers and suppressing Th17 cell numbers. In this manner, a normal balance of both these cell types can be achieved and immune homeostatis restored. Furthermore, since selective RXR agonists achieve these therapeutic effects without activation of RARs, they would be optimally effective and beneficial in treating an autoimmune disorder, in particular a demyelination related disease.

Thus, aspects of the present specification provide, in part, a RXR agonist. As used herein, the term "RXR agonist", is

synonymous with "RXR selective agonist" and refers to a compound that selectively binds to one or more RXR receptors like a RXRα, a RXRβ, or a RXRγ in a manner that elicits gene transcription via an RXR response element. As used herein, the term "selectively binds," when made in reference to a RXR agonist, refers to the discriminatory binding of a RXR agonist to the indicated target receptor like a RXRα, a RXRβ, or a RXRγ such that the RXR agonist does not substantially bind with non-target receptors like a RARα, a RARβ or a RARγ.

In one embodiment, the selective RXR agonist does not activate to any appreciable degree the permissive heterodimers PPAR/RXR, FXR/RXR, and LXR/RXR. In another embodiment, the RXR agonist activates the permissive heterodimer Nurr1/RXR. One example of such a selective RXR agonist is 3,7-dimethyl-6(S),7(S)-methano,7-[1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphth-7-yl]2(E),4(E) heptadienoic acid (IRX4204, 194204, Formula XXIX) disclosed herein, the structure of which is shown in Formula XXIX. In other aspects of this embodiment, the RXR agonist activates the permissive heterodimers PPAR/RXR, FXR/RXR, or LXR/RXR by 1% or less, 2% or less, 3% or less, 4% or less, 5% or less, 6% or less, 7% or less, 8% or less, 9% or less, or 10% or less relative to the ability of an activating RXR agonist to activate the same permissive heterodimer. Examples of an RXR agonist which activates one or more of PPAR/RXR, FXR/RXR, or LXR/RXR include, e.g., LGD1069 (bexarotene) and LGD268.

IRX4204, like many other RXR ligands, does not activate non-permissive heterodimers such as RAR/RXR. However, IRX4204 is unique in that it specifically activates the Nurr1/RXR heterodimer and does not activate other permissive RXR heterodimers such as PPAR/RXR, FXR/RXR, and LXR/RXR. Other RXR ligands generally activate these permissive RXR heterodimers. Thus, all RXR ligands cannot be classified as belonging to one class. IRX4204 belongs to a unique class of RXR ligands which specifically activate RXR homodimers and only one of the permissive RXR heterodimers, namely the Nurr1/RXR heterodimer. This unique receptor profile enables IRX4204 to have both immunomodulatory and neural repair properties. Thus, the use of specific RXR homodimer, Nurr1/RXR activators, such as IRX4204, provides a uniquely effective ways of treating demyelination-related disorders, such as multiple sclerosis.

Selective binding of a RXR agonist to a RXR receptor includes binding properties such as, e.g., binding affinity and binding specificity. Binding affinity refers to the length of time a RXR agonist resides at its RXR receptor binding site, and can be viewed as the strength with which a RXR agonist binds its a RXR receptor. Binding affinity can be described as a RXR agonist's equilibrium dissociation constant (KD), which is defined as the ratio Kd/Ka at equilibrium, where Ka is a RXR agonist's association rate constant and kd is a RXR agonist's dissociation rate constant. Binding affinity is determined by both the association and the dissociation and alone neither high association nor low dissociation can ensure high affinity. The association rate constant (Ka), or on-rate constant (Kon), measures the number of binding events per unit time, or the propensity of a RXR agonist and its RXR receptor to associate reversibly into its agonist-receptor complex. The association rate constant is expressed in M^{-1} s^{-1}, and is symbolized as follows: $[Ag] \times [Rc] \times Kon$. The larger the association rate constant, the more rapidly a RXR agonist binds to its RXR receptor, or the higher the binding affinity between agonist and receptor. The dissociation rate constant (Kd), or off-rate constant (Koff), measures the

number of dissociation events per unit time propensity of an agonist-receptor complex to separate (dissociate) reversibly into its component molecules, namely the RXR agonist and the RXR receptor. The dissociation rate constant is expressed in s^{-1}, and is symbolized as follows: $[Ag+Rc] \times Koff$. The smaller the dissociation rate constant, the more tightly bound a RXR agonist is to its RXR receptor, or the higher the binding affinity between agonist and receptor. The equilibrium dissociation constant (KD) measures the rate at which new agonist-receptor complexes formed equals the rate at which agonist-receptor complexes dissociate at equilibrium. The equilibrium dissociation constant is expressed in M, and is defined as $Koff/Kon=[Ag] \times [Rc]/[Ag+Rc]$, where [Ag] is the molar concentration of a RXR agonist, [Rc] is the molar concentration of the RXR receptor, and [Ag+Rc] is the of molar concentration of the agonist-receptor complex, where all concentrations are of such components when the system is at equilibrium. The smaller the equilibrium dissociation constant, the more tightly bound a RXR agonist is to its RXR receptor, or the higher the binding affinity between agonist and receptor.

In aspects of this embodiment, the binding affinity of a RXR agonist that selectively binds to a RXR receptor can have an association rate constant of, e.g., less than 1×10^5 $M^{-1} s^{-1}$, less than $1 \times 10^6 M^{-1} s^{-1}$, less than $1 \times 10^7 M^{-1} s^{-1}$, or less than $1 \times 10^8 M^{-1} s^{-1}$. In another embodiment, the binding affinity of a RXR agonist that selectively binds to a RXR receptor can have an association rate constant of, e.g., more than $1 \times 10^5 M^{-1} s^{-1}$, more than $1 \times 10^6 M^{-1} s^{-1}$, more than $1 \times 10^7 M^{-1} s^{-1}$, or more than $1 \times 10^8 M^{-1} s^{-1}$. In other aspects, the binding affinity of a RXR agonist that selectively binds to a RXR receptor can have an association rate constant between, e.g., $1 \times 10^5 M^{-1} s^{-1}$ to $1 \times 10^8 M^{-1} s^{-1}$, $1 \times 10^6 M^{-1} s^{-1}$ to $1 \times 10^8 M^{-1} s^{-1}$, $1 \times 10^5 M^{-1} s^{-1}$ to $1 \times 10^7 M^{-1} s^{-1}$, or $1 \times 10^6 M^{-1} s^{-1}$ to $1 \times 10^7 M^{-1} s^{-1}$.

In other aspects of this embodiment, the binding affinity of a RXR agonist that selectively binds to a RXR receptor can have a disassociation rate constant of, e.g., less than $1 \times 10^{-3} s^{-1}$, less than $1 \times 10^{-4} s^{-1}$, or less than $1 \times 10^{-5} s^{-1}$. In another embodiment, the binding affinity of a RXR agonist that selectively binds to a RXR receptor can have a disassociation rate constant of, e.g., more than $1 \times 10^{-3} s^{-1}$, more than $1 \times 10^{-4} s^{-1}$, or more than $1 \times 10^{-5} s^{-1}$. In other aspects, the binding affinity of a RXR agonist that selectively binds to a RXR receptor can have a disassociation rate constant between, e.g., $1 \times 10^{-3} s^{-1}$ to $1 \times 10^{-5} s^{-1}$, $1 \times 10^{-3} s^{-1}$ to $1 \times 10^{-4} s^{-1}$, or $1 \times 10^{-4} s^{-1}$ to $1 \times 10^{-5} s^{-1}$.

In yet other aspects of this embodiment, the binding affinity of a RXR agonist that selectively binds to a RXR receptor can have an equilibrium disassociation constant of less than 100 nM. In aspects of this embodiment, the binding affinity of a RXR agonist that selectively binds to a RXR receptor can have an equilibrium disassociation constant of, e.g., less than 100 nM, less than 90 nM, less than 80 nM, less than 70 nM, less than 60 nM, less than 50 nM, less than 40 nM, less than 30 nM, less than 20 nM, or less than 10 nM. In aspects of this embodiment, the binding affinity of a RXR agonist that selectively binds to a RXR receptor can have an equilibrium disassociation between, e.g., 0.1 nM to 10 nM, 0.1 nM to 50 nM, 0.1 nM to 100 nM, 0.5 nM to 10 nM, 0.5 nM to 50 nM, 0.5 nM to 100 nM, 1 nM to 10 nM, 1 nM to 50 nM, or 1 nM to 100 nM.

In still other aspects of this embodiment, the binding affinity of a RXR agonist that selectively binds to a RXR can have an association rate constant for a RAR receptor of, e.g., less than $1 \times 10^0 M^{-1} s^{-1}$, less than $1 \times 10^1 M^{-1} s^{-1}$, less than $1 \times 10^2 M^{-1} s^{-1}$, less than $1 \times 10^3 M^{-1} s^{-1}$, or less than 1×10^4

$M^{-1} s^{-1}$. In another embodiment, the binding affinity of a RXR agonist that selectively binds to a RXR receptor can have an association rate constant of a RAR receptor of, e.g., at most $1 \times 10^0 M^{-1} s^{-1}$, at most $1 \times 10^1 M^{-1} s^{-1}$, at most 1×10^2 $M^{-1} s^{-1}$, at most $1 \times 10^3 M^{-1} s^{-1}$, or at most $1 \times 10^4 M^{-1} s^{-1}$.

In further aspects of this embodiment, the binding affinity of a RXR agonist that selectively binds to a RXR receptor can have an equilibrium disassociation constant for a RAR receptor of, e.g., more than 500 nM, for than 1,000 nM, more than 5,000 nm, or more than 10,000 nM. In another embodiment, the binding affinity of a RXR agonist that selectively binds to a RXR receptor can have an equilibrium disassociation constant for a RAR receptor between, e.g., 500 nM to 10,000 nM, 1,000 nM to 10,000 nM, or 5,000 nM to 10,000 nM.

Binding specificity is the ability of a RXR agonist to discriminate between a RXR receptor and a receptor that does not contain its binding site, such as, e.g., a RAR receptor. One way to measure binding specificity is to compare the Kon association rate of a RXR agonist for its RXR relative to the Kon association rate of a RXR agonist for a receptor that does not contain its binding site. For example, comparing the Ka of a RXR agonist for its RXR receptor relative to a RAR receptor

In aspects of this embodiment, a RXR agonist that selectively binds to a RXR receptor can have a Ka for a receptor not comprising its binding site of, e.g., less than $1 \times 10^0 M^{-1}$ s^{-1}, less than $1 \times 10^1 M^{-1} s^{-1}$, less than $1 \times 10^2 M^{-1} s^{-1}$, less than $1 \times 10^3 M^{-1} s^{-1}$ or less than $1 \times 10^4 M^{-1} s^{-1}$. In other aspects of this embodiment, a RXR agonist that selectively binds to a RXR receptor can have a Ka for a receptor not comprising its binding site of, e.g., at most $1 \times 10^0 M^{-1} s^{-1}$, at most $1 \times 10^1 M^{-1} s^{-1}$, at most $1 \times 10^2 M^{-1} s^{-1}$, at most 1×10^3 $M^{-1} s^{-1}$ or at most $1 \times 10^4 M^{-1} s^{-1}$.

In other aspects of this embodiment, a RXR agonist that selectively binds to a RXR receptor can have a Ka for a receptor not comprising its binding site of, e.g., at least 2-fold more, at least 3-fold more, at least 4-fold more, at least 5-fold more, at least 6-fold more, at least 7-fold more, at least 8-fold more, or at least 9-fold more. In further aspects of this embodiment, a RXR agonist that selectively binds to a RXR receptor can have a Ka for a receptor not comprising its binding site of, e.g., at least 10-fold more, at least 100-fold more, at least 1,000-fold more or at least 10,000-fold more. In yet other aspects of this embodiment, a RXR agonist that selectively binds to a RXR receptor can have a Ka for a receptor not comprising its binding site of, e.g., at most 1-fold more, at most 2-fold more, at most 3-fold more, at most 4-fold more, at most 5-fold more, at most 6-fold more, at most 7-fold more, at most 8-fold more, or at most 9-fold more. In yet other aspects of this embodiment, a RXR agonist that selectively binds to a RXR receptor can have a Ka for a receptor not comprising its binding site of, e.g., at most 10-fold more, at most 100-fold more, at most 1,000-fold more or at most 10,000-fold more.

The binding specificity of a RXR agonist that selectively binds to a RXR receptor can also be characterized as a binding ratio that such a RXR agonist can discriminate its RXR receptor relative to a receptor not comprising its binding site, such as, e.g., a RAR receptor. In aspects of this embodiment, a RXR agonist that selectively binds to a RXR receptor has a binding ratio for its RXR receptor relative to a receptor not comprising its binding site of, e.g., at least 2:1, at least 3:1, at least 4:1, at least 5:1, at least 64:1, at least 7:1, at least 8:1, at least 9:1, at least 10:1, at least 15:1, at least 20:1, at least 25:1, at least 30:1, at least 35:1, or at least 40:1. In other aspects of this embodiment, a RXR agonist that
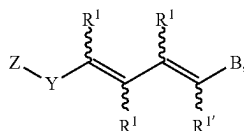
selectively binds to a RXR receptor has a binding ratio for its RXR receptor relative to a RAR receptor of, e.g., at least 2:1, at least 3:1, at least 4:1, at least 5:1, at least 64:1, at least 7:1, at least 8:1, at least 9:1, at least 10:1, at least 15:1, at least 20:1, at least 25:1, at least 30:1, at least 35:1, or at least 40:1.
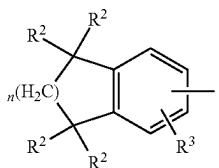
In aspects of this embodiment, a RXR agonist will have a ratio of activity at a RXR receptor relative to a RAR receptor of, e.g., at least 5 greater, at least 10 greater, at least 15, or at least 20 greater.

The binding specificity of a RXR agonist that selectively binds to a RXR receptor can also be characterized as an activity ratio that such a RXR agonist can exert activity through binding to its RXR receptor relative to a receptor not comprising its binding site, such as, e.g., a RAR receptor. In aspects of this embodiment, a RXR agonist that selectively binds to a RXR receptor has an activity ratio through its RXR receptor relative to a receptor not comprising its binding site of, e.g., at least 2:1, at least 3:1, at least 4:1, at least 5:1, at least 64:1, at least 7:1, at least 8:1, at least 9:1, at least 10:1, at least 15:1, at least 20:1, at least 25:1, at least 30:1, at least 35:1, or at least 40:1. In other aspects of this embodiment, a RXR agonist that selectively binds to a RXR receptor has an activity ratio through its RXR receptor relative to a RAR receptor of, e.g., at least 2:1, at least 3:1, at least 4:1, at least 5:1, at least 64:1, at least 7:1, at least 8:1, at least 9:1, at least 10:1, at least 15:1, at least 20:1, at least 25:1, at least 30:1, at least 35:1, or at least 40:1.

In an aspect of this embodiment, a RXR agonist is a compound having the structure of formula I:

(I)

wherein Z is a radical having the structure of Formula II:


(II)

Y is cycloalkyl or cycloalkenyl of 3 to 8 carbons optionally substituted with one or two R^4 groups, or Y is selected from phenyl, pyridyl, thienyl, furyl, pyrrolyl, pyridazinyl, pyrimidiyl, pyrazinyl, thiazolyl, oxazolyl, and imidazolyl, the groups being optionally substituted with one or two R^4 groups, the divalent Y radical being substituted by the Z and —(CR^1=CR^1—CR^1=CR^1)— groups on adjacent carbons; R^1 and R^2 independently are H, lower alkyl or fluoroalkyl; R^3 is hydrogen, lower alkyl, Cl or Br; R^4 is lower alkyl, fluoroalkyl or halogen, and B is hydrogen, —COOH or a pharmaceutically acceptable salt thereof, —$COOR^8$, —$CONR^9R^{10}$, —CH_2OH, —CH_2OR^{11}, —CH_2OCOR^{11}, —CHO, —$CH(OR^{12})_2$, —$CHOR^{13}O$, —$OCOR^7$, —$CR^7(OR^{12})_2$, —$CR^7OR^{13}O$, or tri-lower alkylsilyl, where R^7 is an alkyl, cycloalkyl or alkenyl group, containing 1 to 5 carbons, R^8 is an alkyl group of 1 to 10 carbons, a cycloalkyl
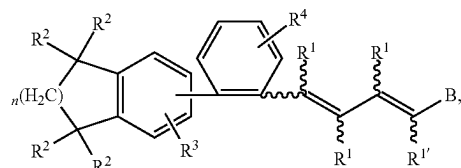
group of 5 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or R^8 is phenyl or lower alkylphenyl, R^9 and R^{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R^{11} is lower alkyl, phenyl or lower alkylphenyl, R^{12} is lower alkyl, R^{13} is divalent alkyl radical of 2-5 carbons; and n is 1 or 2.

In an aspect of this embodiment, a RXR agonist is a compound having the structure of formula III:

(III)
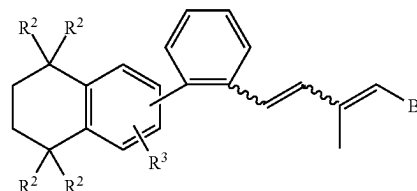
wherein R^2 is hydrogen or lower alkyl; R^3 is hydrogen or lower alkyl, and B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, —$COOR^8$, —$CONR^9R^{10}$, —CH_2OH, —CH_2OR^{11}, —CH_2OCOR^{11}, —CHO, —$CH(OR^{12})_2$, —$CHOR^{13}O$, —COR^7, —$CR^7(OR^{12})_2$, —$CR^7OR^{13}O$, or tri-lower alkylsilyl, where R^7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R^8 is an alkyl group of 1 to 10 carbons, a cycloalkyl group of 5 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or R^8 is phenyl or lower alkylphenyl, R^9 and R^{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R^{11} is lower alkyl, phenyl or lower alkylphenyl, R^{12} is lower alkyl, and R^{13} is divalent alkyl radical of 2-5 carbons.
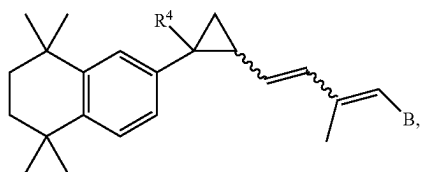
In an aspect of this embodiment, a RXR agonist is a compound having the structure of formula IV:

(IV)

wherein n is 1 or 2; R^1 and R^2 independently are H, lower alkyl or fluoroalkyl; R^3 is hydrogen, lower alkyl, Cl or Br; R^4 is H, lower alkyl, fluoroalkyl or halogen, and B is hydrogen, —COOH or a pharmaceutically acceptable salt thereof, —$COOR^8$, —$CONR^9R^{10}$, —CH_2OH, —CH_2OR^{11}, —CH_2OCOR^{11}, —CHO, —$CH(OR^{12})_2$, —$CHOR^{13}O$, —COR^7, —$CR^7(OR^{12})_2$, —$CR^7OR^{13}O$, or trilower alkylsilyl where R^7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R^8 is an alkyl group of 1 to 10 carbons, or R^8 is phenyl or lower alkylphenyl, R^9 and R^{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R^{11} is lower alkyl, phenyl or lower alkylphenyl, R^{12} is lower alkyl, and R^{13} is divalent alkyl radical of 2-5 carbons.

In an aspect of this embodiment, a RXR agonist is a compound having the structure of formula V:

(V)

where R^4 is lower alkyl of 1 to 6 carbons; B is —COOH or —COOR^8 where R^8 is lower alkyl of 1 to 6 carbons, and the configuration about the cyclopropane ring is cis, and the configuration about the double bonds in the pentadienoic acid or ester chain attached to the cyclopropane ring is trans in each of the double bonds, or a pharmaceutically acceptable salt of the compound.

In an aspect of this embodiment, a RXR agonist is a compound having the structure of formula VI:
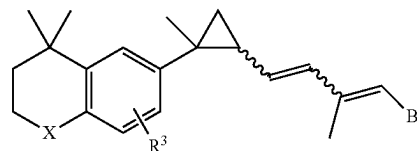
(VI)
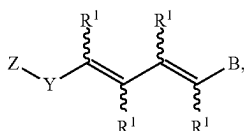
wherein Z is a radical having the structure of Formula VII:
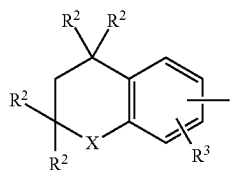
(VII)

Y is cycloalkyl or cycloalkenyl of 3 to 8 carbons optionally substituted with one or two R^4 groups, or Y is selected from phenyl, pyridyl, thienyl, furyl, pyrrolyl, pyridazinyl, pyrimidiyl, pyrazinyl, thiazolyl, oxazolyl, and imidazolyl, the groups being optionally substituted with one or two R^4 groups, the divalent Y radical being substituted by the Z and —(CR^1=CR^1—CR^1=CR^1)— groups on adjacent carbons; X is S or O; R^1 and R^2 independently are H, lower alkyl or fluoroalkyl; R^3 is hydrogen, lower alkyl, Cl or Br; R^4 is lower alkyl, fluoroalkyl or halogen, and B is hydrogen, —COOH or a pharmaceutically acceptable salt thereof, —COOR^8, —CONR^{9}R^{10}, —CH$_2$OH, —CH$_2$OR^{11}, —CH$_2$OCOR^{11}, —CHO, —CH(OR^{12})$_2$, —CHOR^{13}O, —OCOR^7, —CR^7(OR^{12})$_2$, —CR^{7}OR^{13}O, or tri-lower alkylsilyl, where R^7 is an alkyl, cycloalkyl or alkenyl group, containing 1 to 5 carbons, R^8 is an alkyl group of 1 to 10 carbons, a cycloalkyl group of 5 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or R^8 is phenyl or lower alkylphenyl, R^9 and R^{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R^{11} is lower alkyl, phenyl or lower alkylphenyl, R^{12} is lower alkyl, and R^{13} is divalent alkyl radical of 2-5 carbons.

In an aspect of this embodiment, a RXR agonist is a compound having the structure of formula VIII:

(VIII)

wherein X is S or O; R^2 is hydrogen or lower alkyl; R^3 is hydrogen or lower alkyl, and B is hydrogen, —COOH or a pharmaceutically acceptable salt thereof, —COOR^8, —CONR^{9}R^{10}, —CH$_2$OH, —CH$_2$OR^{11}, —CH$_2$OCOR^{11}, —CHO, —CH(OR^{12})$_2$, —CHOR^{13}O, —COR^7, —CR^7 (OR^{12})$_2$, —CR^{7}OR^{13}O, or trilower alkylsilyl, where R^7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R^8 is an alkyl group of 1 to 10 carbons, a cycloalkyl group of 5 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or R^8 is phenyl or lower alkylphenyl, R^9 and R^{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R^{11} is lower alkyl, phenyl or lower alkylphenyl, R^{12} is lower alkyl, and R^{13} is divalent alkyl radical of 2-5 carbons.
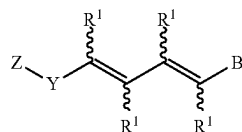
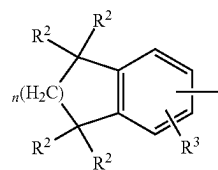In an aspect of this embodiment, a RXR agonist is a compound having the structure of formula IX:

(IX)

wherein Z is a radical having the structure of Formula X:
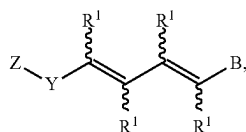
(X)

Y is selected from pyridyl, pyrrolyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, and imidazolyl, the groups being optionally substituted with one or two R^4 groups, the divalent Y radical being substituted by the Z and —(CR^1=CR^1—CR^1=CR^1)— groups on adjacent carbons; X is NR^5; n is 1 or 2; R^1 and R^2 independently are H, lower alkyl or fluoroalkyl; R^3 is hydrogen, lower alkyl, Cl or Br; R^4 is lower alkyl, fluoroalkyl or halogen; R^5 is H or lower alkyl, and B is hydrogen, —COOH or a pharmaceutically acceptable salt thereof, —COOR^8, —CONR^{9}R^{10}, —CH$_2$OH, —CH$_2$OR^{11}, —CH$_2$OCOR^{11}, —CHO, —CH (OR^{12})$_2$, —CHOR^{13}O, —COR^7, —CR^7(OR^{12})$_2$, —CR^{7}OR^{13}O, or trilower alkylsilyl, where R^7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R^8 is an alkyl group of 1 to 10 carbons, a cycloalkyl group of 5 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or R^8 is phenyl or lower alkylphenyl, R^9 and R^{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl

or lower alkylphenyl, R^{11} is lower alkyl, phenyl or lower alkylphenyl, R^{12} is lower alkyl, and R^{13} is divalent alkyl radical of 2 to 5 carbons.

In an aspect of this embodiment, a RXR agonist is a compound having the structure of formula IX:

(IX)

wherein Z is a radical having the structure of Formula X:

(XI)

Y is selected from pyridyl, pyrrolyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, and imidazolyl, the groups being optionally substituted with one or two R^4 groups, the divalent Y radical being substituted by the Z and —$(CR^1\!=\!CR^1\!=\!CR^1\!=\!CR^1)$— groups on adjacent carbons; X is NR^5; n is 1 or 2; R^1 and R^2 independently are H, lower alkyl or fluoroalkyl; R^3 is hydrogen, lower alkyl, Cl or Br; R^4 is lower alkyl, fluoroalkyl or halogen; R^5 is H or lower alkyl, and B is hydrogen, —COOH or a pharmaceutically acceptable salt thereof, —COOR^8, —CONR^{9}R^{10}, —CH$_2$OH, —CH$_2$OR^{11}, —CH$_2$OCOR^{11}, —CHO, —CH(OR^{12})$_2$, —CHOR^{13}O, —COR^7, —CR^7(OR^{12})$_2$, —CR^{7}OR^{13}O, or trilower alkylsilyl, where R^7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R^8 is an alkyl group of 1 to 10 carbons, a cycloalkyl group of 5 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or R^8 is phenyl or lower alkylphenyl, R^9 and R^{10} independently are hydrogen, an alkyl group of 1 to 10 carbons,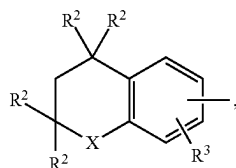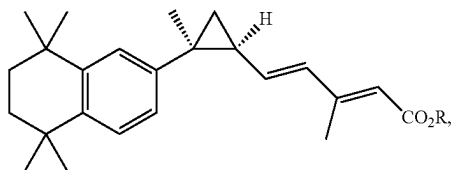 or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R^{11} is lower alkyl, phenyl or lower alkylphenyl, R^{12} is lower alkyl, and R^{13} is divalent alkyl radical of 2 to 5 carbons.

In an aspect of this embodiment, a RXR agonist is a compound having the structure of formula XII:
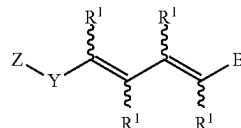
(XII)

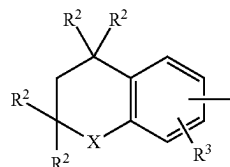wherein R is H, lower alkyl or 1 to 6 carbons, or a pharmaceutically acceptable salt of the compound.

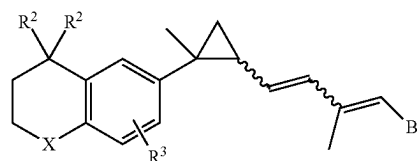In an aspect of this embodiment, a RXR agonist is a compound having the structure of formula XII:

(XIII)

wherein Z is a radical having the structure of Formula XIV:

(XIV)

Y is cyclopropyl, the Y group being optionally substituted with one or two R^4 groups, the divalent Y radical being substituted by the Z and —$(CR^1\!=\!CR^1\!=\!CR^1\!=\!CR^1)$— groups on adjacent carbons; X is NR^5; R^1 and R^2 independently are H, lower alkyl or fluoroalyl; R^3 is hydrogen, lower alkyl, Cl or Br; R^4 is lower alkyl, fluoroalkyl or hydrogen; R^5 is H or lower alkyl, and B is hydrogen, —COOH or a pharmaceutically acceptable salt thereof, —COOR^8, —CONR^{9}R^{10}, —CH$_2$OH, —CH$_2$OR^{11}, —CH$_2$OCOR^{11}, —CHO, —CH(OR^{12})$_2$, —CHOR^{13}O, —COR^7, —CR^7(OR^{12})$_2$, —CR^{7}OR^{13}O, or trilower alkylsilyl, where R^7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R^8 is an alkyl group of 1 to 10 carbons, a cycloalkyl group of 5 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or R^8 is phenyl or lower alkylphenyl, R^9 and R^{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R^{11} is lower alkyl, phenyl or lower alkylphenyl, R^{12} is lower alkyl, and R^{13} is divalent alkyl radical of 2 to 5 carbons.

In an aspect of this embodiment, a RXR agonist is a compound having the structure of formula XV:

(XV)

wherein X is NR^5; R^5 is H or lower alkyl; R^2 is H or lower alkyl; R^3 is H or lower alkyl, and B is hydrogen, —COOH or a pharmaceutically acceptable salt thereof, —COOR^8, —CONR^{9}R^{10}, —CH$_2$OH, —CH$_2$OR^{11}, —CH$_2$OCOR^{11}, —CHO, —CH(OR^{12})$_2$, —CHOR^{13}O, —COR^7, —CR^7(OR^{12})$_2$, —CR^{7}OR^{13}O, or trilower alkylsilyl, where R^7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R^8 is an alkyl group of 1 to 10 carbons, a cycloalkyl group of 5 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or R^8 is phenyl or lower alkylphenyl, R^9 and R^{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R^{11} is lower alkyl, phenyl or lower alkylphenyl, R^{12} is lower alkyl, and R^{13} is divalent alkyl radical of 2 to 5 carbons.

In an aspect of this embodiment, a RXR agonist is a compound having the structure of formula XVI:
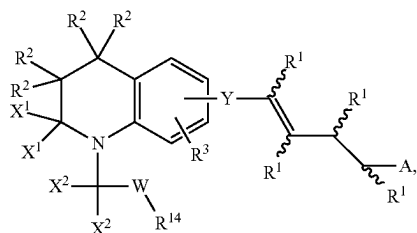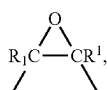

(XVI)

where Y is a bivalent radical having the structure of Formula XVII:

(XVII)

the two X^1 groups jointly represent an oxo ($=O$) or thione ($=S$) function, or X^1 is independently selected from H or alkyl of 1 to 6 carbons; the two X^2 groups jointly represent an oxo ($=O$) or a thione ($=S$) function, or X^2 independently selected from H or alkyl of 1 to 6 carbons, with the proviso that one of the joint X^1 grouping or of the joint X^2 grouping represents an oxo ($=O$) or thione ($=S$) function; W is O, $C(R^1)_2$, or W does not exist; R^1 is independently H, lower alkyl of 1 to 6 carbons, or lower fluoroalkyl of 1 to 6 carbons; R^2 is independently H, lower alkyl of 1 to 6 carbons, or lower fluoroalkyl of 1 to 6 carbons; R^3 is hydrogen, lower alkyl of 1 to 6 carbons, OR^1, fluoro substituted lower alkyl of 1 to 6 carbons halogen, NO_2, NH_2, —NHCO(C_1-C_6) alkyl, or —NHCO(C_1-C_6) alkenyl; A is hydrogen, —COOH or a pharmaceutically acceptable salt thereof, —OCOR^8, —CONR^{9}R^{10}, —CH$_2$OH, —CH$_2$OR^{11}, —CH$_2$OCOR^{11}, —CHO, —CH(OR^{12})$_2$, —CH(OR^{13}O), —COR^7, —CR^7(OR^{12})$_2$, —CR^7(OR^{13}O), or —Si(C_1-C_6)$_3$, where R^7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R^8 is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R^8 is phenyl or lower alkylphenyl, R^9 and R^{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl, hydroxyphenyl or lower alkylphenyl, R^{11} is lower alkyl, phenyl or lower alkylphenyl, R^{12} is lower alkyl, and R^{13} is divalent alkyl radical of 2 to 5 carbons, and R^{14} is H, alkyl of 1 to 10 carbons, fluoro-substituted alkyl of 1 to 10 carbons, alkenyl of 2 to 10 carbons and having 1 to 3 double bonds.

In an aspect of this embodiment, a RXR agonist is a compound having the structure of formula XVIII:

(XVIII)
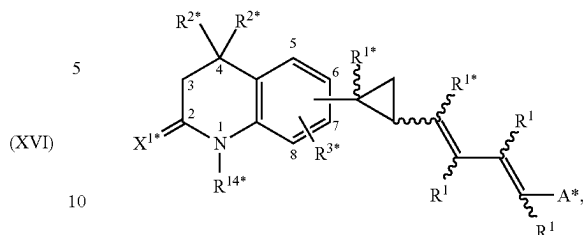
wherein R^1 is independently H, lower alkyl of 1 to 6 carbons, or lower fluoroalkyl of 1 to 6 carbons; R^{1*} is hydrogen or C_{1-6}-alkyl; R^{2*} is independently H, lower alkyl of 1 to 6 carbons, or lower fluoroalkyl of 1 to 6 carbons; R^{3*} is hydrogen, lower alkyl of 1 to 6 carbons, fluoro substituted lower alkyl of 1 to 6 carbons or halogen; X^{1*} is an oxo ($=O$) or a thione ($=S$) group; A^* is hydrogen, —COOH or a pharmaceutically acceptable salt thereof, —COOR^8, —CONR^{9}R^{10}, where R^8 is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R^8 is phenyl or lower alkylphenyl, R^9 and R^{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl, hydroxyphenyl or lower alkylphenyl, and the cyclopropyl group is attached to the 6 or 7 position of the tetrahydroquinoline moiety, and R^{14*} is alkyl of 1 to 10 carbons or fluoro-substituted alkyl of 1 to 10 carbons.

In an aspect of this embodiment, a RXR agonist is a compound having the structure of formulae XIX, XX, or XXI:

(XIX)

(XX)

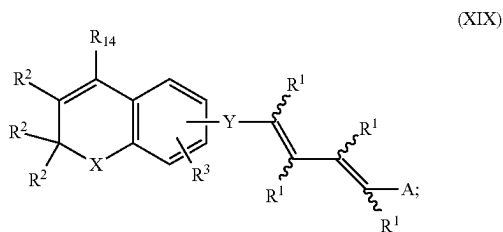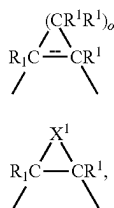

(XXI)
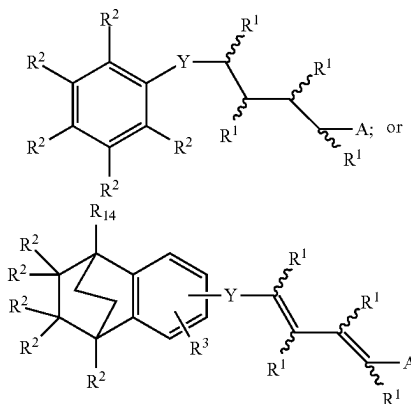
where X is O, S, or $(CR^1R^1)_n$ where n is 0, 1 or 2; Y is a bivalent radical having the structure of Formulae XXII or XXIII where o is an integer between 1 through 4

(XXII)

(XXIII)

or Y is a bivalent aryl or 5 or 6 membered heteroaryl radical having 1 to 3 heteroatoms selected from N, S and O, the aryl or heteroaryl groups being unsubstituted, or substituted with 1 to 3 C_{1-6} alkyl or with 1 to 3 C_{1-6} fluoroalkyl groups with the proviso that when the compound is in accordance with Formula II then Y is not a 5 or 6 membered ring; X^1 is S or NH; R^1 is independently H, lower alkyl of 1 to 6 carbons, or lower fluoroalkyl of 1 to 6 carbons; R^2 is independently H, lower alkyl of 1 to 6 carbons, OR^1, adamantly, or lower fluoroalkyl of 1 to 6 carbons, or the two R^2 groups jointly represent an oxo ($=O$) group with the proviso that when the compound is in accordance with Formula II then at least one of the R^2 substituents is branched-chain alkyl or adamantly; R^3 is hydrogen, lower alkyl of 1 to 6 carbons, OR^1, fluoro substituted lower alkyl of 1 to 6 carbons or halogen, NO_2, NH_2, —NHCO(C_1-C_6) alkyl, or —NHCO(C_1-C_6) alkenyl; A is —COOH or a pharmaceutically acceptable salt thereof, $COOR^8$, —$CONR^9R^{10}$, —CH_2OH, —CH_2OR^{11}, —CH_2OCOR^{11}, —CHO, —$CH(OR^{12})_2$, —$CH(OR^{13}O)$, —COR^7, —$CR^7(OR^{12})_2$, —$CR^7(OR^{13}O)$, or —$Si(C_{1-6}$alkyl$)_3$, where R^7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R^8 is an alkyl group of 1 to 10 carbons or (trimethylsilyl) alkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R^8 is phenyl or lower alkylphenyl, R^9 and R^{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl, hydroxyphenyl or lower alkylphenyl, R^{12} is lower alkyl, and R^{13} is divalent alkyl radical of 2-5 carbons, and R^{14} is alkyl of 1 to 10 carbons, fluoro-substituted alkyl of 1 to 10 carbons, alkenyl of 2 to 10 carbons and having 1 to 3 double bonds, alkynyl having 2 to 10 carbons and 1 to 3 triple bonds, carbocyclic aryl selected from the group consisting of phenyl, C_1-C_{10}-alkylphenyl, naphthyl, C_1-C_{10}-alkylnaphthyl, phenyl-C_1-C_{10}-alkyl, naphthyl-C_1-C_{10} alkyl, C_1-C_{10}-alkenylphenyl having 1 to 3 double bonds, C_1-C_{10}-alkynylphenyl having 1 to 3 triple bonds, phenyl-C_1-C_{10} alkenyl having 1 to 3 double bonds, phenyl-C_1-C_{10} alkenyl having 1 to 3 triple bonds, hydroxyl alkyl of 1 to 10 carbons, hydroxyalkenyl having 2 to 10 carbons and 1 to 3 double bonds, hydroxy-alkynyl having 2 to 10 carbons and 1 to 3 triple bonds, acyloxyalkyl of 1 to 10 carbons, acyloxyalkenyl having 2 to 10 carbons and 1 to 3 double bonds, or acyloxyalkynyl of 2 to 10 carbons and 1 to 3 triple bonds, acyloxyalkyl of 1 to 10 carbons, acyloxyalkenyl having 2 to 10 carbons and 1 to 3 double bonds, or acyloxyalkynyl of 2 to 10 carbons and 1 to 3 triple bonds where the acyl group is represented by —COR^8, or R^{14} is a 5 or 6 membered heteroaryl group having 1 to 3 heteroatoms, the heteroatoms being selected from a group consisting of O, S, and N, the heteroaryl group being unsubstituted or substituted with a C_1-C_{10} alkyl group, with a C_1-C_{10} fluoroalkyl group, or with halogen, and the dashed line in Formula XXII represents a bond or absence of a bond.

In an aspect of this embodiment, a RXR agonist is a compound having the structure of formula XXIV:

(XXIV)
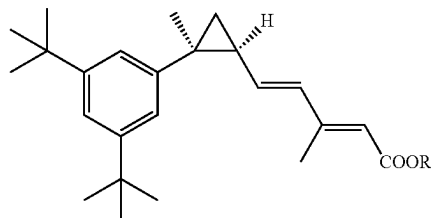
wherein R is H, lower alkyl of 1 to 6 carbons, or a pharmaceutically acceptable salt of the compound.

In an aspect of this embodiment, a RXR agonist is a compound having the structure of formula XXV:

(XXV)
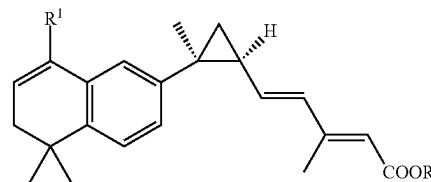
wherein R is H, lower alkyl of 1 to 6 carbons, and R^1 is iso-propyl or tertiary-butyl, or a pharmaceutically acceptable salt of the compound.

In an aspect of this embodiment, a RXR agonist is a compound having the structure of formula XXVI:

(XXVI)
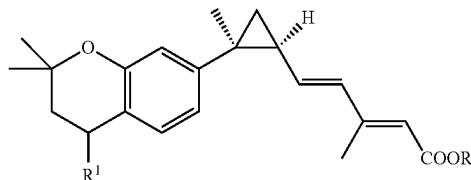
wherein R is H, lower alkyl of 1 to 6 carbons, and R^1 is iso-propyl, n-butyl or tertiary-butyl, or a pharmaceutically acceptable salt of the compound.

In an aspect of this embodiment, a RXR agonist is a compound having the structure of formula XXVII:

(XXVII)
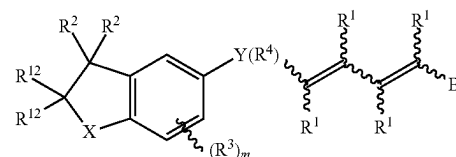
where X is O or S; Y is a bivalent cycloalkyl or cycloalkenyl radical optionally substituted with one to four R^4 groups, the cycloalkenyl radical having 5 to 6 carbons and one double

bond, or Y is a bivalent aryl or 5 or 6 membered heteroaryl radical having 1 to 3 heteroatoms selected from N, S and O, the aryl or heteroaryl groups optionally substituted with 1 to 4 R^4 groups with the proviso that the cycloalkyl or the cycloalkenyl radical is not substituted on the same carbon with the condensed cyclic moiety and with the diene containing moiety; R^1 is independently H, alkyl of 1 to 6 carbons, or fluoroalkyl of 1 to 6 carbons; R^2 is independently H, alkyl of 1 to 8 carbons, or fluoroalkyl of 1 to 8 carbons; R^{12} is independently H, alkyl of 1 to 8 carbons, or fluoroalyl of 1 to 8 carbons; R^3 is hydrogen, alkyl of 1 to 10 carbons, fluoro substituted alkyl of 1 to 10 carbons, halogen, alkoxy of 1 to 10 carbons, or alkylthio of 1 to 10 carbons; NO_2, NH_2, —$NHCO(C_1-C_6)$ alkyl, —$NHCO(C_1-C_6)$ alkenyl, —NR^1H or $N(R^1)_2$, benzyloxy, C_1-C_6 alkyl-substituted benzyloxy, or R^3 is selected from the groups shown below:

R^4 is H, halogen, alkyl of 1 to 10 carbons, fluoro substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 10 carbons, or alkylthio of 1 to 10 carbons; m is an integer having the values of 0 to 3; r is an integer having the values of 1 to 10; s is an integer having the values 1 to 4; t is an integer having the values 1 to 5;

represents a 5 or 6 membered heteroaryl ring having 1 to 3 heteroatoms selected from the group consisting of N, S and O; B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, —$COOR^8$, —$CONR^9R^{10}$, —CH_2OH, —CH_2OR^{11}, —CH_2OCOR^{11}, —CHO, —$CH(OR^{12})_2$, —$CHOR^{13}O$, —COR^7, —$CR^7(OR^{12})_2$, —$CR^7OR^{13}O$, or trilower alkylsilyl, where R^7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R^8 is an alkyl group of 1 to 10 carbons, a cycloalkyl group of 5 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or R^8 is phenyl or lower alkylphenyl, R^9 and R^{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or

lower alkylphenyl, R^{11} is lower alkyl, phenyl or lower alkylphenyl, R^{12} is lower alkyl, and R^{13} is divalent alkyl radical of 2 to 5 carbons.

In an aspect of this embodiment, a RXR agonist is a compound having the structure of formula XXVIII:

(XXVIII)

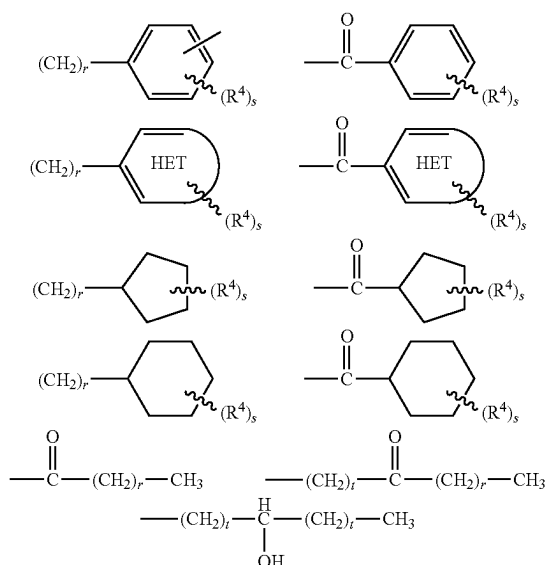wherein R^1 is H or methyl; R^8 is H, alkyl of 1 to 6 carbons, or a pharmaceutically acceptable cation, and R^3 is hydrogen, alkyl of 1 to 10 carbons, halogen, alkoxy of 1 to 10 carbons, or R^3 is selected from the groups shown below:
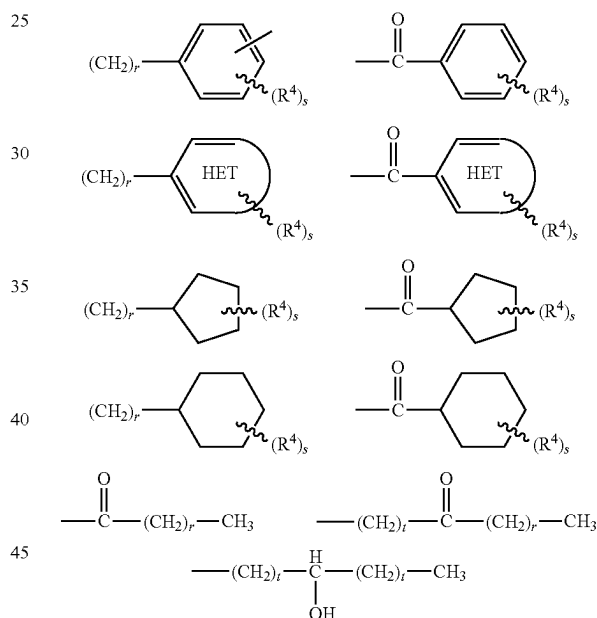
where R^4 is H, halogen, alkyl of 1 to 10 carbons, carbons, alkoxy of 1 to 10; r is an integer having the values of 1 to 10; s is an integer having the values 1 to 4;
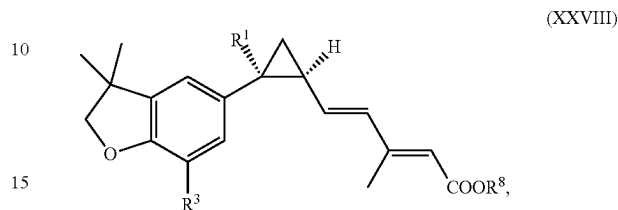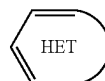
represents a 5 or 6 membered heteroaryl ring having 1 to 3 heteroatoms selected from the group consisting of N, S and O, and t is an integer having the values 1 to 5.

In an aspect of this embodiment, a RXR agonist is 3,7-dimethyl-6(S),7(S)-methano,7-[1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphth-7-yl]2(E),4(E) heptadienoic acid, and has the structure of formula XXIX:

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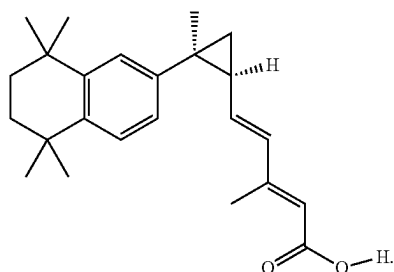
(XXIX)

Aspects of the present specification provide, in part, a RXR agonist having activity that promotes Treg cell differentiation. In aspects of this embodiment, a RXR agonist promotes Treg cell differentiation by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 100%, at least 200%, at least 300%, at least 400%, or at least 500%. In other aspects of this embodiment, a RXR agonist promotes Treg cell differentiation by about 10% to about 25%, about 10% to about 50%, about 10% to about 75%, about 10% to about 100%, about 10% to about 200%, about 10% to about 300%, about 10% to about 400%, about 10% to about 500%, about 25% to about 50%, about 25% to about 75%, about 25% to about 100%, about 25% to about 200%, about 25% to about 300%, about 25% to about 400%, about 25% to about 500%, about 50% to about 100%, about 50% to about 200%, about 50% to about 300%, about 50% to about 400%, or about 50% to about 500%.

In an embodiment, a RXR agonist has activity that results in increased Foxp3 expression in cells exposed to the RXR agonist. In aspects of this embodiment, a RXR agonist increases Foxp3 expression in cells by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 100%, at least 200%, at least 300%, at least 400%, or at least 500%, relative to cells not exposed to the same RXR agonist. In other aspects of this embodiment, a RXR agonist increases Foxp3 expression in cells by about 10% to about 25%, about 10% to about 50%, about 10% to about 75%, about 10% to about 100%, about 10% to about 200%, about 10% to about 300%, about 10% to about 400%, about 10% to about 500%, about 25% to about 50%, about 25% to about 75%, about 25% to about 100%, about 25% to about 200%, about 25% to about 300%, about 25% to about 400%, about 25% to about 500%, about 50% to about 100%, about 50% to about 200%, about 50% to about 300%, about 50% to about 400%, or about 50% to about 500%, relative to cells not exposed to the same RXR agonist. In one embodiment, the cells are naïve CD4$^+$ CD25$^-$ FoxP3$^-$ cells cultured under Treg cell differentiation conditions.

In an embodiment, a RXR agonist has activity that results in increased α4β7 expression in cells exposed to the RXR agonist. In aspects of this embodiment, a RXR agonist increases α4β7 expression in cells by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 100%, at least 200%, at least 300%, at least 400%, or at least 500%, relative to cells not exposed to the same RXR agonist. In other aspects of this embodiment, a RXR agonist increases α4β7 expression in cells by about 10% to about 25%, about 10% to about 50%, about 10% to about 75%, about 10% to about 100%, about 10% to about 200%, about 10% to about 300%, about 10% to about 400%, about 10% to about 500%,

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about 25% to about 50%, about 25% to about 75%, about 25% to about 100%, about 25% to about 200%, about 25% to about 300%, about 25% to about 400%, about 25% to about 500%, about 50% to about 100%, about 50% to about 200%, about 50% to about 300%, about 50% to about 400%, or about 50% to about 500%, relative to cells not exposed to the same RXR agonist. In one embodiment, the cells are naïve CD4$^+$ CD25$^-$ FoxP3$^-$ cells cultured under Treg cell differentiation conditions.

Aspects of the present specification provide, in part, a RXR agonist having activity that inhibits Th17 cell differentiation. In aspects of this embodiment, a RXR agonist inhibits Th17 cell differentiation by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 100%, at least 200%, at least 300%, at least 400%, or at least 500%. In other aspects of this embodiment, a RXR agonist inhibits Th17 cell differentiation by about 10% to about 25%, about 10% to about 50%, about 10% to about 75%, about 10% to about 100%, about 10% to about 200%, about 10% to about 300%, about 10% to about 400%, about 10% to about 500%, about 25% to about 50%, about 25% to about 75%, about 25% to about 100%, about 25% to about 200%, about 25% to about 300%, about 25% to about 400%, about 25% to about 500%, about 50% to about 100%, about 50% to about 200%, about 50% to about 300%, about 50% to about 400%, or about 50% to about 500%.

In an embodiment, a RXR agonist has activity that results in decreased IL-17A expression in cells exposed to the RXR agonist. In aspects of this embodiment, a RXR agonist decreases IL-17A expression in cells by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 100%, at least 200%, at least 300%, at least 400%, or at least 500%, relative to cells not exposed to the same RXR agonist. In other aspects of this embodiment, a RXR agonist decreases IL-17A expression in cells by about 10% to about 25%, about 10% to about 50%, about 10% to about 75%, about 10% to about 100%, about 10% to about 200%, about 10% to about 300%, about 10% to about 400%, about 10% to about 500%, about 25% to about 50%, about 25% to about 75%, about 25% to about 100%, about 25% to about 200%, about 25% to about 300%, about 25% to about 400%, about 25% to about 500%, about 50% to about 100%, about 50% to about 200%, about 50% to about 300%, about 50% to about 400%, or about 50% to about 500%, relative to cells not exposed to the same RXR agonist. In one embodiment, the cells are naïve CD4$^+$ CD25$^-$ FoxP3$^-$ cells cultured under Treg cell differentiation conditions.

Aspects of the present specification provide, in part, a RXR agonist having activity that both promotes Treg cell differentiation and inhibits Th17 cell differentiation. In aspects of this embodiment, a RXR agonist promotes Treg cell differentiation by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 100%, at least 200%, at least 300%, at least 400%, or at least 500% as well as inhibits Th17 cell differentiation by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 100%, at least 200%, at least 300%, at least 400%, or at least 500%. In other aspects of this embodiment, a RXR agonist promotes Treg cell differentiation by about 10% to about 25%, about 10% to about 50%, about 10% to about 75%, about 10% to about 100%, about 10% to about 200%, about 10% to about 300%, about 10% to about 400%, about 10% to about 500%, about 25% to about 50%, about 25% to about

75%, about 25% to about 100%, about 25% to about 200%, about 25% to about 300%, about 25% to about 400%, about 25% to about 500%, about 50% to about 100%, about 50% to about 200%, about 50% to about 300%, about 50% to about 400%, or about 50% to about 500%, as well as inhibits Th17 cell differentiation by about 10% to about 25%, about 10% to about 50%, about 10% to about 75%, about 10% to about 100%, about 10% to about 200%, about 10% to about 300%, about 10% to about 400%, about 10% to about 500%, about 25% to about 50%, about 25% to about 75%, about 25% to about 100%, about 25% to about 200%, about 25% to about 300%, about 25% to about 400%, about 25% to about 500%, about 50% to about 100%, about 50% to about 200%, about 50% to about 300%, about 50% to about 400%, or about 50% to about 500%.

In an embodiment, a RXR agonist has activity that results in increased FoxP3 and/or $\alpha 4\beta 7$ expression as well as decreases IL-17A expression in cells exposed to the RXR agonist. In aspects of this embodiment, a RXR agonist increases FoxP3 and/or $\alpha 4\beta 7$ expression in cells by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 100%, at least 200%, at least 300%, at least 400%, or at least 500%, as well as decreases IL-17A expression in cells by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 100%, at least 200%, at least 300%, at least 400%, or at least 500%, relative to cells not exposed to the same RXR agonist. In other aspects of this embodiment, a RXR agonist increases FoxP3 and/or $\alpha 4\beta 7$ expression in cells by about 10% to about 25%, about 10% to about 50%, about 10% to about 75%, about 10% to about 100%, about 10% to about 200%, about 10% to about 300%, about 10% to about 400%, about 10% to about 500%, about 25% to about 50%, about 25% to about 75%, about 25% to about 100%, about 25% to about 200%, about 25% to about 300%, about 25% to about 400%, about 25% to about 500%, about 50% to about 100%, about 50% to about 200%, about 50% to about 300%, about 50% to about 400%, or about 50% to about 500%, as well as decreases IL-17A expression in cells by about 10% to about 25%, about 10% to about 50%, about 10% to about 75%, about 10% to about 100%, about 10% to about 200%, about 10% to about 300%, about 10% to about 400%, about 10% to about 500%, about 25% to about 50%, about 25% to about 75%, about 25% to about 100%, about 25% to about 200%, about 25% to about 300%, about 25% to about 400%, about 25% to about 500%, about 50% to about 100%, about 50% to about 200%, about 50% to about 300%, about 50% to about 400%, or about 50% to about 500%, relative to cells not exposed to the same RXR agonist.

In yet other aspects of this embodiment, a RXR agonist increases myelination in the central or peripheral nervous system by at least about 10% to at least about 25%, at least about 10% to at least about 50%, at least about 10% to at least about 75%, at least about 10% to at least about 100%, at least about 10% to at least about 200%, at least about 10% to at least about 300%, at least about 10% to at least about 400%, at least about 10% to at least about 500%, at least about 25% to at least about 50%, at least about 25% to at least about 75%, at least about 25% to at least about 100%, at least about 25% to at least about 200%, at least about 25% to at least about 300%, at least about 25% to at least about 400%, at least about 25% to at least about 500%, at least about 50% to at least about 100%, at least about 50% to at least about 200%, at least about 50% to at least about 300%, at least about 50% to at least about 400%, or at least about

50% to at least about 500%, relative to myelination levels in the absence of treatment with the RXR agonist.

In yet other aspects of this embodiment, a RXR agonist increases differentiation of oligodendrocyte progenitor cell differentiation into oligodendrocytes in the central or peripheral nervous system by at least about 10% to at least about 25%, at least about 10% to at least about 50%, at least about 10% to at least about 75%, at least about 10% to at least about 100%, at least about 10% to at least about 200%, at least about 10% to at least about 300%, at least about 10% to at least about 400%, at least about 10% to at least about 500%, at least about 25% to at least about 50%, at least about 25% to at least about 75%, at least about 25% to at least about 100%, at least about 25% to at least about 200%, at least about 25% to at least about 300%, at least about 25% to at least about 400%, at least about 25% to at least about 500%, at least about 50% to at least about 100%, at least about 50% to at least about 200%, at least about 50% to at least about 300%, at least about 50% to at least about 400%, or at least about 50% to at least about 500%, relative to differentiation levels in the absence of treatment with the RXR agonist.

In yet another aspect of the present specification, a RXR agonist increases the rate of myelin repair in the central nervous system by at least about 10% to at least about 25%, at least about 10% to at least about 50%, at least about 10% to at least about 75%, at least about 10% to at least about 100%, at least about 10% to at least about 200%, at least about 10% to at least about 300%, at least about 10% to at least about 400%, at least about 10% to at least about 500%, at least about 25% to at least about 50%, at least about 25% to at least about 75%, at least about 25% to at least about 100%, at least about 25% to at least about 200%, at least about 25% to at least about 300%, at least about 25% to at least about 400%, at least about 25% to at least about 500%, at least about 50% to at least about 100%, at least about 50% to at least about 200%, at least about 50% to at least about 300%, at least about 50% to at least about 400%, or at least about 50% to at least about 500%, relative to myelin repair rates in the absence of treatment with the RXR agonist.

Aspects of the present specification provide, in part, a composition comprising a RXR agonist. A RXR agonist includes the compounds disclosed herein. The compositions disclosed herein may, or may not, comprise any number and combination of compounds disclosed herein. For instance, a composition can comprise, e.g., two or more compounds disclosed herein, three or more compounds disclosed herein, four or more compounds disclosed herein, or five or more compounds disclosed herein.

A compound disclosed herein, or a composition comprising such a compound, is generally administered to an individual as a pharmaceutical composition. Pharmaceutical compositions may be prepared by combining a therapeutically effective amount of at least one compound as disclosed herein, or a pharmaceutically acceptable acid addition salt thereof, as an active ingredient, with conventional acceptable pharmaceutical excipients, and by preparation of unit dosage forms suitable for therapeutic use. As used herein, the term "pharmaceutical composition" refers to a therapeutically effective concentration of an active compound, such as, e.g., any of the compounds disclosed herein. Preferably, the pharmaceutical composition does not produce an adverse, allergic, or other untoward or unwanted reaction when administered to an individual. A pharmaceutical composition disclosed herein is useful for medical and veterinary applications. A pharmaceutical composition may be administered to an individual alone, or in combination with other

supplementary active compounds, agents, drugs or hormones. The pharmaceutical compositions may be manufactured using any of a variety of processes, including, without limitation, conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, and lyophilizing. The pharmaceutical composition can take any of a variety of forms including, without limitation, a sterile solution, suspension, emulsion, lyophilizate, tablet, pill, pellet, capsule, powder, syrup, elixir, or any other dosage form suitable for administration.

A pharmaceutical composition produced using the methods disclosed herein may be a liquid formulation, semi-solid formulation, or a solid formulation. A formulation disclosed herein can be produced in a manner to form one phase, such as, e.g., an oil or a solid. Alternatively, a formulation disclosed herein can be produced in a manner to form two phase, such as, e.g., an emulsion. A pharmaceutical composition disclosed herein intended for such administration may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions.

Liquid formulations suitable for parenteral injection or for nasal sprays may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions and sterile powders for reconstitution into sterile injectable solutions or dispersions. Formulations suitable for nasal administration may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propylene glycol, polyethyleneglycol (PEG), glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

Pharmaceutical formulations suitable for administration by inhalation include fine particle dusts or mists, which may be generated by means of various types of metered, dose pressurized aerosols, nebulizers, or insufflators.

Semi-solid formulations suitable for topical administration include, without limitation, ointments, creams, salves, and gels. In such solid formulations, the active compound may be admixed with at least one inert customary excipient (or carrier) such as, a lipid and/or polyethylene glycol.

Solid formulations suitable for oral administration include capsules, tablets, pills, powders and granules. In such solid formulations, the active compound may be admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol and silicic acid, (b) binders, as for example, carboxymethylcellulose, alignates, gelatin, polyvinylpyrrolidone, sucrose and acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates and sodium carbonate, (e) solution retarders, as for example, paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol and glycerol monostearate, (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate or mixtures thereof. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents.

In liquid and semi-solid formulations, a concentration of a therapeutic compound disclosed herein typically may be between about 50 mg/mL to about 1,000 mg/mL. In aspects of this embodiment, a therapeutically effective amount of a therapeutic compound disclosed herein may be from, e.g., about 50 mg/mL to about 100 mg/mL, about 50 mg/mL to about 200 mg/mL, about 50 mg/mL to about 300 mg/mL, about 50 mg/mL to about 400 mg/mL, about 50 mg/mL to about 500 mg/mL, about 50 mg/mL to about 600 mg/mL, about 50 mg/mL to about 700 mg/mL, about 50 mg/mL to about 800 mg/mL, about 50 mg/mL to about 900 mg/mL, about 50 mg/mL to about 1,000 mg/mL, about 100 mg/mL to about 200 mg/mL, about 100 mg/mL to about 300 mg/mL, about 100 mg/mL to about 400 mg/mL, about 100 mg/mL to about 500 mg/mL, about 100 mg/mL to about 600 mg/mL, about 100 mg/mL to about 700 mg/mL, about 100 mg/mL to about 800 mg/mL, about 100 mg/mL to about 900 mg/mL, about 100 mg/mL to about 1,000 mg/mL, about 200 mg/mL to about 300 mg/mL, about 200 mg/mL to about 400 mg/mL, about 200 mg/mL to about 500 mg/mL, about 200 mg/mL to about 600 mg/mL, about 200 mg/mL to about 700 mg/mL, about 200 mg/mL to about 800 mg/mL, about 200 mg/mL to about 900 mg/mL, about 200 mg/mL to about 1,000 mg/mL, about 300 mg/mL to about 400 mg/mL, about 300 mg/mL to about 500 mg/mL, about 300 mg/mL to about 600 mg/mL, about 300 mg/mL to about 700 mg/mL, about 300 mg/mL to about 800 mg/mL, about 300 mg/mL to about 900 mg/mL, about 300 mg/mL to about 1,000 mg/mL, about 400 mg/mL to about 500 mg/mL, about 400 mg/mL to about 600 mg/mL, about 400 mg/mL to about 700 mg/mL, about 400 mg/mL to about 800 mg/mL, about 400 mg/mL to about 900 mg/mL, about 400 mg/mL to about 1,000 mg/mL, about 500 mg/mL to about 600 mg/mL, about 500 mg/mL to about 700 mg/mL, about 500 mg/mL to about 800 mg/mL, about 500 mg/mL to about 900 mg/mL, about 500 mg/mL to about 1,000 mg/mL, about 600 mg/mL to about 700 mg/mL, about 600 mg/mL to about 800 mg/mL, about 600 mg/mL to about 900 mg/mL, or about 600 mg/mL to about 1,000 mg/mL.

In semi-solid and solid formulations, an amount of a therapeutic compound disclosed herein typically may be between about 0.01% to about 45% by weight. In aspects of this embodiment, an amount of a therapeutic compound disclosed herein may be from, e.g., about 0.1% to about 45% by weight, about 0.1% to about 40% by weight, about 0.1% to about 35% by weight, about 0.1% to about 30% by weight, about 0.1% to about 25% by weight, about 0.1% to about 20% by weight, about 0.1% to about 15% by weight, about 0.1% to about 10% by weight, about 0.1% to about 5% by weight, about 1% to about 45% by weight, about 1% to about 40% by weight, about 1% to about 35% by weight, about 1% to about 30% by weight, about 1% to about 25% by weight, about 1% to about 20% by weight, about 1% to about 15% by weight, about 1% to about 10% by weight, about 1% to about 5% by weight, about 5% to about 45% by weight, about 5% to about 40% by weight, about 5% to about 35% by weight, about 5% to about 30% by weight, about 5% to about 25% by weight, about 5% to about 20% by weight, about 5% to about 15% by weight, about 5% to about 10% by weight, about 10% to about 45% by weight, about 10% to about 40% by weight, about 10% to about 35% by weight, about 10% to about 30% by weight, about 10% to about 25% by weight, about 10% to about 20% by weight, about 10% to about 15% by weight, about 15% to about 45% by weight, about 15% to about 40% by weight, about 15% to about 35% by weight, about 15% to about 30% by weight, about 15% to about 25% by weight, about 15% to about 20% by weight, about 20% to about 45% by weight, about 20%

to about 40% by weight, about 20% to about 35% by weight, about 20% to about 30% by weight, about 20% to about 25% by weight, about 25% to about 45% by weight, about 25% to about 40% by weight, about 25% to about 35% by weight, or about 25% to about 30% by weight.

A pharmaceutical composition disclosed herein can optionally include a pharmaceutically acceptable carrier that facilitates processing of an active compound into pharmaceutically acceptable compositions. As used herein, the term "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem complications commensurate with a reasonable benefit/risk ratio. As used herein, the term "pharmacologically acceptable carrier" is synonymous with "pharmacological carrier" and refers to any carrier that has substantially no long term or permanent detrimental effect when administered and encompasses terms such as "pharmacologically acceptable vehicle, stabilizer, diluent, additive, auxiliary, or excipient." Such a carrier generally is mixed with an active compound or permitted to dilute or enclose the active compound and can be a solid, semi-solid, or liquid agent. It is understood that the active compounds can be soluble or can be delivered as a suspension in the desired carrier or diluent. Any of a variety of pharmaceutically acceptable carriers can be used including, without limitation, aqueous media such as, e.g., water, saline, glycine, hyaluronic acid and the like; solid carriers such as, e.g., starch, magnesium stearate, mannitol, sodium saccharin, talcum, cellulose, glucose, sucrose, lactose, trehalose, magnesium carbonate, and the like; solvents; dispersion media; coatings; antibacterial and antifungal agents; isotonic and absorption delaying agents; or any other inactive ingredient. Selection of a pharmacologically acceptable carrier can depend on the mode of administration. Except insofar as any pharmacologically acceptable carrier is incompatible with the active compound, its use in pharmaceutically acceptable compositions is contemplated. Non-limiting examples of specific uses of such pharmaceutical carriers can be found in Pharmaceutical Dosage Forms and Drug Delivery Systems (Howard C. Ansel et al., eds., Lippincott Williams & Wilkins Publishers, 7th ed. 1999); Remington: The Science and Practice of Pharmacy (Alfonso R. Gennaro ed., Lippincott, Williams & Wilkins, 20th ed. 2000); Goodman & Gilman's The Pharmacological Basis of Therapeutics (Joel G. Hardman et al., eds., McGraw-Hill Professional, 10th ed. 2001); and Handbook of Pharmaceutical Excipients (Raymond C. Rowe et al., APhA Publications, 4th edition 2003). These protocols are routine and any modifications are well within the scope of one skilled in the art and from the teaching herein.

A pharmaceutical composition disclosed herein can optionally include, without limitation, other pharmaceutically acceptable components (or pharmaceutical components), including, without limitation, buffers, preservatives, tonicity adjusters, salts, antioxidants, osmolality adjusting agents, physiological substances, pharmacological substances, bulking agents, emulsifying agents, wetting agents, sweetening or flavoring agents, and the like. Various buffers and means for adjusting pH can be used to prepare a pharmaceutical composition disclosed herein, provided that the resulting preparation is pharmaceutically acceptable. Such buffers include, without limitation, acetate buffers, borate buffers, citrate buffers, phosphate buffers, neutral buffered saline, and phosphate buffered saline. It is under-

stood that acids or bases can be used to adjust the pH of a composition as needed. Pharmaceutically acceptable antioxidants include, without limitation, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole, and butylated hydroxytoluene. Useful preservatives include, without limitation, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate, phenylmercuric nitrate, a stabilized oxy chloro composition, such as, e.g., sodium chlorite and chelants, such as, e.g., DTPA or DTPA-bisamide, calcium DTPA, and CaNaDTPA-bisamide. Tonicity adjustors useful in a pharmaceutical composition include, without limitation, salts such as, e.g., sodium chloride, potassium chloride, mannitol or glycerin and other pharmaceutically acceptable tonicity adjustor. The pharmaceutical composition may be provided as a salt and can be formed with many acids, including but not limited to, hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms. It is understood that these and other substances known in the art of pharmacology can be included in a pharmaceutical composition useful in the invention.

A compound disclosed herein, or a composition comprising such a compound, may also be incorporated into a drug delivery platform in order to achieve a controlled compound release profile over time. Such a drug delivery platform comprises a compound disclosed herein dispersed within a polymer matrix, typically a biodegradable, bioerodible, and/or bioresorbable polymer matrix. As used herein, the term "polymer" refers to synthetic homo- or copolymers, naturally occurring homo- or copolymers, as well as synthetic modifications or derivatives thereof having a linear, branched or star structure. Copolymers can be arranged in any form, such as, e.g., random, block, segmented, tapered blocks, graft, or triblock. Polymers are generally condensation polymers. Polymers can be further modified to enhance their mechanical or degradation properties by introducing cross-linking agents or changing the hydrophobicity of the side residues. If crosslinked, polymers are usually less than 5% crosslinked, usually less than 1% crosslinked.

Suitable polymers include, without limitation, alginates, aliphatic polyesters, polyalkylene oxalates, polyamides, polyamidoesters, polyanhydrides, polycarbonates, polyesters, polyethylene glycol, polyhydroxyaliphatic carboxylic acids, polyorthoesters, polyoxaesters, polypeptides, polyphosphazenes, polysaccharides, and polyurethanes. The polymer usually comprises at least about 10% (w/w), at least about 20% (w/w), at least about 30% (w/w), at least about 40% (w/w), at least about 50% (w/w), at least about 60% (w/w), at least about 70% (w/w), at least about 80% (w/w), or at least about 90% (w/w) of the drug delivery platform. Examples of biodegradable, bioerodible, and/or bioresorbable polymers and methods useful to make a drug delivery platform are described in, e.g., U.S. Pat. Nos. 4,756,911; 5,378,475; 7,048,946; U.S. Patent Publication 2005/0181017; U.S. Patent Publication 2005/0244464; U.S. Patent Publication 2011/0008437; each of which is incorporated by reference in its entirety.

In aspects of this embodiment, a polymer composing the matrix is a polypeptide such as, e.g., silk fibroin, keratin, or collagen. In other aspects of this embodiment, a polymer composing the matrix is a polysaccharide such as, e.g., cellulose, agarose, elastin, chitosan, chitin, or a glycosaminoglycan like chondroitin sulfate, dermatan sulfate, keratan sulfate, or hyaluronic acid. In yet other aspects of this embodiment, a polymer composing the matrix is a polyester

such as, e.g., D-lactic acid, L-lactic acid, racemic lactic acid, glycolic acid, caprolactone, and combinations thereof.

One of ordinary skill in the art appreciates that the selection of a suitable polymer for forming a suitable disclosed drug delivery platform depends on several factors. The more relevant factors in the selection of the appropriate polymer(s), include, without limitation, compatibility of polymer with drug, desired release kinetics of drug, desired biodegradation kinetics of platform at implantation site, desired bioerodible kinetics of platform at implantation site, desired bioresorbable kinetics of platform at implantation site, in vivo mechanical performance of platform, processing temperatures, biocompatibility of platform, and patient tolerance. Other relevant factors that, to some extent, dictate the in vitro and in vivo behavior of the polymer include the chemical composition, spatial distribution of the constituents, the molecular weight of the polymer and the degree of crystallinity.

A drug delivery platform includes both a sustained release drug delivery platform and an extended release drug delivery platform. As used herein, the term "sustained release" refers to the release of a compound disclosed herein over a period of about seven days or more. As used herein, the term "extended release" refers to the release of a compound disclosed herein over a period of time of less than about seven days.

In aspects of this embodiment, a sustained release drug delivery platform releases a compound disclosed herein with substantially first order release kinetics over a period of, e.g., about 7 days after administration, about 15 days after administration, about 30 days after administration, about 45 days after administration, about 60 days after administration, about 75 days after administration, or about 90 days after administration. In other aspects of this embodiment, a sustained release drug delivery platform releases a compound disclosed herein with substantially first order release kinetics over a period of, e.g., at least 7 days after administration, at least 15 days after administration, at least 30 days after administration, at least 45 days after administration, at least 60 days after administration, at least 75 days after administration, or at least 90 days after administration.

In aspects of this embodiment, a drug delivery platform releases a compound disclosed herein with substantially first order release kinetics over a period of, e.g., about 1 day after administration, about 2 days after administration, about 3 days after administration, about 4 days after administration, about 5 days after administration, or about 6 days after administration. In other aspects of this embodiment, a drug delivery platform releases a compound disclosed herein with substantially first order release kinetics over a period of, e.g., at most 1 day after administration, at most 2 days after administration, at most 3 days after administration, at most 4 days after administration, at most 5 days after administration, or at most 6 days after administration.

Aspects of the present disclosure provide, in part, a demyelination-related disorder. A demyelination-related disorder is any disease or disorder of the nervous system in which the myelin sheath of neurons is damaged. This damage impairs the conduction of signals in the affected nerves. In turn, the reduction in conduction ability causes deficiency in sensation, movement, cognition, or other functions depending on which nerves are involved. Both the central nervous system and the peripheral nervous system can be involved.

Some demyelination-related disorders are caused by genetics, some by infectious agents or toxins, some by autoimmune reactions, some by radiation injury, and some

by unknown factors. Neuroleptics can also cause demyelination. The precise mechanism of demyelination is not clearly understood but there is substantial evidence that the body's own immune system is at least partially responsible, causing demyelination-related disorders to be considered autoimmune disorders.

Autoimmune disorders, including some demyelination disorders, arise from an overactive immune response of the body against substances and tissues normally present in the body resulting in a break in tolerance toward self-antigens. In other words, the body actually attacks its own cells because the immune system mistakes some part of the body as a pathogen and attacks it. Characterized by the development of pathogenic T cell populations infiltrating the target organ or tissue, autoimmune disorders may be restricted to certain organs or involve a particular tissue in different places.

Demyelination-related disorders can be broadly divided into central and peripheral nervous system disorders, depending on the organs most affected by the demyelination. Central nervous system demyelination-related disorders include, without limitation, multiple sclerosis, diffuse white matter injury in pre-term infants, neuromyelitis optica, acute disseminated encephalomyelitis, Marburg multiple sclerosis, diffuse myelinoclastic sclerosis (Schilder's disease), Balo concentric sclerosis, solitary sclerosis, optic neuritis, transverse myelitis, amyotrophic lateral sclerosis, leukodystrophy (multiple variants, e.g. adrenoleukodystrophy, adrenomyeloneuropathy), Parkinson's disease, Alzheimer's disease, progressive supranuclear palsy, stroke, traumatic brain injury, radiation induced neuroinflammation, radiation somnolence syndrome, Devic's disease, inflammatory demyelinating diseases, CNS neuropathies like those produced by vitamin B12 deficiency, central pontine myelinolysis, myelopathies like Tabes dorsalis (syphilitic myelopathy), leukoencephalopathies like progressive multifocal leukoencephalopathy, radiation induced central nervous system inflammation and leukodystrophies. Peripheral nervous system demyelination-related disorders include, without limitation, Guillain-Barré Syndrome, acute inflammatory demyelinating polyneuropathy, chronic inflammatory demyelinating polyneuropathy, demyelinating diabetic neuropathy, progressive inflammatory neuropathy, drug- or toxin-induced neuropathy, such as chemotherapy-induced neuropathy or radiation-induced neuropathy or organophosphate-induced neuropathy, anti-MAG peripheral neuropathy, Charcot-Marie-Tooth Disease, radiation induced neuropathy, and copper deficiency.

In one embodiment, the demyelination-related disorder is multiple sclerosis (MS). Multiple sclerosis is currently treated by several immunomodulatory drugs that provide clinical benefit by modulating patient immune responses and producing anti-inflammatory effects. These drugs delay disease progression but do not reverse disease pathology or restore neurological function by restoring myelination of damaged neurons. The RXR agonist IRX4204 (194204, Formula XXIX) has an unique mechanism of action in that it is a specific activator of RXR homodimers and RXR/Nurr1 heterodimers and simultaneously provides immunomodulatory activities and promotes remyelination. IRX4204 promotes the differentiation of suppressive Treg cells while simultaneously inhibiting the differentiation of pro-inflammatory Th17 cells, thereby favorably affecting the aberrantly skewed Th17/Treg cell ratio which underlies human autoimmune diseases such as MS. Thus, by virtue of its effects on Th17/Treg cell ratios, IRX4204 is expected to have clinical benefits similar to, or better than, current standard of

care treatments in MS. IRX4204 additionally promotes remyelination of demyelinated CNS neurons. Accordingly, IRX4204 will not only delay disease progression in MS but also effect neural repair by regenerating healthy axons and neurons.

Aspects of the present disclosure includes, in part, reducing at least one symptom associated with a demyelination-related disorder. The actual symptoms associated with a demyelination-related disorder disclosed herein are well known and can be determined by a person of ordinary skill in the art by taking into account factors, including, without limitation, the location of the demyelination-related disorder, the cause of the demyelination-related disorder, the severity of the demyelination-related disorder, the tissue or organ affected by the demyelination-related disorder, and the demyelination-related disorder associated with the inflammation. Non-limiting examples of symptoms reduced by a method of treating a demyelination-related disorder disclosed herein include inflammation, fatigue, dizziness, malaise, elevated fever and high body temperature, extreme sensitivity to cold in the hands and feet, weakness and stiffness in muscles and joints, weight changes, digestive or gastrointestinal problems, low or high blood pressure, irritability, anxiety, depression, blurred or double vision, ataxia, clonus, dysarthria, clumsiness, hand paralysis, hemiparesis, genital anaesthesia, incoordination, paresthesias, ocular paralysis, impaired muscle coordination, weakness (muscle), loss of sensation, impaired vision, neurological symptoms, unsteady gait, spastic paraparesis, incontinence, hearing problems, and speech problems.

Aspects of the methods of the present disclosure include, in part, treatment of a mammal. A mammal includes a human, and a human can be a patient. Other aspects of the present disclosure provide, in part, an individual. An individual includes a mammal and a human, and a human can be a patient.

Aspects of the present disclosure include, in part, administering a compound or a composition disclosed herein. As used herein, the term "administering" means any delivery mechanism that provides a compound or a composition disclosed herein to an individual that potentially results in a clinically, therapeutically, or experimentally beneficial result.

Administration of a compound or a composition disclosed herein include a variety of enteral or parenteral approaches including, without limitation, oral administration in any acceptable form, such as, e.g., tablet, liquid, capsule, powder, or the like; topical administration in any acceptable form, such as, e.g., drops, spray, creams, gels or ointments; buccal, nasal, and/or inhalation administration in any acceptable form; rectal administration in any acceptable form; vaginal administration in any acceptable form; intravascular administration in any acceptable form, such as, e.g., intravenous bolus injection, intravenous infusion, intra-arterial bolus injection, intra-arterial infusion and catheter instillation into the vasculature; peri- and intra-tissue administration in any acceptable form, such as, e.g., intraperitoneal injection, intramuscular injection, subcutaneous injection, subcutaneous infusion, intraocular injection, retinal injection, or sub-retinal injection or epidural injection; intravesicular administration in any acceptable form, such as, e.g., catheter instillation; and by placement device, such as, e.g., an implant, a stent, a patch, a pellet, a catheter, an osmotic pump, a suppository, a bioerodible delivery system, a non-bioerodible delivery system or another implanted extended or slow release system. An exemplary list of biodegradable polymers and methods of use are described in, e.g., *Hand-*

book of Biodegradable Polymers (Abraham J. Domb et al., eds., Overseas Publishers Association, 1997).

A compound or a composition disclosed herein can be administered to a mammal using a variety of routes. Routes of administration suitable for treating a demyelination-related disorder as disclosed herein include both local and systemic administration. Local administration results in significantly more delivery of a composition to a specific location as compared to the entire body of the mammal, whereas, systemic administration results in delivery of a composition to essentially the entire body of the individual. Routes of administration suitable for or treating a demyelination-related disorder as disclosed herein also include both central and peripheral administration. Central administration results in delivery of a compound or a composition to essentially the central nervous system of the individual and includes, e.g., nasal administration, intrathecal administration, epidural administration as well as a cranial injection or implant. Peripheral administration results in delivery of a compound or a composition to essentially any area of an individual outside of the central nervous system and encompasses any route of administration other than direct administration to the spine or brain. The actual route of administration of a compound or a composition disclosed herein used can be determined by a person of ordinary skill in the art by taking into account factors, including, without limitation, the type of demyelination-related disorder, the location of the demyelination-related disorder, the cause of the demyelination-related disorder, the severity of the demyelination-related disorder, the duration of treatment desired, the degree of relief desired, the duration of relief desired, the particular compound or composition used, the rate of excretion of the compound or composition used, the pharmacodynamics of the compound or composition used, the nature of the other compounds to be included in the composition, the particular route of administration, the particular characteristics, history and risk factors of the individual, such as, e.g., age, weight, general health and the like, the response of the individual to the treatment, or any combination thereof. An effective dosage amount of a compound or a composition disclosed herein can thus readily be determined by the person of ordinary skill in the art considering all criteria and utilizing his best judgment on the individual's behalf.

In an embodiment, a compound or a composition disclosed herein is administered systemically to a mammal. In another embodiment, a compound or a composition disclosed herein is administered locally to a mammal. In an aspect of this embodiment, a compound or a composition disclosed herein is administered to a site of a demyelination-related disorder of a mammal. In another aspect of this embodiment, a compound or a composition disclosed herein is administered to the area of a demyelination-related disorder of a mammal.

In another embodiment, the compound or composition is administered directly to the central nervous system by intrathecal administration, epidural administration, cranial injection or implant, or nasal administration.

Aspects of the present specification provide, in part, administering a therapeutically effective amount of a compound or a composition disclosed herein. As used herein, the term "therapeutically effective amount" is synonymous with "therapeutically effective dose" and when used in reference to treating a demyelination-related disorder means the minimum dose of a compound or composition disclosed herein necessary to achieve the desired therapeutic effect and includes a dose sufficient to reduce at least one symptom associated with a demyelination-related disorder. In aspects

of this embodiment, a therapeutically effective amount of a compound or a composition disclosed herein reduces at least one symptom associated with a demyelination-related disorder by, e.g., at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90% or at least 100%. In other aspects of this embodiment, a therapeutically effective amount of a compound or a composition disclosed herein reduces at least one symptom associated with a demyelination-related disorder by, e.g., at most 10%, at most 20%, at most 30%, at most 40%, at most 50%, at most 60%, at most 70%, at most 80%, at most 90% or at most 100%. In yet other aspects of this embodiment, a therapeutically effective amount of a compound or a composition disclosed herein reduces at least one symptom associated with a demyelination-related disorder by, e.g., about 10% to about 100%, about 10% to about 90%, about 10% to about 80%, about 10% to about 70%, about 10% to about 60%, about 10% to about 50%, about 10% to about 40%, about 20% to about 100%, about 20% to about 90%, about 20% to about 80%, about 20% to about 20%, about 20% to about 60%, about 20% to about 50%, about 20% to about 40%, about 30% to about 100%, about 30% to about 90%, about 30% to about 80%, about 30% to about 70%, about 30% to about 60%, or about 30% to about 50%. In still other aspects of this embodiment, a therapeutically effective amount of a compound or a composition disclosed herein is the dosage sufficient to reduces at least one symptom associated with a demyelination-related disorder for, e.g., at least one week, at least one month, at least two months, at least three months, at least four months, at least five months, at least six months, at least seven months, at least eight months, at least nine months, at least ten months, at least eleven months, or at least twelve months.

The amount of active component in a compound or a composition disclosed herein for treating a demyelination-related disorder can be varied so that a suitable dosage is obtained. The actual therapeutically effective amount of a compound or a composition disclosed herein to be administered to a mammal can be determined by a person of ordinary skill in the art by taking into account factors, including, without limitation, the type of the demyelination-related disorder, the location of the demyelination-related disorder, the cause of the demyelination-related disorder, the severity of the demyelination-related disorder, the duration of treatment desired, the degree of relief desired, the duration of relief desired, the particular compound or composition used, the rate of excretion of the compound or composition used, the pharmacodynamics of the compound or composition used, the nature of the other compounds to be included in the composition, the particular route of administration, the particular characteristics, history and risk factors of the individual, such as, e.g., age, weight, general health and the like, the response of the individual to the treatment, or any combination thereof. An effective dosage amount of a compound or a composition disclosed herein can thus readily be determined by the person of ordinary skill in the art considering all criteria and utilizing his best judgment on the individual's behalf.

Additionally, where repeated administration of a compound or a composition disclosed herein is used, the actual effect amount of a compound or a composition disclosed herein will further depend upon factors, including, without limitation, the frequency of administration, the half-life of the compound or composition disclosed herein, or any combination thereof. In is known by a person of ordinary skill in the art that an effective amount of a compound or a composition disclosed herein can be extrapolated from in

vitro assays and in vivo administration studies using animal models prior to administration to humans. Wide variations in the necessary effective amount are to be expected in view of the differing efficiencies of the various routes of administration. For instance, oral administration generally would be expected to require higher dosage levels than administration by intravenous or intravitreal injection. Variations in these dosage levels can be adjusted using standard empirical routines of optimization, which are well-known to a person of ordinary skill in the art. The precise therapeutically effective dosage levels and patterns are preferably determined by the attending physician in consideration of the above-identified factors.

As a non-limiting example, when administering a compound or a composition disclosed herein to a mammal, a therapeutically effective amount generally is in the range of about 0.001 mg/kg/day to about 100.0 mg/kg/day. In aspects of this embodiment, an effective amount of a compound or a composition disclosed herein can be, e.g., about 0.01 mg/kg/day to about 0.1 mg/kg/day, about 0.03 mg/kg/day to about 3.0 mg/kg/day, about 0.1 mg/kg/day to about 3.0 mg/kg/day, or about 0.3 mg/kg/day to about 3.0 mg/kg/day. In yet other aspects of this embodiment, a therapeutically effective amount of a compound or a composition disclosed herein can be, e.g., at least 0.001 mg/kg/day, at least 0.01 mg/kg/day, at least 0.1 mg/kg/day, at least 1.0 mg/kg/day, at least 10 mg/kg/day, or at least 100 mg/kg/day. In yet other aspects of this embodiment, a therapeutically effective amount of a compound or a composition disclosed herein can be, e.g., at most 0.001 mg/kg/day, at most 0.01 mg/kg/day, at most 0.1 mg/kg/day, at most 1.0 mg/kg/day, at most 10 mg/kg/day, or at most 100 mg/kg/day.

As another non-limiting example, when administering a compound or a composition disclosed herein to a mammal, a therapeutically effective amount generally is in the range of about 0.001 mg/m^2/day to about 100.0 mg/m^2/day. In aspects of this embodiment, an effective amount of a compound or a composition disclosed herein can be, e.g., about 0.01 mg/m^2/day to about 0.1 mg/m^2/day, about 0.03 mg/m^2/day to about 3.0 mg/m^2/day, about 0.1 mg/m^2/day to about 3.0 mg/m^2/day, or about 0.3 mg/m^2/day to about 3.0 mg/m^2/day. In yet other aspects of this embodiment, a therapeutically effective amount of a compound or a composition disclosed herein can be, e.g., at least 0.001 mg/m^2/day, at least 0.01 mg/m^2/day, at least 0.1 mg/m^2/day, at least 1.0 mg/m^2/day, at least 10 mg/m^2/day, or at least 100 mg/m^2/day. In yet other aspects of this embodiment, a therapeutically effective amount of a compound or a composition disclosed herein can be, e.g., at most 0.001 mg/m^2/day, at most 0.01 mg/m^2/day, at most 0.1 mg/m^2/day, at most 1.0 mg/m^2/day, at most 10 mg/m^2/day, or at most 100 mg/m^2/day.

Dosing can be single dosage or cumulative (serial dosing), and can be readily determined by one skilled in the art. For instance, treatment of a demyelination-related disorder may comprise a one-time administration of an effective dose of a compound or a composition disclosed herein. As a non-limiting example, an effective dose of a compound or a composition disclosed herein can be administered once to a mammal, e.g., as a single injection or deposition at or near the site exhibiting a symptom of a demyelination-related disorder or a single oral administration of the compound or a composition. Alternatively, treatment of a demyelination-related disorder may comprise multiple administrations of an effective dose of a compound or a composition disclosed herein carried out over a range of time periods, such as, e.g., daily, once every few days, weekly, monthly or yearly. As a

non-limiting example, a compound or a composition disclosed herein can be administered once or twice weekly to a mammal. The timing of administration can vary from mammal to mammal, depending upon such factors as the severity of a mammal's symptoms. For example, an effective dose of a compound or a composition disclosed herein can be administered to a mammal once a month for an indefinite period of time, or until the mammal no longer requires therapy. A person of ordinary skill in the art will recognize that the condition of the mammal can be monitored throughout the course of treatment and that the effective amount of a compound or a composition disclosed herein that is administered can be adjusted accordingly.

A compound or a composition disclosed herein as disclosed herein can also be administered to a mammal in combination with other therapeutic compounds to increase the overall therapeutic effect of the treatment. The use of multiple compounds to treat an indication can increase the beneficial effects while reducing the presence of side effects.

Aspects of the present specification may also be described as follows:

EXAMPLES

The following non-limiting examples are provided for illustrative purposes only in order to facilitate a more complete understanding of representative embodiments now contemplated. These examples should not be construed to limit any of the embodiments described in the present specification, including those pertaining to the methods of treating an autoimmune disorder, in particular a demyelination-related disorder using the RXR agonists disclosed herein, uses of a RXR agonists disclosed herein to manufacture a medicament and/or treat an autoimmune disorder, in particular a demyelination-related disorder, methods of promoting Treg cell differentiation in an individual, inhibiting Th17 cell differentiation, or both, as well as uses of a RXR agonists disclosed herein to promote Treg cell differentiation in an individual, inhibit Th17 cell differentiation, or both.

Example 1

RXR Agonists Induce Treg Cell Differentiation

To determine whether a RXR agonist can induce Treg cell differentiation, the ability of an RXR agonist to promote Treg cell differentiation under Treg cell differentiation conditions was assessed by monitoring Foxp3 and $\alpha 4\beta 7$ expression. Naïve $CD4^+$ $CD25^-$ $FoxP3^-$ cells were purified from a Foxp3-GFP mouse using flow cytometry by sorting and isolating based upon a GFP^- phenotype. These cells were then cultured under Treg cell differentiation conditions by treating the cells with $\alpha CD3$ and $\alpha CD28$ polyclonal antibodies in the presence of IL-2 and TGF-β. The cultured cells were incubated with RXR agonist 194204 (Formula XXIX, IRX4204) at 0.1 nM, 1.0 nM and 10 nM and the expression of Foxp3 and $\alpha 4\beta 7$ was analyzed. The results indicate that RXR agonist exerted significant impact on the expression of Foxp3, inducing nearly 100% $Foxp3^+$ T cells at concentrations of 1 nM or higher. FIG. **1A**. These results also indicate

that RXR agonist 194204 also induced expression of $\alpha 4\beta 7$ (a gut homing receptor). FIG. **1B**. These results indicate that RXR agonists could be useful in reducing a symptom of an autoimmune disorder or a transplant rejection.

Example 2

RXR Agonists Regulate T Cell Differentiation

To determine whether a RXR agonist can regulate T cell differentiation, the ability of an RXR agonist to promote Treg cell differentiation and inhibit Th17 cell differentiation under Th17 cell differentiation conditions was assessed by monitoring Foxp3 and IL-17A expression. Naive $CD4^+$ $CD25^-$ $FoxP3^-$ cells were purified from a Foxp3-GFP mouse using flow cytometry by sorting and isolating based upon a GFP^- phenotype. These cells were then cultured under Th17 cell differentiation conditions in media with 0 nM, 1 nM, 10 nM, and 100 nM of RXR agonist 194204 (Formula XXIX, IRX4204) and the expression of Foxp3 and IL-17A was analyzed. See, e.g., Elias, et al., Blood 111(3): 1-13-1020 (2008). The results indicated that as the concentration of the RXR agonist increased, Foxp3 expression increased, indicating an increased presence of Treg cells (FIG. **2A**). Additionally, the data demonstrate that as the concentration of the RXR agonist increased, IL-17A expression decreased, indicating a decreased presence of Th17 cells (FIG. **2B**). These results indicate that RXR agonists regulate T cell differentiation by promoting differentiation of immunosuppressive Treg cells and concurrently inhibiting differentiation of inflammatory Th17 cells from naïve T cells in vitro.

Example 3

RXR Agonists Regulate T Cell Differentiation Independent of RAR Signaling

To determine whether a RXR agonist can mediate its effects via RAR/RXR receptor heterodimers, via RXR receptor homodimers, or via some other RXR containing complex, T cells were incubated with a RXR agonist in the presence of a pan-RAR antagonist and the expression of Foxp3 was assessed. Naïve $CD4^+$ $CD25^-$ $FoxP3^-$ cells were purified from a Foxp3-GFP mouse using flow cytometry by sorting and isolating based upon a GFP^- phenotype. These cells were then cultured under Treg cell differentiation conditions by treating the cells with $\alpha CD3$ and $\alpha CD28$ polyclonal antibodies in the presence of IL-2 and TGF-β. The cultured cells were incubated with RXR agonist 194204 at 1.0 nM together with 0 nM, 1 nM, or 10 nM of a pan-RAR antagonist 194310. The cultured cells were then assayed for the expression of Foxp3. The results indicate that the inclusion of a pan-RAR antagonist only partially blocked the induction of Foxp3 expression observed with an RXR agonist alone. FIG. **3**. However, this partial inhibition of Fox3p expression may actually be due to the blocking of the effects of endogenous retinoic acid in the culture medium. As such, these results indicate that the observed conversion of T cells into Treg cells appears to occur through the use of

RXR receptor homodimers and/or some other RXR containing complex, and not through a RAR-mediated mechanism.

Example 4

T Cell Differentiation is Mediated Through RXR Signaling by RXR Agonists

To determine whether a RXR agonist can mediate its effects via an RXRα receptor homodimers, RXRβ receptor homodimers, RXRγ receptor homodimers, or any combination thereof, or the corresponding RAR/RXR heterodimers, receptor-mediated transactivation assays were performed. For transactivation assays assessing RXR homodimer signaling, CV-1 cells were transfected with 1) an expression construct including a full length RXRα, RXRβ, or RXRγ; and 2) a rCRBPII/RXRE-tk-Luc reporter construct that included RXR homodimer-specific RXRE/DR1 responsive element linked to a luciferase gene. For transactivation assays assessing RAR/RXR heterodimer signaling, CV-1 cells were transfected with 1) an expression construct comprising a fusion protein including an estrogen receptor (ER) DNA binding domain linked to the ligand binding domain of RARα, RARβ, or RARγ and 2) a ERE-tk-Luc reporter construct that included an estrogen receptor responsive element linked to a luciferase gene. The ER-RAR fusion proteins provided an accurate readout of only the transfected ER-RAR. After transfection, CV-1 cells were treated with RXR agonist 194204 at increasing concentrations for 20 hours before measuring luciferase activity. Luciferase activity is expressed as percent of maximal activity obtained using 1 μM RXR agonist 194204 for RXRs and 1 μM all-trans-retinoic acid (ATRA) for RARs (Table 1). Data are mean values±SE from five independent experiments.
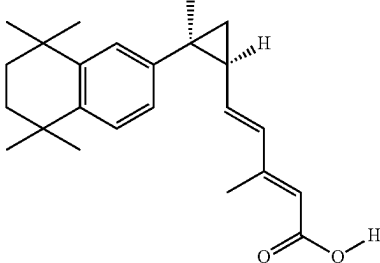
tors. These results indicate that Treg differentiation was mediated through a RXR signaling pathway and not via a RAR signaling pathway. Also, using appropriate receptor and reporter constructs, RXR agonist 194204 was shown not to transactivate so called "permissive RXR heterodimers" PPAR/RXR, FXR/RXR and LXR/RXR (FIG. 8A-C). In this regard, RXR agonist 194204 is distinct from other RXR agonists. Additionally, 194204 selectively activates the Nurr1/RXR permissive heterodimer (FIG. 8D). Thus, RXR agonist 194204 has a unique profile in that it selectively activates only RXR homodimers and Nurr1/RXR heterodimers.

Example 5

Binding Affinity of RXR Agonists

To determine the binding affinity for a RXR agonist, competitive displacement assays were performed. RXRα, RXRβ, RXRγ, RARα, RARβ, or RARγ were expressed in SF21 cells using a baculovirus expression system and the resulting proteins were purified. To determine the binding affinity for a RXR agonist for an RXR, purified RXRα, RXRβ, and RXRγ were separately incubated with 10 nM [^{3}H]-9CRA, and the binding affinity of the RXR agonist 194204 was determined by competitive displacement of [^{3}H]-9CRA from the receptor. To determine the binding affinity for a RXR agonist for an RAR, purified RARα, RARβ, and RARγ were incubated with 5 nM [^{3}H]-ATRA, and the binding affinity of the RXR agonist 194204 was determined by competitive displacement of [^{3}H]-ATRA from the receptor. Ki values are mean values of at least two
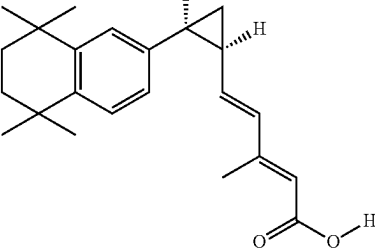
TABLE 1

| | | RXR Agonist Potencies in Activating RXRs and RARs | | | | | |
| | | EC$_{50}$ (nM) Efficacy (% of 1 μM 194204) | | | EC$_{50}$ (nM) Efficacy (% of 1 μM ATRA) | | |
Compound	Structure	RXRα	RXRβ	RXRγ	RARα	RARβ	RARγ
194204 (IRX4204)		0.08 ±0.01 100	0.47 ±0.05 100	0.09 ±0.01 100	>1,000	>1,000	>1,000

These results indicate that RXR agonist 194204 activated RXR receptors with very high potency (EC$_{50}$<0.5 nM) for all three RXR subtypes (Table 1). In contrast, EC$_{50}$ of the RXR agonist for RARs was >1,000 nM with minimal activity detected at ≥1 μM. This difference represents >2,000-fold selectivity for RXRs over RARs in functional transactivation assays. Additionally, these data demonstrate that RXR agonist 194204 was more than 1,000-fold more potent in activating RXR receptors rather than RAR recep-

independent experiments (Table 2). Standard errors (±) among independent experiments are indicated.

As shown in Table 2, RXR agonist 194204 displayed high affinity for RXRα, RXRβ, and RXRγ with Ki values being 1.7, 16, and 43 nM, respectively. In contrast, the RXR agonist 194204 bound with very low affinity to each of the RARs (Ki values being >1,000 nM). These data indicate that 194204 is highly selective for the RXRs relative to the RARs.

TABLE 2

RXR Agonist Binding Affinities

Compound	Structure	RXR Binding Affinity Ki (nM)			RAR Binding Affinity Ki (nM)		
		RXRα	RXRβ	RXRγ	RARα	RARβ	RARγ
194204		1.7 ± 0.1	16 ± 1.0	43 ± 3.0	6344 ± 674	7552 ± 638	4742 ± 405

Example 6

RXR Agonists Attenuate EAE in B6 Mice

To determine whether a RXR agonist can attenuate multiple sclerosis, C57BL/6 (B6) mice were immunized (day 0) to induce experimental autoimmune encephalomyelitis (EAE) by subcutaneous (s.c.) injection at the base of their spine with 200 μL of adjuvant containing 125 μg myelin oligodendrocyte glycoprotein peptide (35-55) (MOG peptide; Peptides International, Louisville, KY) and 400 μg non-viable *M. tuberculosis* H37 desiccate emulsified in a mixture of incomplete Freund's adjuvant and phosphate buffered saline (PBS). Mice were also given 200 ng of pertussis toxin in PBS administered by inter-peritoneal (i.p.) injection on the same day as MOG emulsion injection (day 0) and 2 days later (day 2). Starting on day 7 after immunization, mice were given the RXR agonist IRX4204 (50 μg) or vehicle control i.p. every other day for the duration of the experiment (n=6-7 mice/group). Statistics show the results of a Mann Whitney test (analyzed from start of treatment to the end of the experiment). Mice were scored using the following scale: 0—Mice have no disease, 1—Mice have distal limp tail or rear leg weakness (paresis), 1.5—Mice have distal limp tail and rear leg weakness, 2—Mice have complete limp tail and rear leg weakness, 2.5—Mice have complete limp tail and weakness in both rear legs, 3—Mice have complete limp tail and paralysis in both rear legs, 3.5—Mice have complete limp tail, paralysis in both rear legs, and forelimb weakness. Mice receiving a score of 3.5 were immediately euthanized.

FIG. 5 depicts scores of disease severity over time. The results indicate that administration of a RXR agonist (194204, IRX4204) at 50 μg significantly reduces the symptoms of EAE in mice. Efficacy of the RXR agonist was observed after the first administration (day 7) and maintained throughout the course of the study (day 20).

A dose titration experiment was also conducted in EAE mice. EAE was induced in 28 B6 mice with MOG/CFA and PT as above. Mice were scored on day 7 as indicated above and divided into groups by score so means are as equal as possible. Starting day 8, mice were scored and injected with a vehicle control or IRX4204 (50 μg, 100 μg, or 200 μg) every day.

The mice were weighed at the beginning of experiment and every day they had a score of 2.5 or higher and mice were euthanized if they lost 15% or more of their start weight. All mice were treated with IRX4204 had significantly less disease overall (FIG. 10). At the completion of the experiment, the vehicle control and 200 μg/day groups were euthanized and spleen and CNS samples obtained.

The spleen samples were evaluated for CD49d (FIG. 11A) and CCR6 (FIG. 11B), and IRX4204 treatment lowered CCR6, but not CD49d, expression on CD4 T cells. Additionally, CD4+ CD25hi cells (generally consisting of TReg) were reduced, although the frequency was not altered (FIGS. 12A and 12B). The total number of effector and memory CD4 T cells, as indicated by CD44 expression, decreased with IRX4204 treatment (FIG. 12C) and the total number of recently activated CD4 T cells, as indicated by expression of both CD69 and CD44, was also decreased with IRX4204 treatment (FIG. 12D).

In the CNS, the total the total number of infiltrating CD4 T cells was reduced with IRX4204 treatment (FIG. 13). Restimulation with PMA/Ionomycin was used to help detect the cytokine production. Both IFNγ (FIGS. 14A and 14B) and TNF (FIGS. 14C and 14D) were significantly reduced with treatment. Co-expression of IFNg and IL-17A by CD4 T cells in CNS was quantified, but was not significantly different between groups (FIG. 15A-15C).

Example 7

RXR Agonist-Treated Mice have Reduced Central Nervous System Infiltrating Cells

To determine whether a RXR agonist can reduce central nervous system (CNS) infiltrating cells, C57BL/6 (B6) mice were treated as described in Example 6. On day 20 after immunization, mice were sacrificed and perfused with phosphate buffered saline (PBS). Brain and spinal cord tissue was isolated, digested with DNase and LIBERASE DL® (Roche Diagnostics, Indianapolis, IN) for 30 minutes, and homogenized through 70 micron nylon mesh filters. Resulting cells were placed over a Percoll gradient to remove myelin. The remaining cells (microglia and CNS infiltrating cells) were counted, stained for molecules of interest, and run on a flow cytometer. Based on the frequencies obtained by FACS of these cell populations, total cell numbers of CNS infiltrating leukocytes expressing CD45, including CD4+ T cells and CD11c+ CD11b+ myeloid dendritic cells (DC), were calculated.

FIG. 6 depicts the number of CD4+ cells (FIG. 6A) or CD11c+ CD11b+ cells (myeloid DC; FIG. 6B) in mice

treated with the RXR agonist 194204 verses the vehicle control. There was a significant reduction in the infiltration of both CD4⁺ cells and CD11c⁺ CD11b⁺ cells in animals treated with a RXR agonist as compared to the control. As disease is propagated in the CNS through the CD4⁺ cells infiltrating the CNS and becoming re-activated by CD11c⁺ CD11b⁺ cells, this suggests that part of the mechanism of action in this model is to limit the presence of the cells in the CNS.

Example 8

RXR Agonists Attenuate EAE in SJL Mice

To determine whether a RXR agonist can attenuate multiple sclerosis, SJL mice were immunized to induce EAE by s.c. injection at the base of their spine with 200 μL of adjuvant containing 200 μg proteolipid proteins (139-151) (PLP peptide; Peptides International, Louisville, KY) and 400 μg of non-viable *M. tuberculosis* H37 desiccate emulsified in a mixture of incomplete Freund's adjuvant and PBS. Mice were also given 150 ng of pertussis toxin in PBS i.p. on the same day as PLP emulsion injection and 2 days later. Starting day 7 after immunization, mice were given the RXR agonist IRX4204 (50 μg) or vehicle control i.p. every other day for the duration of the experiment (n=6 mice/group). Mice were scored using the scale described in Example 6.

The results indicate that administration of a RXR agonist (194204, IRX4204) significantly reduces the symptoms of EAE in mice. Table 3 shows the features of a RXR agonist IRX4204 treatment in SLJ mice. FIG. **7** depicts scores of disease severity over time. Efficacy of the RXR agonist was observed after the second administration (day 8) and maintained throughout the course of the study (day 14).

TABLE 3

RXR agonist Treatment in SJL Mice		
Clinical Features	Vehicle	IRX4204
Mean Maximum Score	3.2 ± 0.6	1.5 ± 1.4
Disease Incidence	6/6	4/6
Death from Disease	4/6	0/6

Example 9

RXR Agonist IRX4204 as a Selective Activator of Nurr1/RXR Permissive Heterodimer

In order to determine which permissive RXR heterodimer is activated by the RXR agonist IRX4204 (194204), receptor transactivation assays were carried out as follows for PPARγ/RXR, FXR/RXR, LXRα/RXR, LXRβ/RXR, and Nurr1/RXR. For PPARγ: CV-1 cells were transfected with 3×(rAOX/DR1)-tk-Luc reporter gene and an expression vector for PPARγ. For FXR:CV-1 cells were transfected with 3×(IBABP/IRI)-tk-Luc reporter gene and vectors for FXR and RXRα. For LXR:CV-1 cells were transfected with 3×(PLTP/LXRE)-tk-Luc reporter gene with vectors for LXRα or LXRβ. For Nurr1: COS7 cells were transfected with 3×NBRE-tk-luc reporter gene and full length Nurr-1 with or without full-length RXRα plasmid. Cells were then treated with vehicle or IRX4204 for 20 hr. Luciferase data were normalized to co-transfected β-gal activity. Luciferase activity was expressed as percent of maximal activity

obtained using specific agonists. Rosiglitazone (PPARγ), GW4064 (FXR), T0901317 (LXR). The data indicate that IRX4204 does not activate FXR/RXR (FIG. **8A**), LXRα/RXR or LXRβ/RXR (FIG. **8B**), or PPARγ/RXR (FIG. **8C**). In contrast, IRX4204 potently (EC_{50}<1 nm) activates the Nurr1/RXR heterodimer. These data collectively indicate that IRX4204 (194204) is a unique RXR agonist in that it selectively activates the Nurr1/RXR heterodimer but not the PPARγ/RXR, FXR/RXR or LXR/RXR heterodimers.

Example 10

Effect of RXR Agonists on Oligodendrocyte Precursor Cell Differentiation

The goal of this study was to evaluate the effect of IRX4204 on differentiation of oligodendrocyte precursor cells (OPCs) into oligodendrocytes. OPCs were generated from a neurosphere culture of E14.5 PLP-EGFP (on C57BL/6J background) mouse brains. The isolated OPCs were treated with IRX4204 to evaluate the expression of green fluorescent protein (EGFP), which correlates with differentiation of OPCs into oligodendrocytes. The EGFP expressing cells were quantified with Cellomics Neuronal Profiling Algorithm. The positive (T3) control demonstrated differentiation of OPCs as expected. The results demonstrate that IRX4204 promotes OPC differentiation into oligodendrocytes as shown by the increase in the number of the EGFP positive cells compared to negative control (DMSO). All tested concentrations but the lowest concentration (1^{-6} μM) showed a significant increase in OPC differentiation into oligodendrocytes (FIG. **9**, data for IRX4204 are shown as open bars with concentrations expressed in μM).

The EGFP expressing cells in controls and all compounds were quantified with Cellomics Neuronal Profiling Algorithm. The experiment was successful as demonstrated by the significant increase in % EGFP cells in positive control (T3; 8.5%) compared to the negative control (DMSO; 2.3%). IRX4204 promotes OPC differentiation into oligodendrocytes as demonstrated by the dose dependent increase in the number of the EGFP positive cells compared to negative control (DMSO). IRX4204 did not show any differences in total cell number and pyknotic cells compared to controls. The results from this study demonstrate that IRX4204 promotes OPC differentiation. The data show a dose-dependent increase in the percentage of EGFP cells compared to the negative control. These date indicate that IRX4204 promotes the growth of myelin-forming cells in cell culture.

Example 11

IRX4204 Enhances Central Nervous System (CNS) Remyelination in an In Vivo Model by Acting Directly on the Remyelination Process

A focal toxin (ethidium bromide) induced rat model of demyelination is used to ascertain the direct effects of IRX4204 on acute demyelination independent of the immunomodulatory effects of IRX4204. The experiment uses rats of relatively advanced age (1 year) since such rats undergo remyelination in a less efficient manner, thereby providing data that are more relevant to the clinical treatment of human patients with multiple sclerosis or other demyelination disorders.

Focal demyelination is induced in one year old rats (approximately 300 g in weight) by injecting stereotactically

5 µl of ethidium bromide solution (0.01% vol/vol in saline) in a bilateral manner into the caudal cerebellar peduncles (CCP). Starting seven days after injection of the ethidium bromide, the rats are treated by oral gavage with 10 mg/kg/day of IRX4204 (in DMSO and corn oil) or vehicle (DMSO and corn oil) for fourteen days (day 7 to day 21 post-ethidium bromide treatment). The rats are killed on day 24 post-ethidium bromide treatment for analysis of remyelination by quantitative polymerase chain reaction (qPCR) and microscopy.

Analysis of the lesions revealed the following: the densities of Olig2$^+$ oligodendrocyte lineage cells and CC1+ differentiated oligodendrocytes increased in IRX4204-treated animals relative to vehicle treated animals; Nkx2.2+ oligodendrocyte precursor cells (OPCs) increased in IRX4204-treated lesions relative to vehicle treated lesions. Also, real-time qPCR analysis of lesion samples show an increase in Mbp expression and an increase in Pdgfra expression indicating higher levels of myelin regeneration in IRX4204-treated animals. Ultrastructural analyses of CCP lesions further demonstrate that IRX4204 treatment results in more remyelinated axons in animals than vehicle treatment. AG-ratio analysis (this ratio is that of axon diameter to myelinated axon) also shows that IRX4204-treated animals have a lower G-ratio than vehicle treated animals and that this lower ratio is due to the formation of thicker remyelinated sheaths surrounding axons in IRX4204-treated animals. All these findings are consistent with an increase in CNS remyelination in IRX4204-treated animals.

Example 12

IRX4204 Accelerates Remyelination in a Mouse Model of Demyelination

The cuprizone (bis-cyclohexanone oxaldihydrazone) model facilitates reliable, reproducible and unequivocal analysis of myelin parameters in both white and grey matter. The cuprizone model is a model for toxic demyelination. In this model, young mice are fed with the copper chelator cuprizone, leading to oligodendrocyte death and a subsequent reversible demyelination. cuprizone-fed mice with rapamycin, a drug that blocks mTOR and spontaneous remyelination, allowing better quantification of oligodendrocyte turnover. In the acute cuprizone paradigm, male C57BL/6 mice at 6 to 9 weeks of age are fed a diet of chow mixed with 0.2% cuprizone over the course of 6 weeks. By the third week of cuprizone feeding, consistent demyelination can be observed in the corpus callosum, the largest white matter tract in the mouse brain. Demyelination reaches a maximum at 5 or 6 weeks. Chronic demyelination can be induced if C57BL/6 mice are maintained on a diet with cuprizone for 12 weeks.

In this study, the acute (6-week) model will be used to assess remyelination potential of IRX4204. Mice are fed a cuprizone-containing diet and injected with rapamycin daily for 6 weeks to induce demyelination. One group of animals is sacrificed at 6 weeks to evaluate demyelination. The remaining mice are continued on the cuprizone/rapamycin regimen, and treatment with IRX4204 or vehicle control is initiated for a three week treatment period. At the end of the study, all mice are sacrificed and one or more of the following parameters are determined: (1) PPD (p-phenylenediamine) staining to visualize and quantify myelinated axons in corpus callosum to assess demyelination and remyelination in white matter; (2) myelin proteolipid protein (PLP) immunostaining to visualize and quantify myelin in

hippocampus to assess demyelination and remyelination in grey matter (hippocampus); (3) PLP immunostaining to visualize and quantify myelin in cortex to assess demyelination and remyelination in grey matter (cortex); (4) PDGFRα immunostaining to visualize and quantify OPCs in corpus callosum; (5) GSTpi immunostaining to visualize and quantify oligodendrocytes in corpus callosum; (6) Iba1 (ionized calcium-binding adapter molecule 1) and/or Mac-2 (galectin-3) immunostaining to visualize and quantify total and activated microglia in corpus callosum; (7) GFAP (glial fibrillary acidic protein) immunostaining to visualize and quantify astrocytes in corpus callosum To assess astroglial activation; and (8) 3D-electron microscopy in corpus callosum to assess ratio of myelinated and non-myelinated axons, internodal length, G-ratio, mitochondrial changes, etc.

Example 13

A Human Clinical Trial to Ascertain Effects of IRX4204 Treatment on Myelin Repair in Multiple Sclerosis Patients with Relapsing-Remitting Disease

A proof of concept clinical trial of IRX4204 is conducted in multiple sclerosis (MS) patients to ascertain the direct effects of IRX4204 on myelin repair in patients with relapsing-remitting MS. Patients with relapsing-remitting MS are recruited to participate in the clinical trial and are provided informed consent describing risks and potential benefits of participation. The MS patients are treated with one of several dose levels of IRX4204, ranging from 1 mg/day to 40 mg/day, administered orally as capsules, once per day. Some patients are randomized to receive a placebo dose using matching capsules, which do not contain IRX4204. Patients are dosed for a minimum of 30 days, and as long as 180 days. Patients are assessed for the status of myelin damage and speed of repair of demyelination in MS lesions that occur over this period of time in their brains, spinal cords, and/or optic nerves. Quantitation of myelin damage and repair is performed at baseline and periodically through the dosing, using specialized imaging methods, which specifically examine and quantitate myelin damage and repair in these parts of the nervous system. Such methods include, but are not limited to, Positron Emission Tomography (PET) scanning, utilizing imaging agents such as the thioflavine-T derivative 2-(4'-methylaminophenyl)-6-hydroxybenzothiazole (PIB), which also binds to amyloid plaques. This compound is useful for useful for quantitating myelin repair. Alternatively, magnetic resonance imaging (MRI) using special contrast agents that bind to or enhance the appearance of areas of myelin damage or repair is utilized; or special MRI analytical algorithms, such as magnetization transfer imaging, or diffusion tensor imaging, are utilized to quantitate myelin damage and repair in the IRX4204-treated patients compared to the placebo-treated patients. Dose response relationships of IRX4204 to myelin protection or repair are analyzed across the cohorts of patients treated with various dose levels of IRX4204. In addition to the quantitation of myelin damage and repair by imaging methods, the clinical status of the MS patients' disease progression is preliminarily evaluated using standard clinical endpoints for MS clinical trials, such as the Expanded Disability Status Scale (EDSS). The EDSS is a 10 point scale which quantitates the MS patients' levels of disability by evaluating physical activities of daily life, such as walking, swallowing, bowel and bladder function, etc. In addition, visual

acuity testing is performed to quantitate effects of IRX4204 on myelin damage and repair in the optic nerves.

Example 14

A Human Clinical Trial to Evaluate the Effects of IRX4204 Treatment on Progression of Disability in Multiple Sclerosis Patients with Relapsing-Remitting Disease

A clinical trial to provide definitive evidence of benefit of IRX4204 treatment on progression of disability in MS is conducted in MS patients with relapsing-remitting MS. Patients with relapsing-remitting MS are recruited to participate in the clinical trial and are provided informed consent describing risks and potential befits of participation. The MS patients are randomized to treatment with a dose level of IRX4204, in the range of 1 to 40 mg/day administered orally, or matching placebo, for 24 months. The primary clinical efficacy outcome measure is the EDSS, a 10 point scale which quantitates the MS patients' levels of disability by evaluating physical activities of daily life, such as walking, swallowing, bowel and bladder function, etc. The clinical trial uses a sample size selected to demonstrate to a statistically significant level, a difference in change in the mean EDSS over time, of a least 1 point, between the IRX4204-treated group, and the placebo-treated group, at the end of 24 months of treatment. In addition, in this clinical trial visual acuity testing is performed to quantitate effects of IRX4204 on myelin damage and repair in the optic nerves. A sample size is selected which will demonstrate to a statistically level, a difference in change in visual acuity over time, of a least 1 line on the standard visual acuity chart, between the IRX4204-treated group, and the placebo-treated group, at the end of 24 months of treatment.

In closing, it is to be understood that although aspects of the present specification are highlighted by referring to specific embodiments, one skilled in the art will readily appreciate that these disclosed embodiments are only illustrative of the principles of the subject matter disclosed herein. Therefore, it should be understood that the disclosed subject matter is in no way limited to a particular methodology, protocol, and/or reagent, etc., described herein. As such, various modifications or changes to or alternative configurations of the disclosed subject matter can be made in accordance with the teachings herein without departing from the spirit of the present specification. Lastly, the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention, which is defined solely by the claims. Accordingly, the present invention is not limited to that precisely as shown and described.

Certain embodiments of the present invention are described herein, including the best mode known to the inventors for carrying out the invention. Of course, variations on these described embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventor expects skilled artisans to employ such variations as appropriate, and the inventors intend for the present invention to be practiced otherwise than specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described embodiments in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

Groupings of alternative embodiments, elements, or steps of the present invention are not to be construed as limitations. Each group member may be referred to and claimed individually or in any combination with other group members disclosed herein. It is anticipated that one or more members of a group may be included in, or deleted from, a group for reasons of convenience and/or patentability. When any such inclusion or deletion occurs, the specification is deemed to contain the group as modified thus fulfilling the written description of all Markush groups used in the appended claims.

Unless otherwise indicated, all numbers expressing a characteristic, item, quantity, parameter, property, term, and so forth used in the present specification and claims are to be understood as being modified in all instances by the term "about." As used herein, the term "about" means that the characteristic, item, quantity, parameter, property, or term so qualified encompasses a range of plus or minus ten percent above and below the value of the stated characteristic, item, quantity, parameter, property, or term. Accordingly, unless indicated to the contrary, the numerical parameters set forth in the specification and attached claims are approximations that may vary. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical indication should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques. Notwithstanding that the numerical ranges and values setting forth the broad scope of the invention are approximations, the numerical ranges and values set forth in the specific examples are reported as precisely as possible. Any numerical range or value, however, inherently contains certain errors necessarily resulting from the standard deviation found in their respective testing measurements. Recitation of numerical ranges of values herein is merely intended to serve as a shorthand method of referring individually to each separate numerical value falling within the range. Unless otherwise indicated herein, each individual value of a numerical range is incorporated into the present specification as if it were individually recited herein.

The terms "a," "an," "the" and similar referents used in the context of describing the present invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein is intended merely to better illuminate the present invention and does not pose a limitation on the scope of the invention otherwise claimed. No language in the present specification should be construed as indicating any non-claimed element essential to the practice of the invention.

Specific embodiments disclosed herein may be further limited in the claims using consisting of or consisting essentially of language. When used in the claims, whether as filed or added per amendment, the transition term "consisting of" excludes any element, step, or ingredient not specified in the claims. The transition term "consisting essentially of" limits the scope of a claim to the specified materials or steps and those that do not materially affect the basic and novel characteristic(s). Embodiments of the present invention so claimed are inherently or expressly described and enabled herein.

All patents, patent publications, and other publications referenced and identified in the present specification are

individually and expressly incorporated herein by reference in their entirety for the purpose of describing and disclosing, for example, the compositions and methodologies described in such publications that might be used in connection with the present invention. These publications are provided solely for their disclosure prior to the filing date of the present application. Nothing in this regard should be construed as an admission that the inventors are not entitled to antedate such disclosure by virtue of prior invention or for any other reason. All statements as to the date or representation as to the contents of these documents is based on the information available to the applicants and does not constitute any admission as to the correctness of the dates or contents of these documents.

What is claimed is:

1. A method of generating T regulatory cells (Treg) in vitro comprising culturing lymphocytes in the presence of an RXR agonist, wherein the RXR agonist is a compound having the structure of formula XXIX:
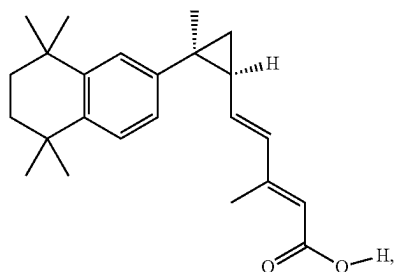
(XXIX)

and
    wherein the concentration of formula XXIX is at least 0.1 nM.

2. The method of claim 1, wherein the compound is a pharmaceutically acceptable salt of formula XXIX.

3. The method of claim 1, wherein the lymphocytes are CD4+ lymphocytes.

4. The method of claim 1, wherein the lymphocytes are peripheral blood lymphocytes.

5. The method of claim 1, wherein the lymphocytes are obtained from leukapheresis.

6. The method of claim 1, wherein the method further comprises culturing the lymphocytes cells in the presence of interleukin-2 (IL-2).

7. The method of claim 1, wherein the method increases the number of differentiated Treg cells in the culture.

8. The method of claim 7, wherein the differentiated Treg express FoxP3.

9. The method of claim 1, wherein the method produces Treg cells with increased immunosuppressive activity.

10. A method of treating a demyelination-associated disorder comprising administering to a subject in need thereof Treg cells produced by the method of claim 1.

11. The method of claim 10, wherein the demyelination-associated disorder is multiple sclerosis.

12. The method of claim 10, wherein the demyelination-associated disorder is amyotrophic lateral sclerosis.

13. The method of claim 10, wherein the Treg are produced from lymphocytes isolated from the subject to be treated.

14. The method of claim 10, wherein as a result of the administration of Treg, a Treg/T17 imbalance is corrected in the subject.

15. A method of growing oligodendrocytes or oligodendrocyte precursor cells in vitro comprising culturing oligodendrocytes or oligodendrocyte precursor cells in the presence of an RXR agonist, wherein the RXR agonist is a compound having the structure of formula XXIX:
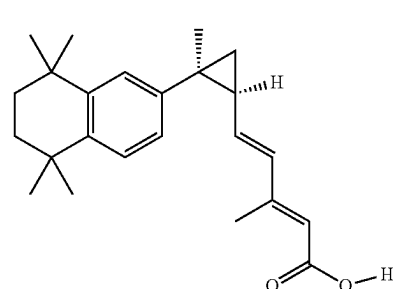
(XXIX)

and
    wherein the concentration of formula XXIX is at least 0.1 nM.

16. The method of claim 15, wherein the compound is a pharmaceutically acceptable salt of formula XXIX.

17. The method of claim 15, wherein the cells are oligodendrocyte precursor cells.

18. The method of claim 15, wherein the cells are oligodendrocytes.

19. A method for treating a demyelination-associated disorder, comprising administering to a subject in need thereof oligodendrocytes or oligodendrocyte precursor cells grown by the method of claim 15.

20. The method of claim 19, wherein the oligodendrocytes or oligodendrocyte precursor cells are isolated from the subject to be treated.

21. The method of claim 19, wherein administering oligodendrocytes or oligodendrocyte precursor cells to a subject in need thereof results in remyelination of demyelinated neurons.

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