suggest that LRP1 is essential for inhibitory myelin signaling. LRP1 emerges as a possible target for neutralizing inhibitory myelin-associated inhibitory proteins in the injured CNS.

SUMMARY OF THE INVENTION

[0009] In one aspect, the invention provides methods for increasing, promoting, restoring or enhancing nerve growth and/or neuronal regeneration, comprising contacting a neuron with an inhibitor or antagonist of low density lipoprotein receptor-related protein-1 (LRP-1) in the presence of a myelin-associated inhibitor protein (a.k.a, myelin-associated inhibitory factor (MAIF)).

[0010] In another aspect, the invention provides methods for increasing, promoting, restoring or enhancing nerve growth and/or neuronal regeneration in a subject in need thereof, comprising administering to the subject an effective amount of an inhibitor or antagonist of low density lipoprotein receptor-related protein-1 (LRP-1).

[0011] In a further aspect, the invention provides methods for inhibiting CNS myelin-mediated neurite outgrowth inhibition and/or for promoting or restoring axonal regeneration. In some embodiments, the methods comprise contacting a neuron with a LRP-1 inhibitor or antagonist, wherein the LRP-1 inhibitor or antagonist inhibits CNS myelin-induced neurite outgrowth inhibition and/or promotes axonal regeneration. In various embodiments, the LRP-1 inhibitor or antagonist competitively displaces, reduces, inhibits and/or prevents binding of myelin-associated inhibitory proteins (e.g., myelin associated glycoprotein (MAG), oligodendrocyte myelin glycoprotein (OMgp), Nogo-A, Nogo-B, Nogo-C and/or fragments thereof) to LRP-1.

[0012] In a further aspect, the invention provides methods for increasing, promoting, restoring or enhancing neurite outgrowth or axonal regeneration in a subject. In some embodiments, the methods comprise administering to a subject in need thereof an effective amount of a LRP-1 inhibitor or antagonist, wherein the LRP-1 inhibitor or antagonist increases, promotes or enhances neurite outgrowth or axonal regeneration in the subject.

[0013] In a further aspect, the invention provides methods of treating a central nervous system disease, disorder or injury in a subject. In some embodiments, the methods comprise administering to a subject in need thereof an effective amount of a LRP-1 inhibitor or antagonist; wherein the LRP-1 inhibitor or antagonist inhibits CNS myelin-induced neurite outgrowth inhibition and/or promotes axonal regeneration.

[0014] In a related aspect, the invention provides methods for inhibiting degeneration of a neuron, the method comprising contacting the neuron with an inhibitor or antagonist of LRP-1, thereby inhibiting degeneration of the neuron.

[0015] With respect to the embodiments of the methods, in some embodiments, the neuron is a central nervous system neuron. The neuron can be in vitro or in vivo.

[0016] In various embodiments, the myelin-associated inhibitory protein is selected from the group consisting of myelin associated glycoprotein (MAG), oligodendrocyte myelin glycoprotein (OMgp), Nogo-A, Nogo-B, Nogo-C, ephrin-B3, Sema4D/CD100, repulsive guidance molecule b, and/or fragments thereof.

[0017] In some embodiments, the inhibitor of LRP-1 is receptor associated protein (RAP). As appropriate, RAP can be delivered to the neuron as a polypeptide (or variants or fragments thereof), or as a polynucleotide encoding RAP (e.g., in a plasmid or viral vector).

[0018] In various embodiments, the inhibitor of LRP-1 is a soluble extracellular ligand binding domain of LRP-1. As appropriate, the soluble extracellular ligand binding domain of LRP-1 can be delivered to the neuron as a polypeptide (or variants or fragments thereof), or as a polynucleotide encoding the soluble extracellular ligand binding domain of LRP-1 (e.g., in a plasmid or viral vector). In some embodiments, the soluble extracellular ligand binding domain of LRP-1 is selected from the group consisting of LRP-1(6-94) (SEQ ID NO:3), LRP 1(787-1164) (SEQ ID NO:4), LRP-1(804-1185) (SEQ ID NO:5), LRP-1(2462-2923) (SEQ ID NO:6), LRP-1(3274-3764) (SEQ ID NO:7), LRP1(3331-3778) (SEQ ID NO:8), and fragments thereof. In some embodiments, the soluble extracellular ligand binding domain of LRP-1 is selected from the group consisting of LRP-1(787-1164) (SEQ ID NO:4), LRP-1(804-1185) (SEQ ID NO:5), LRP-1(3274-3764) (SEQ ID NO:7), LRP1(3331-3778) (SEQ ID NO:8), and fragments thereof. In some embodiments, the soluble extracellular ligand binding domain of LRP-1 has at least 80%, 85%, 90%, 93%, 95%, 97% or 99% sequence identity to a soluble extracellular ligand binding domain of LRP-1 selected from the group consisting of LRP-1(6-94) (SEQ ID NO:3), LRP1(787-1164) (SEQ ID NO:4), LRP-1(804-1185) (SEQ ID NO:5), LRP-1(2462-2923) (SEQ ID NO:6), LRP-1(3274-3764) (SEQ ID NO:7), LRP1(3331-3778) (SEQ ID NO:8), and fragments thereof. In some embodiments, the soluble extracellular ligand binding domain of LRP-1 comprises one or more of the LRP-1 CII domain (LRP-1(804-1185) (SEQ ID NO:5)) and the LRP-1 CIV domain LRP1(3331-3778) (SEQ ID NO:8)). In various embodiments, one or more soluble extracellular ligand binding domains of LRP-1 can be fused together. In some embodiments, the soluble extracellular ligand binding domain of LRP-1 is attached (e.g., conjugated or fused) to an immunoglobulin Fc domain. In various embodiments, the soluble extracellular ligand binding domain of LRP-1 competitively displaces myelin-associated inhibitory proteins (e.g., myelin associated glycoprotein (MAG), oligodendrocyte myelin glycoprotein (OMgp), Nogo-A, Nogo-B, Nogo-C and/or fragments thereof), thereby inhibiting, reducing and/or preventing myelin-associated inhibitory proteins (e.g., myelin associated glycoprotein (MAG), oligodendrocyte myelin glycoprotein (OMgp), Nogo-A, Nogo-B, Nogo-C and/or fragments thereof) from binding to LRP-1.

[0019] In some embodiments, the inhibitor of LRP-1 is an inhibitory nucleic acid that inhibits the expression of LRP-1. For example, the inhibitory nucleic acid that inhibits the expression of LRP-1 can be a siRNA, a shRNA, an antisense RNA or a ribozyme. As appropriate, the inhibitory nucleic acid can be delivered in a viral vector, for example, a neurotropic viral vector. In some embodiments, the inhibitor of LRP-1 is a siRNA or shRNA that specifically inhibits the expression of LRP-1. As appropriate, the siRNA or shRNA can be delivered in a lentiviral vector, a herpesvirus vector or an adenoviral vector.

[0020] In some embodiments, the inhibitor of LRP-1 reduces or inhibits binding and/or endocytosis of myelin. In some embodiments, the inhibitor of LRP-1 reduces or inhibits binding and/or endocytosis of one or more myelin-associated inhibitory proteins (e.g., myelin associated glycoprotein (MAG), oligodendrocyte myelin glycoprotein