Supplementary material

Table S1. Description of the search strategy.

Names of platform and databases searched	Platform: Ovid Databases: MEDLINE, Embase, EBM Review
Database time coverage	January 2014 - January 2020
Date searched	16 January 2020
Search database strategy from each database	
MEDLINE / EBM Review	1. exp multiple sclerosis/ or (multiple sclerosis or disseminated sclerosis or insular sclerosis or sclerosis multiplex).ti,ab,kf,kw. 2. exp nerve regeneration/ or exp wound healing/ or exp Cuprizone/ or ethidium/ 3. Galactosylceramides/im [Immunology] 4. Lysophosphatidylcholines/ 5. (healing or healed or heal or cicatrix or cicatrisation or cicatrization or neurogenerat* or neuroprotect* or remyelinat* or axon* or cuprizone or Biscyclohexanone oxaldihydrazone or bis-cyclohexanon oxaldihydrazone or bicyclohexone oxaldihydrazone or bis-cyclohexanone or bis cyclohexanone or oxaldihydrazone or Lysolethicin or lysophosphatidylcholine? or lysolecithin? or Ethidium bromide or Ethidium or anti-galactocerebroside or anti-gal or antigalactocerebroside).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 6. ((lesion* or spinal cord or nerve or myelin*) adj5 (repair* or reconstruct* or rebuild* or restor* or regenerat*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 7. 2 or 3 or 4 or 5 or 6 8. 1 and 7 9. exp myelin sheath/ or exp oligodendroglia/ or Demyelinating Diseases/ or Ranvier's Nodes/ or Neurilemma/ 10. (myelin* or demyelinat* or oligodendroglia or olygodendrocyte? or nodes of ranvier or ranvier nodes or ranviers nodes or neurilemma or neurolemma or schwann sheath or sheath or schwann).ab,kf,kw,ti. 11. 9 or 10 12. 8 and 11 13. limit 12 to (english language and yr="2014 -Current")

Ovid EMBASE	1. exp multiple sclerosis/ or (multiple sclerosis or disseminated sclerosis or insular sclerosis or sclerosis multiplex).ti,ab,kw. 2. exp nerve regeneration/ or exp wound healing/ or exp Cuprizone/ or ethidium/ 3. Galactosylceramides/im [Immunology] 4. Lysophosphatidylcholines/ 5. (healing or healed or heal or cicatrix or cicatrisation or cicatrization or neurogenerat* or neuroprotect* or remyelinat* or axon* or cuprizone or Biscyclohexanone oxaldihydrazone or bis-cyclohexanon oxaldihydrazone or bicyclohexone oxaldihydrazone or bis-cyclohexanone or bis cyclohexanone or oxaldihydrazone or Lysolethicin or lysophosphatidylcholine? or lysolecithin? or Ethidium bromide or Ethidium or anti-galactocerebroside or anti-gal or antigalactocerebroside).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 6. ((lesion* or spinal cord or nerve or myelin*) adj5 (repair* or reconstruct* or rebuild* or restor* or regenerat*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 7. 2 or 3 or 4 or 5 or 6 8. 1 and 7 9. exp myelin sheath/ or exp oligodendroglia/ or Demyelinating Diseases/ or Ranvier's Nodes/ or Neurilemma/ 10. (myelin* or demyelinat* or oligodendroglia or olygodendrocyte? or nodes of ranvier or ranvier nodes or ranviers nodes or neurilemma or neurolemma or schwann sheath or sheath or schwann).ab,kw,ti. 11. 9 or 10 12. 8 and 11 13. limit 12 to (english language and yr="2014 -Current")

Table S2. Inclusion and exclusion criteria for article screening.

Inclusion	Human study or clinical trial	• Written in English
		• Original data and peer reviewed
		• Full paper accessible by at least one of our institutions
		• Study evaluates intervention for individuals with a diagnosed form of MS
		• Clinical trial protocol is registered with ClinicalTrials.gov (all trial phases included)
		• Includes appropriate controls (i.e. patient matching, randomization, standard medication group, etc.)
		• Includes at least one measure of the following outcomes:
		  ○ Myelin content, lesion burden and/or atrophy, as determined by MRI or equivalent
		  ○ Disability and/or motor function
		  ○ Cognition
		  ○ Relapse rate and/or severity
		  ○ Progression
		  ○ Visual evoked potential

	Preclinical study	• Written in English
		• Original data and peer reviewed
		• Full paper accessible by at least one of our institutions
		• Study evaluates intervention in an animal model representative of one or more aspects of the neuropathology of MS
		• Findings from immune-mediated animal models (i.e. experimental autoimmune encephalomyelitis, EAE) were included if the studies noted one or more of the following:
		  ○ A negative result for changes in peripheral immune cell activity (activation, infiltration and/or inflammatory functions of T cells, B cells and/or macrophages) following systemic administration of a treatment, obtained using flow cytometric, ELISA/ELISPOT, histological or equivalent method
		  ○ Direct administration of the treatment to the site of damage (intrathecal, intracerebroventricular, etc.) to circumvent peripheral immune cells
		  ○ Confirmation of an observed effect in a complementary animal model with minimal peripheral immune cell involvement (cuprizone, LPC, etc.)
		• Includes appropriate group sizes and controls (e.g. vehicle treatment and animal model comparator groups)
		• Includes at least one measure of the following outcomes:
		  ○ Myelin content
		  ○ Remyelination (as determined by axonal imaging)
		  ○ Oligodendrocyte viability and genesis
		  ○ OPC migration and/or proliferation and/or differentiation
		  ○ Neuron integrity and/or axonal regeneration
		  ○ Motor function and/or clinical symptomology
		  ○ Oxidative stress or neuronal dysfunction (as measured by mitochondrial function, reactive oxygen species generation, apoptosis, etc.)
		  ○ Growth/inhibitory factor expression and/or inflammatory glial cell activity

Exclusion	Human study or clinical trial	• Does not meet inclusion criteria • Review article or book chapter

Preclinical study	• Does not meet inclusion criteria • Review article or book chapter • Measured outcomes for Schwann cells or peripheral nervous system • Insufficient distinction of potential indirect effects on outcomes due to peripheral immune system modulation (i.e. immune-mediated animal models such as EAE) • Non-mammalian animal models • Intervention utilizes in vivo gene editing • Article is a poster abstract

Table S3. Complete list of publications included for data extraction and review.

Article number	Author and date	Title	Experimental design
1	Abdallah 2019	Evaluation of treatment of experimentally induced canine model of multiple sclerosis using laser activated non-expanded adipose derived stem cells.	Animal study
2	Akbari 2018	Adenosine A2A receptor blockade attenuates spatial memory deficit and extent of demyelination areas in lysolecithin-induced demyelination model.	Animal study
3	Mohamed 2019	Effects of enhanced environment and induced depression on cuprizone mouse model of demyelination	Animal study
4	Alazrag 2019	The role of LINGO-1 and myelin basic protein mRNAs in central remyelination in ethidium bromide-induced demyelination in rats	Animal Study
5	Alme 2015	Fingolimod does not enhance cerebellar remyelination in the cuprizone model.	Animal study
6	Atkinson 2019	Diffusion tensor imaging identifies aspects of therapeutic estrogen receptor beta ligand-induced remyelination in a mouse model of multiple sclerosis.	Animal study
7	Azin 2015	Fibroblast growth factor-2 enhanced the recruitment of progenitor cells and myelin repair in experimental demyelination of rat hippocampal formations	Animal study
8	Bae 2016	Comparative Effects of Human Neural Stem Cells and Oligodendrocyte Progenitor Cells on the Neurobehavioral Disorders of Experimental Autoimmune Encephalomyelitis Mice.	Animal study
9	Bando 2019	Disease modifying mitochondrial uncouplers, MP101, and a slow release ProDrug, MP201, in models of Multiple Sclerosis.	Animal study
10	Baradaran 2018	Hesperetin reduces myelin damage and ameliorates glial activation in lysolecithin-induced focal demyelination model of rat optic chiasm	Animal study
11	Barati 2019	Mesenchymal stem cell mediated effects on microglial phenotype in cuprizone-induced demyelination model	Animal study
12	Barkhof 2019	Gnbac1 shows efficacy on MRI measures of neurodegeneration in relapsing-remitting MS patients over 48 weeks	Clinical trial (NCT02782858)
13	Beckmann 2018	Brain region-specific enhancement of remyelination and prevention of demyelination by the CSF1R kinase inhibitor BLZ945	Animal study
14	Beigi Boroujeni 2020	Intranasal delivery of SDF-1 alpha- preconditioned bone marrow mesenchymal cells improves remyelination in the cuprizone- induced mouse model of multiple sclerosis	Animal study
15	Bellizzi 2016	Platelet-activating factor receptors mediate excitatory postsynaptic hippocampal injury in experimental autoimmune encephalomyelitis	Animal study
16	Berghoff 2017	Dietary cholesterol promotes repair of demyelinated lesions in the adult brain	Animal study

17	Bernal-Chico 2015	Blockade of monoacylglycerol lipase inhibits oligodendrocyte excitotoxicity and prevents demyelination in vivo	Animal study
18	Biname 2019	Disruption of Sema3A/Plexin-A1 inhibitory signalling in oligodendrocytes as a therapeutic strategy to promote remyelination	Animal study
19	Blanc 2015	Sphingosine-1-Phosphate Receptor Antagonism Enhances Proliferation and Migration of Engrafted Neural Progenitor Cells in a Model of Viral-Induced Demyelination	Animal study
20	Bonetto 2017	The novel synthetic microneurotrophin BNN27 protects mature oligodendrocytes against cuprizone-induced death, through the NGF receptor TrkA	Animal study
21	Brambilla 2016	Early effect of dalfampridine in patients with MS: A multi-instrumental approach to better investigate responsiveness	Human study
22	Busto 2018	Ellagic acid protects from myelin-associated sphingolipid loss in experimental autoimmune encephalomyelitis	Animal study
23	Cadavid 2019	Safety and efficacy of opicinumab in patients with relapsing multiple sclerosis (SYNERGY): a randomised, placebo-controlled, phase 2 trial	Clinical trial (NCT01864148)
24	Carvalho 2015	Anthocyanins suppress the secretion of proinflammatory mediators and oxidative stress, and restore ion pump activities in demyelination	Animal study
25	Cerina 2018	Protective potential of dimethyl fumarate in a mouse model of thalamocortical demyelination	Animal study
26	Chamberlain 2017	Creatine enhances mitochondrial-mediated oligodendrocyte survival after demyelinating injury	Animal study
27	Chami 2017	Acid sphingomyelinase deficiency enhances myelin repair after acute and chronic demyelination	Animal study
28	Chen 2014	n-3 PUFA supplementation benefits microglial responses to myelin pathology	Animal study
29	Chen 2017	Histamine receptor 3 negatively regulates oligodendrocyte differentiation and remyelination	Animal study
30	Chen 2019	Sephin1, which prolongs the integrated stress response, is a promising therapeutic for multiple sclerosis	Animal study
31	Chen 2019	Butyrate suppresses demyelination and enhances remyelination	Animal study
32	Choi 2016	A Diet Mimicking Fasting Promotes Regeneration and Reduces Autoimmunity and Multiple Sclerosis Symptoms	Animal study and pilot clinical trial (NCT01538355)
33	Church 2017	E6020, a synthetic TLR4 agonist, accelerates myelin debris clearance, Schwann cell infiltration, and remyelination in the rat spinal cord	Animal study
34	Cisneros-Mejorado 2019	Demyelination-Remyelination of the Rat Caudal Cerebellar Peduncle Evaluated with Magnetic Resonance Imaging	Animal study
35	Cree 2018	A Phase 1, multiple-dose study of elezanumab (ABT-555) in patients with relapsing forms of multiple sclerosis	Clinical trial (NCT02601885)
36	Cui 2018	The antibody rHIgM22 facilitates hippocampal remyelination and ameliorates memory deficits in the cuprizone mouse model of demyelination	Animal study

37	Cui 2019	Donepezil, a drug for Alzheimer's disease, promotes oligodendrocyte generation and remyelination	Animal study
38	Daneshdoust 2017	Pregabalin enhances myelin repair and attenuates glial activation in lysolecithin-induced demyelination model of rat optic chiasm	Animal study
39	deSantana Nunes 2016	Phosphodiesterase-5 inhibition promotes remyelination by MCP-1/CCR-2 and MMP-9 regulation in a cuprizone-induced demyelination model	Animal study
40	DiBiase 2014	Eicosapentaenoic acid pre-treatment reduces biochemical changes induced in total brain and myelin of weanling Wistar rats by cuprizone feeding	Animal study
41	Duan 2018	Sulfasalazine alters microglia phenotype by competing endogenous RNA effect of miR-136-5p and long non-coding RNA HOTAIR in cuprizone-induced demyelination	Animal study
42	Ehling 2015	Impact of glatiramer acetate on paraclinical markers of neuroprotection in multiple sclerosis: A prospective observational clinical trial	Human study
43	Eisen 2017	A double-blind, placebo-controlled, single ascending-dose study of remyelinating antibody rHIgM22 in people with multiple sclerosis	Clinical trial (NCT01803867)
44	El-Akabawy 2015	Beneficial effects of bone marrow-derived mesenchymal stem cell transplantation in a non-immune model of demyelination	Animal study
45	El-Etr 2015	Progesterone and nestorone promote myelin regeneration in chronic demyelinating lesions of corpus callosum and cerebral cortex	Animal study
46	Elbaz 2018	Neuroprotective effect of linagliptin against cuprizone-induced demyelination and behavioural dysfunction in mice: A pivotal role of AMPK/SIRT1 and JAK2/STAT3/NF-kappaB signalling pathway modulation	Animal study
47	Feliu 2015	A Sativex-like combination of phytocannabinoids as a disease-modifying therapy in a viral model of multiple sclerosis	Animal study
48	Feliu 2017	2-arachidonoylglycerol reduces proteoglycans and enhances remyelination in a progressive model of demyelination	Animal study
49	Feng 2017	Using diffusion tensor imaging to quantify effects of autologous mesenchymal stem cell transplantation in multiple sclerosis patients	Human study
50	Freeman 2015	Safety and tolerability of anti-lingo-1 monoclonal antibody BIIB033 in acute optic neuritis: The renew trial.	Clinical trial (NCT01721161)
51	Gao 2016	GDNF Enhances Therapeutic Efficiency of Neural Stem Cells-Based Therapy in Chronic Experimental Allergic Encephalomyelitis in Rat	Animal study
52	Gelibter 2017	Chronic 4-aminopyridine treatment enhances intracortical glutamatergic transmission in progressive multiple sclerosis	Human study
53	Ghaiad 2017	Resveratrol Promotes Remyelination in Cuprizone Model of Multiple Sclerosis: Biochemical and Histological Study	Animal study

54	Ghasemi 2014	Transplantation of human adipose-derived stem cells enhances remyelination in lysolecithin-induced focal demyelination of rat spinal cord	Animal study
55	Gilani 2014	Evaluation of GABAergic transmission modulation as a novel functional target for management of multiple sclerosis: Exploring inhibitory effect of GABA on glutamate-mediated excitotoxicity	Animal study
56	Glenn 2015	Disparate effects of mesenchymal stem cells in experimental autoimmune encephalomyelitis and cuprizone-induced demyelination	Animal study
57	Gol 2017	Fingolimod enhances myelin repair of hippocampus in pentylenetetrazol-induced kindling model	Animal study
58	Gonzalez 2016	Tamoxifen accelerates the repair of demyelinated lesions in the central nervous system	Animal study
59	Green 2017	Clemastine fumarate as a remyelinating therapy for multiple sclerosis (ReBUILD): a randomised, controlled, double-blind, crossover trial.	Clinical trial (NCT02040298)
60	Greenberg 2014	Two-photon imaging of remyelination of spinal cord axons by engrafted neural precursor cells in a viral model of multiple sclerosis.	Animal study
61	Gresle 2016	Blocking LINGO-1 in vivo reduces degeneration and enhances regeneration of the optic nerve.	Animal study
62	Guo 2018	Vitamin C promotes oligodendrocytes generation and remyelination.	Animal study
63	Gurevich 2018	Fingolimod-improved axonal and myelin integrity of white matter tracts associated with multiple sclerosis-related functional impairments.	Human study
64	Hainz 2017	Probenecid-treatment reduces demyelination induced by cuprizone feeding.	Animal study
65	Hamaguchi 2019	Circulating transforming growth factor-beta1 facilitates remyelination in the adult central nervous system.	Animal study
66	Hartley 2019	Myelin repair stimulated by CNS-selective thyroid hormone action.	Animal study
67	Hashimoto 2017	The flavonoid Baicalein attenuates cuprizone-induced demyelination via suppression of neuroinflammation.	Animal study
68	He 2019	Ethyl pyruvate enhances spontaneous remyelination by targeting microglia phagocytosis.	Animal study
69	Hlavica 2017	Intrathecal insulin-like growth factor 1 but not insulin enhances myelin repair in young and aged rats.	Animal study
70	Hundehege 2018	Targeting Voltage-Dependent Calcium Channels with Pregabalin Exerts a Direct Neuroprotective Effect in an Animal Model of Multiple Sclerosis.	Animal study
71	Hundehege 2019	The next-generation sphingosine-1 receptor modulator BAF312 (siponimod) improves cortical network functionality in focal autoimmune encephalomyelitis.	Animal study
72	Ineichen 2017	Nogo-A antibodies enhance axonal repair and remyelination in neuro-inflammatory and demyelinating pathology.	Animal study
73	Ingwersen 2018	Nimodipine confers clinical improvement in two models of experimental autoimmune encephalomyelitis	Animal study
74	Itoh 2017	Bedside to bench to bedside research: Estrogen receptor beta ligand as a candidate neuroprotective treatment for multiple sclerosis.	Animal study

75	Iwasa 2014	Prostaglandin F2alpha FP receptor inhibitor reduces demyelination and motor dysfunction in a cuprizone-induced multiple sclerosis mouse model	Animal study
76	Jensen 2018	Multimodal Enhancement of Remyelination by Exercise with a Pivotal Role for Oligodendroglial PGC1alpha.	Animal study
77	Jia 2019	Cordycepin (3'-deoxyadenosine) promotes remyelination via suppression of neuroinflammation in a cuprizone-induced mouse model of demyelination.	Animal study
78	Jiang 2017	Amelioration of experimental autoimmune encephalomyelitis through transplantation of placental derived mesenchymal stem cells.	Animal study
79	Jin 2019	Leonurine suppresses neuroinflammation through promoting oligodendrocyte maturation.	Animal study
80	Karamita 2017	Therapeutic inhibition of soluble brain TNF promotes remyelination by increasing myelin phagocytosis by microglia.	Animal study
81	Kashani 2014	Protective effects of melatonin against mitochondrial injury in a mouse model of multiple sclerosis.	Animal study
82	Kashani 2015	Progesterone Enhanced Remyelination in the Mouse Corpus Callosum after Cuprizone Induced Demyelination.	Animal study
83	Kataria 2018	Neuregulin-1 promotes remyelination and fosters a pro-regenerative inflammatory response in focal demyelinating lesions of the spinal cord.	Animal study
84	Keough 2016	An inhibitor of chondroitin sulfate proteoglycan synthesis promotes central nervous system remyelination.	Animal study
85	Khan 2014	SIRT1 activating compounds reduce oxidative stress mediated neuronal loss in viral induced CNS demyelinating disease.	Animal study
86	Khan 2017	Mitochondrial Uncoupler Prodrug of 2,4-Dinitrophenol, MP201, Prevents Neuronal Damage and Preserves Vision in Experimental Optic Neuritis.	Animal study
87	Khodanovich 2019	Plant polyprenols reduce demyelination and recover impaired oligodendrogenesis and neurogenesis in the cuprizone murine model of multiple sclerosis.	Animal study
88	Kim 2018	Functional antagonism of sphingosine-1-phosphate receptor 1 prevents cuprizone-induced demyelination.	Animal study
89	Komegae 2017	Multiple functional therapeutic effects of TnP: A small stable synthetic peptide derived from fish venom in a mouse model of multiple sclerosis.	Animal study
90	Kramann 2016	Laquinimod prevents cuprizone-induced demyelination independent of Toll-like receptor signaling.	Animal study
91	Kuboyama 2017	Protamine neutralizes chondroitin sulfate proteoglycan-mediated inhibition of oligodendrocyte differentiation.	Animal study
92	Kumar 2018	Preclinical Explorative Assessment of Dimethyl Fumarate-Based Biocompatible Nanolipoidal Carriers for the Management of Multiple Sclerosis.	Animal study
93	Kumar 2019	Oral Delivery of Methylthioadenosine to the Brain Employing Solid Lipid Nanoparticles: Pharmacokinetic, Behavioral, and Histopathological Evidences.	Animal study
94	Kuroda 2017	Peripherally derived FGF21 promotes remyelination in the central nervous system.	Animal study

95	Laflamme 2018	mCSF-Induced Microglial Activation Prevents Myelin Loss and Promotes Its Repair in a Mouse Model of Multiple Sclerosis.	Animal study
96	Largani 2019	Oligoprotective effect of metformin through the AMPK-dependent on restoration of mitochondrial hemostasis in the cuprizone-induced multiple sclerosis model.	Animal study
97	Li 2017	LINGO-1-Fc-Transduced Neural Stem Cells Are Effective Therapy for Chronic Stage Experimental Autoimmune Encephalomyelitis.	Animal study
98	Li 2019	Ginkgolide K supports remyelination via induction of astrocytic IGF/PI3K/Nrf2 axis.	Animal study
99	Liang 2015	Epimedium flavonoids ameliorate neuropathological changes and increases IGF-1 expression in C57BL/6 mice exposed to cuprizone.	Animal study
100	Liu 2015	Electroacupuncture Promotes the Differentiation of Transplanted Bone Marrow Mesenchymal Stem Cells Preinduced With Neurotrophin-3 and Retinoic Acid Into Oligodendrocyte-Like Cells in Demyelinated Spinal Cord of Rats.	Animal study
101	Lu 2019	Shikimic Acid Promotes Oligodendrocyte Precursor Cell Differentiation and Accelerates Remyelination in Mice.	Animal study
102	Luo 2017	Inhibition of Drp1 hyper-activation is protective in animal models of experimental multiple sclerosis.	Animal study
103	Luo 2018	Modulation of proteoglycan receptor PTPsigma enhances MMP-2 activity to promote recovery from multiple sclerosis.	Animal study
104	Madadi 2019	Astrocyte ablation induced by La-aminoadipate (L-AAA) potentiates remyelination in a cuprizone demyelinating mouse model.	Animal study
105	Madsen 2017	Prolonged stimulation of a brainstem raphe region attenuates experimental autoimmune encephalomyelitis.	Animal study
106	Makinodan 2016	Social isolation impairs remyelination in mice through modulation of IL-6.	Animal study
107	Mandolesi 2019	Voluntary running wheel attenuates motor deterioration and brain damage in cuprizone-induced demyelination.	Animal study
108	Manterola 2018	Deregulation of the endocannabinoid system and therapeutic potential of ABHD6 blockade in the cuprizone model of demyelination.	Animal study
109	Marzban 2018	Effect of Multiple Intraperitoneal Injections of Human Bone Marrow Mesenchymal Stem Cells on Cuprizone Model of Multiple Sclerosis.	Animal study
110	Mashayekhi 2015	Administration of leukemia inhibitory factor increases Opalin and myelin oligodendrocyte glycoprotein expression in the cerebral cortex in a cuprizone-induced model of demyelination.	Animal study
111	Mashayekhi 2016	Administration of vitamin D3 induces CNPase and myelin oligodendrocyte glycoprotein expression in the cerebral cortex of the murine model of cuprizone-induced demyelination.	Animal study
112	McNicholas 2017	A double blind, randomized, placebo controlled, crossover study of the effectiveness of oral fampridine in improving upper limb function in progressive multiple sclerosis	Clinical trial (NCT02208050)

113	Mecha 2019	The endocannabinoid 2-AG enhances spontaneous remyelination by targeting microglia.	Animal study
114	Medina-Rodriguez 2017	Promoting in vivo remyelination with small molecules: a neuroreparative pharmacological treatment for Multiple Sclerosis.	Animal study
115	Mei 2016	Identification of the Kappa-Opioid Receptor as a Therapeutic Target for Oligodendrocyte Remyelination.	Animal study
116	Mellion 2017	Efficacy Results from the Phase 2b SYNERGY Study: treatment of Disabling Multiple Sclerosis with the Anti-LINGO-1 Monoclonal Antibody Opicinumab	Clinical trial (NCT01864148)
117	MikaeiliAgah 2014	Therapeutic effect of transplanted human Wharton's jelly stem cell-derived oligodendrocyte progenitor cells (hWJ-MSC-derived OPCs) in an animal model of multiple sclerosis.	Animal study
118	Mohammadi-Rad 2019	Evaluation of apamin effects on myelination process in C57BL/6 mice model of multiple sclerosis.	Animal study
119	Moore 2014	Multiple functional therapeutic effects of the estrogen receptor beta agonist indazole-Cl in a mouse model of multiple sclerosis.	Animal study
120	Moreno 2017	Methylthioadenosine promotes remyelination by inducing oligodendrocyte differentiation	Animal study
121	MousaviMajd 2018	Inhibition of GABA A receptor improved spatial memory impairment in the local model of demyelination in rat hippocampus.	Animal study
122	Mullin 2017	rHIgM22 enhances remyelination in the brain of the cuprizone mouse model of demyelination.	Animal study
123	Muramatsu 2015	Prostacyclin prevents pericyte loss and demyelination induced by lysophosphatidylcholine in the central nervous system.	Animal study
124	Naghibzadeh 2018	Effects of Two Training Programs on Transcriptional Levels of Neurotrophins and Glial Cells Population in Hippocampus of Experimental Multiple Sclerosis.	Animal study
125	Najm 2015	Drug-based modulation of endogenous stem cells promotes functional remyelination in vivo.	Animal study
126	Navarrete 2018	Hypoxia mimetic activity of VCE-004.8, a cannabidiol quinone derivative: implications for multiple sclerosis therapy.	Animal study
127	Neelamma 2018	Evaluation of protective neuro pharmacological activity of seeds of cucurbita maxima against ethidium bromide induced demyelination in rat model	Animal study
128	Neumann 2019	Metformin Restores CNS Remyelination Capacity by Rejuvenating Aged Stem Cells.	Animal study
129	Niknam 2019	Modulating proteoglycan receptor PTPsigma using intracellular sigma peptide improves remyelination and functional recovery in mice with demyelinated optic chiasm.	Animal study
130	Nyamoya 2019	Laquinimod Supports Remyelination in Non-Supportive Environments.	Animal study
131	Nystad 2014	Effect of high-dose 1.25 dihydroxyvitamin D3 on remyelination in the cuprizone model.	Animal study
132	Nystad 2018	Effects of vitamin D on axonal damage during de- and remyelination in the cuprizone model.	Animal study
133	Nystad 2020	Fingolimod downregulates brain sphingosine-1-phosphate receptor 1 levels but does not promote remyelination or neuroprotection in the cuprizone model.	Animal study

134	Ohgomori 2019	Cuprizone-induced demyelination in the mouse hippocampus is alleviated by phytoestrogen genistein.	Animal study
135	Olmstead 2018	Transcranial and pulsed focused ultrasound that activates brain can accelerate remyelination in a mouse model of multiple sclerosis.	Animal study
136	Omotoso 2018	Kolaviron protects the brain in cuprizone- induced model of experimental multiple sclerosis via enhancement of intrinsic antioxidant mechanisms: Possible therapeutic applications?	Animal study
137	Omotoso 2018	Kolaviron Protects the Prefrontal Cortex and Hippocampus against Histomorphological and Neurobehavioural Changes in Cuprizone Model of Multiple Sclerosis.	Animal study
138	Ou 2016	Olig2-Targeted G-Protein-Coupled Receptor Gpr17 Regulates Oligodendrocyte Survival in Response to Lysolecithin-Induced Demyelination.	Animal study
139	Oveland 2018	1,25-Dihydroxyvitamin-D3 induces brain proteomic changes in cuprizone mice during remyelination involving calcium proteins.	Animal study
140	Payghani 2018	Effects of levothyroxine on visual evoked potential impairment following local injections of lysolecithin into the rat optic chiasm	Animal study
141	Petersen 2017	Fibrinogen Activates BMP Signaling in Oligodendrocyte Progenitor Cells and Inhibits Remyelination after Vascular Damage.	Animal study
142	Pol 2019	Teriflunomide's Effect on Glia in Experimental Demyelinating Disease: A Neuroimaging and Histologic Study.	Animal study
143	Popescu 2018	Vitamin K enhances the production of brain sulfatides during remyelination.	Animal study
144	Popovic 2015	Neuroprotective arylpiperazine dopaminergic/serotonergic ligands suppress experimental autoimmune encephalomyelitis in rats.	Animal study
145	Pourabdolhossein 2014	Nogo receptor inhibition enhances functional recovery following lysolecithin-induced demyelination in mouse optic chiasm.	Animal study
146	Pourabdolhossein 2017	Nogo receptor blockade enhances subventricular zone's stem cells proliferation and differentiation in demyelination context	Animal study
147	Pringproa 2016	Intravenous transplantation of mouse embryonic stem cells attenuates demyelination in an ICR outbred mouse model of demyelinating diseases.	Animal study
148	Qin 2017	GD1a Overcomes Inhibition of Myelination by Fibronectin via Activation of Protein Kinase A: Implications for Multiple Sclerosis.	Animal study
149	Raftopoulos 2016	Phenytoin for neuroprotection in patients with acute optic neuritis: a randomised, placebo-controlled, phase 2 trial.	Clinical trial (NCT01451593)
150	RagerdiKashani 2017	Protective effects of erythropoietin against cuprizone-induced oxidative stress and demyelination in the mouse corpus callosum	Animal study
151	Rankin 2019	Selective Estrogen Receptor Modulators Enhance CNS Remyelination Independent of Estrogen Receptors.	Animal study

152	Ratzer 2016	Monthly oral methylprednisolone pulse treatment in progressive multiple sclerosis.	Clinical trial (NCT01305837)
153	Razavi 2018	Co-Transplantation of Human Neurotrophic Factor Secreting Cells and Adipose-Derived Stem Cells in Rat Model of Multiple Sclerosis.	Animal study
154	Rinaldi 2016	Galectin-1 circumvents lysolecithin-induced demyelination through the modulation of microglial polarization/phagocytosis and oligodendroglial differentiation.	Animal study
155	Rinker 2016	Results of a pilot trial of lithium in progressive multiple sclerosis	Pilot clinical trial (NCT01259388)
156	Rittchen 2015	Myelin repair in vivo is increased by targeting oligodendrocyte precursor cells with nanoparticles encapsulating leukaemia inhibitory factor (LIF).	Animal study
157	SalinasTejedor 2015	Mesenchymal stem cells do not exert direct beneficial effects on CNS remyelination in the absence of the peripheral immune system.	Animal study
158	Samanta 2015	Inhibition of Gli1 mobilizes endogenous neural stem cells for remyelination.	Animal study
159	Sanadgol 2017	Neuroprotective effects of ellagic acid on cuprizone-induced acute demyelination through limitation of microgliosis, adjustment of CXCL12/IL-17/IL-11 axis and restriction of mature oligodendrocytes apoptosis.	Animal study
160	Sanadgol 2018	Low, but not high, dose triptolide controls neuroinflammation and improves behavioral deficits in toxic model of multiple sclerosis by dampening of NF-kappaB activation and acceleration of intrinsic myelin repair.	Animal study
161	Sanadgol 2018	Alpha-lipoic acid mitigates toxic-induced demyelination in the corpus callosum by lessening of oxidative stress and stimulation of polydendrocytes proliferation.	Animal study
162	Sanchez 2018	Genetic detection of Sonic hedgehog (Shh) expression and cellular response in the progression of acute through chronic demyelination and remyelination.	Animal study
163	Sarswat 2017	Inhibitors of protein arginine deiminases and their efficacy in animal models of multiple sclerosis.	Animal study
164	Schampel 2017	Nimodipine fosters remyelination in a mouse model of multiple sclerosis and induces microglia-specific apoptosis.	Animal study
165	Schwartzbach 2017	Lesion remyelinating activity of GSK239512 versus placebo in patients with relapsing-remitting multiple sclerosis: a randomised, single-blind, phase II study.	Clinical trial (NCT01772199)
166	Semnani 2017	Effects of green tea epigallocatechin-3-gallate on the proteolipid protein and oligodendrocyte transcription factor 1 messenger RNA gene expression in a mouse model of multiple sclerosis.	Animal study
167	Seyedsadr 2019	Inactivation of sphingosine-1-phosphate receptor 2 (S1PR2) decreases demyelination and enhances remyelination in animal models of multiple sclerosis.	Animal study
168	Singhal 2018	Erythropoietin Upregulates Brain Hemoglobin Expression and Supports Neuronal Mitochondrial Activity.	Animal study
169	Skripuletz 2015	Pivotal role of choline metabolites in remyelination.	Animal study

170	Slowik 2015	The sphingosine 1-phosphate receptor agonist FTY720 is neuroprotective after cuprizone-induced CNS demyelination.	Animal study
171	Smith 2015	SEMA4D compromises blood-brain barrier, activates microglia, and inhibits remyelination in neurodegenerative disease.	Animal study
172	Suhs 2014	N-methyl-D-aspartate receptor blockade is neuroprotective in experimental autoimmune optic neuritis.	Animal study
173	Sui 2019	Protective and therapeutic role of Bilobalide in cuprizone-induced demyelination.	Animal study
174	Suo 2019	Inhibition of MAPK/ERK pathway promotes oligodendrocytes generation and recovery of demyelinating diseases.	Animal study
175	Syed 2016	Antibody-mediated neutralization of myelin-associated EphrinB3 accelerates CNS remyelination.	Animal study
176	Tahmasebi 2019	Effect of the CSF1R inhibitor PLX3397 on remyelination of corpus callosum in a cuprizone-induced demyelination mouse model.	Animal study
177	Tanikawa 2017	q-Space Myelin Map imaging for longitudinal analysis of demyelination and remyelination in multiple sclerosis patients treated with fingolimod: A preliminary study.	Human study
178	Tarbali 2016	Vitamin D3 attenuates oxidative stress and cognitive deficits in a model of toxic demyelination.	Animal study
179	Templeton 2019	Clozapine administration enhanced functional recovery after cuprizone demyelination.	Animal study
180	Thiruvalluvan 2016	Survival and Functionality of Human Induced Pluripotent Stem Cell-Derived Oligodendrocytes in a Nonhuman Primate Model for Multiple Sclerosis.	Animal study
181	Thompson 2018	Tuftsin Combines with Remyelinating Therapy and Improves Outcomes in Models of CNS Demyelinating Disease.	Animal study
182	Vakilzadeh 2015	Protective Effect of a cAMP Analogue on Behavioral Deficits and Neuropathological Changes in Cuprizone Model of Demyelination.	Animal study
183	Vakilzadeh 2016	The Effect of Melatonin on Behavioral, Molecular, and Histopathological Changes in Cuprizone Model of Demyelination.	Animal study
184	Villoslada 2019	Axonal and Myelin Neuroprotection by the Peptoid BN201 in Brain Inflammation.	Animal study
185	Voskuhl 2019	Gene expression in oligodendrocytes during remyelination reveals cholesterol homeostasis as a therapeutic target in multiple sclerosis.	Animal study
186	Wang 2014	Lingo-1 inhibited by RNA interference promotes functional recovery of experimental autoimmune encephalomyelitis.	Animal study
187	Wang 2016	Scutellarin Alleviates Behavioral Deficits in a Mouse Model of Multiple Sclerosis, Possibly Through Protecting Neural Stem Cells.	Animal study
188	Wang 2019	Therapeutic effect of oligomeric proanthocyanidin in cuprizone-induced demyelination.	Animal study
189	Wang 2020	CXCR2 antagonism promotes oligodendrocyte precursor cell differentiation and enhances remyelination in a mouse model of multiple sclerosis.	Animal study

190	Wasko 2019	Systemic TLR2 tolerance enhances central nervous system remyelination.	Animal study
191	Way 2015	Pharmaceutical integrated stress response enhancement protects oligodendrocytes and provides a potential multiple sclerosis therapeutic.	Animal study
192	WiesMancini 2019	Microglial modulation through colony-stimulating factor-1 receptor inhibition attenuates demyelination.	Animal study
193	Williams 2014	Targeting CXCR7/ACKR3 as a therapeutic strategy to promote remyelination in the adult central nervous system.	Animal study
194	Wootla 2015	A single dose of a neuron-binding human monoclonal antibody improves brainstem NAA concentrations, a biomarker for density of spinal cord axons, in a model of progressive multiple sclerosis.	Animal study
195	Wootla 2016	Antibody-Mediated Oligodendrocyte Remyelination Promotes Axon Health in Progressive Demyelinating Disease.	Animal study
196	Wootla 2016	A monoclonal natural human IgM protects axons in the absence of remyelination.	Animal study
197	Wu 2019	Multiple functional therapeutic effects of DL-3-n-butylphthalide in the cuprizone model of demyelination.	Animal study
198	Xu 2016	Discovery of CNS Penetrant CXCR2 Antagonists for the Potential Treatment of CNS Demyelinating Disorders.	Animal study
199	Yamamoto 2014	Cyclic phosphatidic acid treatment suppresses cuprizone-induced demyelination and motor dysfunction in mice.	Animal study
200	Yamamoto 2017	Protective and therapeutic role of 2-carba-cyclic phosphatidic acid in demyelinating disease.	Animal study
201	Yao 2016	Clobetasol promotes remyelination in a mouse model of neuromyelitis optica.	Animal study
202	Yazdi 2015	Enhanced remyelination following lysolecithin-induced demyelination in mice under treatment with fingolimod (FTY720).	Animal study
203	Yazdi 2018	Fingolimod Enhances Oligodendrocyte Differentiation of Transplanted Human Induced Pluripotent Stem Cell-Derived Neural Progenitors.	Animal study
204	Youssef 2019	LINGO-1 siRNA nanoparticles promote central remyelination in ethidium bromide-induced demyelination in rats.	Animal study
205	Yu 2018	N-Phenylquinazolin-2-amine Yhhu4952 as a novel promotor for oligodendrocyte differentiation and myelination.	Animal study
206	Yu 2018	Prednisone alleviates demyelination through regulation of the NLRP3 inflammasome in a C57BL/6 mouse model of cuprizone-induced demyelination.	Animal study
207	Zahednasab 2019	The protective effect of rifampicin on behavioral deficits, biochemical, and neuropathological changes in a cuprizone model of demyelination.	Animal study
208	Zendedel 2016	Regulatory effect of triiodothyronine on brain myelination and astrogliosis after cuprizone-induced demyelination in mice.	Animal study
209	Zhai 2015	Blocking GluR2-GAPDH ameliorates experimental autoimmune encephalomyelitis.	Animal study

210	Zhang 2015	Inhibition of LINGO-1 promotes functional recovery after experimental spinal cord demyelination	Animal study
211	Zhang 2015	Thyroid hormone alleviates demyelination induced by cuprizone through its role in remyelination during the remission period.	Animal study
212	Zhang 2016	Myricetin alleviates cuprizone-induced behavioral dysfunction and demyelination in mice by Nrf2 pathway.	Animal study
213	Zhang 2016	Thymosin beta4 promotes oligodendrogenesis in the demyelinating central nervous system.	Animal study
214	Zhang 2016	Treatment of multiple sclerosis by transplantation of neural stem cells derived from induced pluripotent stem cells.	Animal study
215	Zhang 2017	Icariin enhances remyelination process after acute demyelination induced by cuprizone exposure	Animal study
216	Zhang 2018	Adenosine Promotes the Recovery of Mice from the Cuprizone-Induced Behavioral and Morphological Changes while Effecting on Microglia and Inflammatory Cytokines in the Brain.	Animal study
217	Zhang 2019	MiR-146a promotes oligodendrocyte progenitor cell differentiation and enhances remyelination in a model of experimental autoimmune encephalomyelitis.	Animal study
218	Zhang 2019	Venlafaxine improves the cognitive impairment and depression-like behaviors in a cuprizone mouse model by alleviating demyelination and neuroinflammation in the brain	Animal study
219	Zhou 2015	18beta-glycyrrhetinic acid suppresses experimental autoimmune encephalomyelitis through inhibition of microglia activation and promotion of remyelination	Animal study
220	Zhu 2016	Electroacupuncture Promotes Remyelination after Cuprizone Treatment by Enhancing Myelin Debris Clearance.	Animal study
221	Zhu 2019	Repurposing of omeprazole for oligodendrocyte differentiation and remyelination	Animal study

Table S4. Summary of reported in vivo study designs to assess neuroprotective and/or regenerative interventions for MS.

Study Design	Number	Description
Clinical Study	4	An observational assessment of an intervention in human subjects using various sources of data (e.g. retrospective cohort analyses, longitudinal studies, sub-analyses of samples or data collected in clinical trials).
Clinical Trial	15	An assessment of an intervention in human subjects within a controlled trial to determine the safety and efficacy of the intervention for a specified indication. The goal is to produce evidence that an intervention improves outcomes to a greater degree than current options or addresses a different therapeutic need.
Phase 0	3	Also called pilot trials. Phase 0 trials are first-in-human, short-term and exploratory trials of a low dose given to a very small cohort (10 – 15 participants) to determine the safety, pharmacokinetics and preliminary performance of an intervention.
Phase I	3	A trial with a small cohort of healthy participants (20 – 50), or participants within the target population with no underlying health conditions, to determine the tolerable and safe range of dosing, as well as any unexpected and/or serious side effects.
Phase II	8	A longer-term trial with a larger cohort (50 – 100+) to determine the efficacy of the determined safe dose among the target population, while assessing side effects. The intervention may be given adjunct to current treatments.
Phase III	0	A large cohort trial (100 – 1000+) over multiple years designed to compare the safety, tolerability and effectiveness of an intervention to a current standard of care or similar intervention within the target population. Interventions with successful outcomes in phase III are considered for regulatory approval.
Phase IV	1	A trial for post-approval interventions to assess long term efficacy, account for variability in performance among a population with greater diversity and/or the utility of the intervention in treating a different symptomatic or pathological aspect of a condition.
Animal Model	250	A preclinical assessment of the efficacy and potential therapeutic applications of an intervention in animal subjects with a disease or condition that mimics one or more aspects of the pathology of MS. Animal models of MS generally fall into two primary groups: 1. Immune-mediated, which best reflects the systemic and neuroinflammatory aspects of MS (EAE and viral models) or 2. Chemically induced, which best reflects the neurodegenerative and regenerative aspects of MS (Cuprizone, LPC and EtBr models).
Cuprizone	123	Cuprizone is a copper chelating agent that selectively stresses and causes apoptosis of susceptible myelinating oligodendrocytes within particular areas of the brain in laboratory rodents. Short-term or long-term administration of cuprizone in the diet leads to acute or chronic demyelination, respectively, along with activation of glial cells. Cessation of the cuprizone diet leads to remyelination that proceeds in a consistent spatiotemporal pattern. Demyelination in this model occurs with minimal peripheral immune cell infiltration and contribution to damage, which enables the assessment of neuroregenerative strategies while controlling for potential indirect effects through peripheral immunity.
Lysophosphatidylcholine (LPC)	37	LPC, also called lysolethicin, is a phospholipid activator of phospholipase A2 that is injected directly into a predetermined site of the CNS to produce a focal demyelinated area. Demyelination occurs immediately and proceeds along a highly reproducible timeline, followed by spontaneous remyelination. The toxic LPC model is mediated primarily by direct chemical disruption of the myelin sheath and the action of local activated glial cells, with minimal peripheral inflammation and infiltration of the lesion.

Ethidium bromide (EtBr)	10	Ethidium bromide is a DNA intercalating agent used to induce focal demyelinated areas with minimal systemic inflammation. EtBr destroys glial cells, and especially their highly proliferative precursors, by compromising DNA replication. EtBr causes nonspecific apoptosis within the injection site and subsequent demyelination and remyelination of the lesion.
Experimental Autoimmune Encephalomyelitis (EAE)	66	An MS-like disease most often induced in rodents, wherein immunization with myelin antigens generates an autoimmune response to the CNS. Infiltrating myelin-reactive immune cells mediate both direct and indirect damage to the myelin sheath, which prompts widespread demyelination and clinically measurable neurological deficits, most notably an ascending paralysis.
Active induction	59	Active EAE is generated by immunizing animals with myelin peptide or protein (i.e. MOG, PLP, or MBP) combined with an adjuvant, in order to elicit a CNS-directed and predominantly $CD4^+$ T cell mediated autoimmune response. Priming of the adaptive immune response occurs in the periphery, followed by lymphocyte migration and infiltration of the CNS (which may be aided by administering blood-brain barrier permeating agents) and secondary recruitment and activation of local and infiltrating cells that go on to demyelinate axons. The clinical phenotype of the model depends on the genetic strain of laboratory rodent and the immunizing antigen. The following five rows describe the antigens reported to induce EAE.
MOG_{35-55}	42	Myelin oligodendrocyte glycoprotein (MOG) peptide segment 35-55 is the most commonly used antigen to actively induce $CD4^+$ T cell-dependent disease in a variety of susceptible rodent strains. MOG_{35-55} induced EAE in C57Bl/6 mice generates a chronic progressive or monophasic clinical course, whereas in NOD mice, induction results in a chronic relapsing disease.
MOG protein	3	MOG protein induced EAE in C57Bl/6 mice produces a similar clinical phenotype as MOG_{35-55} immunization but with differential activation and involvement of adaptive immune cells in disease pathology. Full length recombinant MOG protein contains multiple encephalitogenic determinants as well as conformational epitopes that generate greater numbers of infiltrating MOG-reactive B cells that can present antigen and produce autoantibodies. Inflammatory B cells can be therapeutically depleted in this model, similar to human MS.
$PLP_{139-151}$	8	Proteolipid protein (PLP) peptide segment 139-151 is commonly used to immunize the SJL mouse strain. The SJL-PLP model is characterized by relapsing clinical paralysis, epitope spreading and female sex bias, similar to RRMS, which makes the model well suited for testing interventions that exert differential sex-based effects or that temporally target episodes of symptom onset and remission.
MP4	1	MP4 is a chimeric fusion protein of PLP and myelin basic protein (MBP). MP4 immunization in SJL mice, which are susceptible to EAE induced with both antigens individually, produces a relapsing remitting clinical course. Similar to MOG protein, MP4 immunization generates a B cell and autoantibody dependent disease in C57Bl/6 mice and results in CNS lesions with histological features more consistent with MS than MOG_{35-55} EAE.
SC homogenate	5	Whole spinal cord (SC) homogenate was the first preparation used to generate EAE in rodents. SC homogenate is used to actively immunize recipients indiscriminately with multiple myelin and non-myelin antigens, resulting in broad immune activation and varying clinical courses depending on the donor and recipient species. Immunization with SC homogenate may not require the inclusion of an adjuvant in some rat strains.
Focal induction	2	Also called targeted EAE. The model involves the generation of reproducible, localized lesions in actively immunized EAE mice. A predetermined site in the CNS of an EAE mouse is injected with interferon-γ and tumor necrosis factor-α

		to preferentially 'target' peripherally activated leukocytes to a single lesion. Focal induction limits the pathology to specific areas, including those that may be less commonly affected by regular induction protocols.
Passive induction	5	Passive EAE is induced by the adoptive transfer of ex vivo stimulated and expanded myelin reactive $CD4^+$ T cells, isolated from the peripheral lymphoid organs of actively induced donors. T cell transfer to a naïve, genetically matched recipient results in a disease with the same clinical and immunopathological characteristics as the actively induced donor, but that bypasses the initial priming step. The resulting disease tends to onset more consistently between animals, with greater symptom severity and incidence. Passive induction is helpful for differentiating the effects of an intervention on the initial priming of the autoimmune response versus the effects on leukocyte migration and CNS-localized pathogenic mechanisms.
Viral Demyelination	11	Chronic CNS demyelination results from intracranial inoculation with a neurotropic viral strain and the subsequent immune response to infection. Viral demyelination models are similar to EAE models in that peripheral immune cells infiltrate the CNS and damage myelin. The site of the initial trigger, however, is within the CNS in viral models, and demyelination occurs secondarily to axonal damage (inside-out mechanism); unlike EAE, in which disease is initiated in the periphery and occurs by primary demyelination that results in axonal damage (outside-in mechanism).
TMEV	8	Theiler's encephalomyelitis virus (TMEV) is a (+)ssRNA p*icorna*virus that, when inoculated directly into the CNS, generates acute encephalitis followed by lymphocyte and macrophage infiltration and incomplete viral clearance. The establishment of persistent infection within glial cells and macrophages of genetically susceptible mice (i.e. SJL) is determined by the expression of specific MHC alleles. Infected susceptible mice exhibit late-onset, chronic inflammatory demyelination resulting from neuro-epitope spreading.
MHV	3	Mouse hepatitis virus (MHV) is a (+)ssRNA coronavirus that produces axonal damage and chronic demyelination throughout the CNS after intracranial inoculation. Similar to the TMEV model, demyelination is a result of incomplete clearance by infiltrating peripheral immune cells responding to infection. The neurotropic demyelinating strains A59 and JHMV are most commonly used to model clinical and histopathological aspects of MS.
Other	3	
NMO	1	An intracerebral injection of anti-aquaporin antibody (AQP4-IgG) and human complement that produces robust neuromyelitis optica (NMO) pathology with demyelination of the brain and minimal axonal injury.
PTZ	1	Pentylenetetrazol (PTZ) is a CNS penetrant and potent GABA receptor antagonist that produces extensive epileptogenic activity in the brain. PTZ administration is used as a model of epileptic seizure and has been shown to result in autoantibody-mediated axonal demyelination in rodents.
Optic Nerve Injury	1	A mechanical injury model in which the optic nerve is surgically damaged, by forceps or a haemostat, at a specified site behind the eye.
Total	269	

Tables S5 (A–L). Structural, mechanistic and regulatory overview of interventions reported to provide neuroprotection and/or promote neuroregeneration in preclinical or clinical studies of MS. Structures, mechanisms, biological effects and approved indications were sourced from the respectively listed data base accession numbers and reviewed articles, as well as FDA drug approval databases and ClinicalTrials.gov, unless otherwise cited with an external reference. To provide a summary of the data, interventions were grouped into a single classification even if there are multiple pharmacological actions. Information presented in these tables is not an exhaustive list.

Table S5A. Small molecule receptor agonists and antagonists

Name	Structure	Mechanism(s) of action	Biological effect(s)	FDA approved indication(s)	Accession number		Article Number
					DrugBank	PubChem CID	
Δ9-tetrahydro-cannabinol-botanical drug substance (Δ9-THC-BDS)	• Phytocannabinoid • Also called Dronabinol • $C_{21}H_{30}O_2$	Partial agonist at the cannabinoid receptors CB1 and CB2	• Psychoactive • Anti-nauseant • Analgesic	Disease-related nausea and weight loss	DB00470	16078	47
2-arachidonoyl-glycerol (2-AG)	• Endocannabinoid fatty acid • $C_{23}H_{38}O_4$	• Endogenous ligand for CB1 and CB2 receptors • Mimics several effects of Δ9-THC	• Anti-inflammatory • Neuroregulatory	-	-	5282280	113
2-carba-cyclic phosphatidic acid (2ccPA)	Synthetic cPA derivative "in which the phosphate oxygen was replaced with a methylene group at the sn-2 position"	• "Metabolically stabilized cPA derivative that showed much more potent biological activity than natural cPA" • Potentially blood-brain barrier permeable • Induces signalling similar to NGF, which "promotes neurite outgrowth and enhances neuronal survival"	• Neuroprotective • Anti-inflammatory	-	-	-	200
Adenosine	• Nucleoside composed of adenine and d-ribose • $C_{10}H_{13}N_5O_4$	• DNA and RNA nucleoside • Potent neuron-glial neurotransmitter • Induces OPC differentiation • Promotes formation of myelin	• Neuromodulatory • Antihypertensive	• Tachycardia • Pulmonary hypertension	DB00640	60961	216
AL-8810[12]	• 11β-fluoro analog of PGF2α • $C_{24}H_{31}FO_4$	Potent and selective prostaglandin F2alpha FP receptor antagonist	Neuroprotective	-	-	5311238	75
Amitriptyline	• Derivative of dibenzo-cycloheptadiene • $C_{20}H_{23}N$	• Tricyclic antidepressant (SNRI) • Mechanism not fully described • Inhibits lysosomal enzyme acid sphingomyelinase	• Antidepressant • Analgesic • Anticholinergic	• Depression • Neuropathic pain	DB00321	2160	27

Bazedoxifene	• Indole derivative • $C_{30}H_{34}N_2O_3$	• Tissue-dependent selective modulator of both nuclear estrogen receptors • Reduces bone resorption	Hormonal/ endocrine	Postmenopausal osteoporosis	DB06401	154257	151
Benztropine	• 3α-diphenyl-methoxytropane • $C_{21}H_{25}NO$	• Inhibitor of presynaptic carrier-mediated dopamine transport and reuptake • Muscarinic receptor antagonist	• Dopaminergic • Antimuscarinic • Antihistaminic	Parkinsonism	DB00245	1201549	125, 181
Bicuculline	• Benzylisoquinoline alkaloid • $C_{20}H_{17}NO_6$	• Competitive antagonist of GABA A receptor • Enhances BDNF expression in the hippocampus	Neuroregulatory	-	DB11562	10237	121
Bilobalide	• Sesquiterpene trilactone • $C_{15}H_{18}O_8$	• Main component of *Ginkgo biloba* extract • Negative allosteric modulator at the GABAA and GABAA-rho receptors • Free radical scavenger • Reduces platelet aggregation and improves circulation	• Neuroprotective • Anti-inflammatory • Antioxidant • Circulatory	-	DB01381	73581	173
BN52021 (Ginkgolide B)[13]	• Diterpenoid trilactone • $C_{20}H_{24}O_{10}$	• Antagonist of GABAA and platelet-activating factor receptors • Reduces platelet aggregation and improves circulation • Protects against hypoxia-induced neuronal injury	• Neuroprotective • Anti-inflammatory • Antioxidant • Circulatory	-	DB06744	65243	15
BNN27	• Novel synthetic microneurotrophin • Member of a chemical library of C17-spiroepoxy derivatives of DHEA • $C_{21}H_{32}O_3$	• Blood-brain barrier permeable analog of DHEA • Promotes neuron survival by activating the NGF receptors	• Neuroprotective • Neurogenic	-	-	-	20
Cannabidiol-botanical drug substance (CBD-BDS)	• Phytocannabinoid • $C_{21}H_{30}O_2$	• Partial agonist at the cannabinoid receptors CB1 and CB2 • Activates 5-HT1A/2A/3A serotonergic and TRPV1–2 vanilloid receptors, antagonizes alpha-1 adrenergic and μ-opioid receptors • Inhibits reuptake of noradrenaline, dopamine, serotonin, GABA and anandamide • Blocks low-voltage-activated calcium channels	• Analgesic • Anticonvulsant • Muscle relaxant • Anxiolytic • Antipsychotic • Neuroprotective • Anti-inflammatory • Antioxidant	• Epilepsy • Neuropathic pain (Health Canada)	DB09061	644019	47
CCX771	• Synthetic • Structure not available • Proprietary compound patented by ChemoCentryx	• Atypical chemokine receptor CXCR7 (ACKR3) antagonist • CXCR7 is expressed on immune cells and in the CNS • CXCR7 mediates activation of CXCR4 during neural and glial precursor differentiation	Immunomodulatory	-	-	-	193
Clemastine fumarate	• Ethanolamine derivative • $C_{21}H_{26}ClNO.C_4H_4O_4$	• Selective histamine H1 receptor antagonist • Blocks the action of endogenous histamine	• Antihistamine • Anticholinergic • Sedative	Allergic symptoms	DB00283	5281069	59, 76
Clobetasol	• Corticosteroid • $C_{22}H_{28}ClFO_4$	• Corticosteroid hormone receptor agonist that modulates glucocorticoid receptor signaling • Promotes Schwann-cell-mediated myelination of peripheral nerves	Anti-inflammatory	Inflammatory skin disorders	DB11750	5311051	125, 201

		• Stimulates OPC proliferation and differentiation • Blood-brain barrier permeable					
Clozapine	• Tricyclic dibenzodiazepine • $C_{18}H_{19}ClN_4$	• Blood-brain barrier permeable • Serotonin 5-HT 2A/2C receptor antagonist • Antagonizes several dopamine receptors but only weak antagonism at the dopamine D2 receptor	• Atypical antipsychotic • Anti-inflammatory	• Schizophrenia • Advanced parkinsonism	DB00363	135398737	179
CYM5442	• Sphingosine-like fungal metabolite • $C_{23}H_{27}N_3O_4$	Short-lived sphingosine 1-phosphate receptor-specific modulator	Immunosuppressant	-	-	25110406	88
Diarylpropionitrile (DPN)	• Acetonitrile • $C_{15}H_{13}NO_2$	• Synthetic, nonsteroidal and highly selective estrogen receptor β agonist • Lacks anti-inflammatory effects	Neuroprotective	-	-	102614	119, 185
Dimethyl fumarate (DMF)	• Orally bioavailable methyl ester of fumaric acid • $C_6H_8O_4$	• Metabolized to active monomethyl fumarate (MMF) • MMF up-regulates the Nrf2 pathway that is activated following oxidative stress • MMF is an agonist of the nicotinic acid receptor • (92) Delivered in DMF-O-solid lipoidal nanoparticles	Anti-inflammatory	RRMS	DB08908	637568	25, 92
ER beta ligand (AC186)	• Nonsteroidal agonist • $C_{18}H_{17}F_3O$	Potent and selective ERβ agonist similar to DPN	Neuroprotective	-	-	71245042	74
FTY720 (Fingolimod)	• Orally available aminodiol • Derivate of myriocin • $C_{19}H_{33}NO_2$	• Non-selective sphingosine 1-phosphate receptor modulator • Blocks T cell egress from lymph nodes and subsequent migration to the CNS	Immunosuppressive	• CIS • RRMS • SPMS	DB08868	107969	5, 19, 57, 63, 88, 127, 133, 170, 177, 202, 203
Genistein	• Isoflavone type of phytoestrogen • $C_{15}H_{10}O_5$	• Plant-derived compound abundant in soy • Estrogen receptor β ligand • Inhibits protein-tyrosine kinase and DNA topoisomerase-II activity (can induce cell cycle arrest)	• Anti-cancer • Anthelminthic • Hormonal/ endocrine	Has completed multiple clinical trials for cancers	DB01645	5280961	134
GSK-239512[14]	• Structure reported in article • $C_{23}H_{27}N_3O_2$	• Potent and selective histamine 3 receptor antagonist • Blood-brain barrier permeable • "… selective H3 receptor antagonists has been shown to enhance the release of neurotransmitters such as histamine, acetylcholine, dopamine and norepinephrine, among others, which play important roles in cognitive processes"	Cognitive	Completed phase II clinical trial for RRMS (NCT01772199)	DB15120	9976892	165
GSK-247246[14]	Structure reported in article	• Blood-brain barrier permeable H3R antagonist • "… selective H3 receptor antagonists has been shown to enhance the release of neurotransmitters such as histamine, acetylcholine, dopamine and norepinephrine, among others, which play important roles in cognitive processes"	• Antihistamine • Neuroregenerative	-	-	-	29

Guanabenz	• 2,6-dichlorobenzylidene aminoguanidine acetate • $C_8H_8Cl_2N_4$	• Selective α2 adrenergic receptor agonist • "Guanabenz can also enhance protective ISR activity by inhibiting the binding of GADD34 to PP1, thereby inhibiting the dephosphorylation of p-eIF2α" expressed in mature oligodendrocytes	Antihypertensive	High blood pressure	DB00629	5702063	191
Iloprost	• Prostacyclin analogue • $C_{22}H_{32}O_4$	• Binds to prostacyclin and prostaglandin EP1 receptors • Inhibits the ADP, thrombin, and collagen-induced aggregation of human platelets • Dilates systemic and pulmonary arterial vascular beds	• Antihypertensive • Antidiuretic	Pulmonary hypertension	DB01088	5311181	123
Indazole chloride	• Phenylpyrazole • $C_{13}H_9ClN_2O_2$	Highly selective estrogen receptor β ligand	• Anti-inflammatory • Neuroprotective	-	-	122458206	6, 119
JTE-013	• Pyrazolopyridine • $C_{17}H_{19}N_7OCl_2$	Selective S1P2 receptor antagonist in humans and rodents	Immunosuppressive	-	-	10223146	167
Laquinimod[15] (ABR-215062)	• Aromatic amide • $C_{19}H_{17}ClN_2O_3$	• Proposed to reduce leukocyte migration to the CNS • Passively enters the CNS • Promotes remyelination in non-supportive environments by targeting NF-κB signalling in astrocytes and microglia	• Immunomodulatory • Neuroprotective	Completed phase III clinical trial for RRMS	DB06685	54677946	90, 130
Memantine hydrochloride	• Primary aliphatic amine • $C_{12}H_{21}N$	• Non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist • NMDA antagonism decreases glutamate induced neuronal excitability and excessive stimulation that can lead to cellular dysfunction	• Neuroregulatory • Dopaminergic • Antidepressant	Alzheimer's disease-related dementia	DB01043	181458	172
Methyl-prednisolone	• Prednisolone derived glucocorticoid • $C_{22}H_{30}O_5$	• Higher potency than prednisone • Blood-brain barrier permeable • Decreases capillary permeability which inhibits leukocyte migration to sites of inflammation • Induces cell differentiation and stimulates apoptosis in sensitive tumor cell populations	Immunomodulatory	• Multiple • Progressive MS	DB00959	6741	152
MK801 (Dizocilpine)	• Organic tricyclic compound • $C_{16}H_{15}N$	• Potent non-competitive N-methyl-D-aspartate receptor antagonist • NMDA antagonism decreases glutamate induced neuronal excitability and excessive stimulation that can lead to cellular dysfunction	• Anticonvulsant • Anesthetic	-	-	180081	172
N-butyl-β-carboline-3-carboxylate (β-CCB)	• β-carboline • $C_{16}H_{16}N_2O_2$	• Stimulates GABAergic signaling in OPCs and myelinating oligodendrocytes • "the cellular mechanism involved in the effect of β-CCB remains unknown"	Neurostimulatory	-	-	128618	34
Novel/ proprietary compound 2	• Synthesis described in methods • Chemical structure reported in article 199	• Blood-brain barrier permeable CXCR2 antagonist that promotes OPC differentiation • CXCR2 is expressed by both inflammatory myeloid cells and oligodendrocytes in the CNS • CXCR2 involvement in MS remains unclear	Immunomodulatory	-	-	-	189

Novel/ proprietary compound 22	• Structure reported in article • Based on urea	• CNS penetrant CXCR2 antagonist • Chemokine receptor CXCR2 is expressed on OPCs and leukocytes • CXCR2 regulates recruitment of immune cells to sites of injury and inflammation	Immunomodulatory	-	-	-	198
Novel/ proprietary compound 6a	• Arylpiperazine • Structure reported in article	• Dopaminergic and serotonergic • D2/5-HT 1A receptor ligand	• Neuroregulatory • Anti-inflammatory	-	-	-	144
Novel/ proprietary compound 6b	• Arylpiperazine • Structure reported in article	• Dopaminergic and serotonergic • D2/5-HT 1A receptor ligand	• Neuroregulatory • Anti-inflammatory	-	-	-	144
Phenobarbitone sodium	• Barbituric acid derivative • $C_{12}H_{12}N_2O_3$	• Nonselective CNS depressant • Binds GABAA receptor • Blocks calcium channel and inhibits the release of excitatory transmitters • Inhibits glutamate induced depolarizations	• Anticonvulsant • Sedative-hypnotic	Epileptic seizures	DB01174	4763	55
Pioglitazone	• Thiazolidinedione • $C_{19}H_{20}N_2O_3S$	• Selective peroxisome proliferator-activated receptor-gamma (PPARγ) agonist • Modulates lipid and glucose metabolism	Antihyperglycemic	Type 2 diabetes mellitus	DB01132	4829	4
Pranlukast	• Chromone • $C_{27}H_{23}N_5O_4$	• Antagonizes Gpr17 activity (GPCR downstream of Olig2) • Cysteinyl leukotriene receptor-1 antagonist • Reduces allergen-induced bronchospasm	• Anti-asthmatic • Anti-inflammatory • Neuroprotective	Asthma (inhalant adjunct therapy)	DB01411	4887	138
Prednisone	• Synthetic glucocorticoid • $C_{21}H_{26}O_5$	• Promotes BDNF and NGF production • Reduces the dilation and permeability of capillaries which inhibits leukocyte migration to sites of inflammation • Binds the glucocorticoid receptor • Inhibits phospholipase A2, NF-Kappa B and other inflammatory transcription factors	• Anti-inflammatory • Neuroprotective	Multiple inflammatory conditions	DB00635	5865	206
Probenecid	• Benzoic acid derivative • $C_{13}H_{19}NO_4S$	• Prototypical uricosuric agent • Increase the excretion of uric acid by competitively inhibiting the tubular reabsorption of urate • Pannexin-1 antagonist	• Anti-inflammatory • Antihyperuricemia	• Gout • Renal impairment	DB01032	4911	64
Quetiapine fumarate	• Dibenzothiazepine • $C_{21}H_{25}N_3O_2S$	• Dopamine type 2 (D2) and serotonin 2A (5HT2A) receptor antagonist • Binds the norepinephrine transporter and other alpha-1, alpha-2 adrenergic and histamine H1 receptors	Atypical antipsychotic	• Schizophrenia • Bipolar disorder	DB01224	5281025	55
Smoothened agonist (SAG)	• Benzothiophene • $C_{28}H_{28}ClN_3OS$	• Agonist of the Smoothened (Smo) receptor • Smo receptor binding induces the proliferation and survival of neuronal and glial precursors	Neuroregulatory	-	-	5284330	162
SCH58261[16]	• Triazolopyrimidine • $C_{18}H_{15}N_7O$	• Selective A2A receptor antagonist • The A2A receptor regulates inflammation and glutamate and dopamine release in the CNS	• Anti-inflammatory • Neuroregulatory	-	-	176408	2

Siponimod (BAF312)	• Orally bioavailable • $C_{29}H_{35}F_3N_2O_3$	• Selective sphingosine-1-phosphate (S1P) receptor modulator • High affinity for S1P receptors 1 and 5	Immunosuppressive	• CIS • RRMS • SPMS	DB12371	44599207	71
Tamoxifen	• Non-steroidal antiestrogen • $C_{26}H_{29}NO$	• Inhibits PKCα activity and prevents DNA synthesis • Modulates estrogen signaling by competitively inhibiting estrogen binding to receptors	Antineoplastic	Estrogen receptor positive breast cancer	DB00675	2733526	58
Timolol	• Propanolamine derivative • $C_{13}H_{24}N_4O_3S$	• Nonselective beta-adrenergic receptor antagonist • Reduces intraocular pressure and prevents retinal ganglion cell loss	Antihypertensive	• Glaucoma • Hypertension	DB00373	33624	184
U-50488	• Monocarboxylic acid amide • Synthetic opiod • $C_{19}H_{26}Cl_2N_2O$	• Highly selective kappa-opioid receptor (KOR) agonist • Does not result in any μ-opioid antagonist effects • Calcium channel blocker • Stimulates the release of adrenocorticotropin	• Diuretic • Analgesic • Antitussive	-	-	3036289	115
VCE-004.8	• Semi-synthetic cannabidiol aminoquinone derivative • $C_{28}H_{35}NO_3$	• Dual PPARγ and CB2 agonist • Inhibits prolyl-hydroxylases (PHDs) • Activates HIF pathway involved in oligodendrocyte migration	Anti-inflammatory	-	-	118465221	126
Venlafaxine	• Synthetic phenethylamine bicyclic derivative • $C_{17}H_{27}NO_2$	• Serotonin-norepinephrine reuptake inhibitor (SNRI) • Weak dopamine reuptake inhibitor	• Antidepressant • Neuroprotective • Anti-inflammatory	• Psychiatric disorders • Neuropathy	DB00285	5656	218
Xaliproden	• Tetrahydropyridine • $C_{24}H_{22}F_3N$	• Neurotrophin mimetic/ stimulant • Non-peptidic serotonin 5-hydroxytryptamine (5-HT) 1A receptor agonist	Neuroprotective	Completed clinical trials for amyotrophic lateral sclerosis and Alzheimer's disease	DB06393	128919	184
Yhhu4952	• N-Phenylquinazolin-2-amine • $C_{18}H_{18}N_4O$	• Limited information • Low-potency partial CB2 receptor agonist • Promotes OPC differentiation by inhibiting the Jagged1-Notch1 pathway	• Neuroregulatory • Immunomodulatory	-	-	-	205

Table S5B. Small molecule enzyme substrates and inhibitors

Name	Structure	Mechanism(s) of action	Biological effect(s)	FDA approved indication(s)	Accession number		Article Number
					DrugBank	PubChem CID	
4-Aminopyridine (4-AP)	• Isomeric amine of pyridine • $C_5H_6N_2$	Blocks juxtaparanodal potassium channels exposed on demyelinated axons	• Neurophysiologic • Enhancement of mobility	MS-related impairments of motor function	DB06637	1727	21, 52, 112
18β-glycyrrhetinic acid	• Also called Enoxolone • Natural pentacyclic triterpenoid aglycone • $C_{30}H_{46}O_4$	• Metabolite of glycyrrhizin (licorice plant) • Inhibits the metabolism of prostaglandins, which inhibits gastric secretion and stimulates intestinal and pancreatic secretion • Causes increased intestinal motility • "Inhibits 11 beta-hydroxysteroid dehydrogenase and other enzymes involved in the conversion of cortisol to cortisone in the kidneys"	• Anti-inflammatory • Neuroprotective • Gastric and hepatoprotective • Antitussive	Cosmetics and food flavoring (Glycyrrhizic acid)	DB13089	10114	219
3-n-butyl-phthalide[5] (D and L isomers)	• Benzofuranone • $C_{12}H_{14}O_2$	• Extracted from Chinese celery • Blood-brain barrier permeable Potential mechanisms include: • Promoting microcirculation • Reducing oxidative stress, mitochondrial dysfunction and inflammation by inhibiting NF-κB signaling	• Antihypertensive • Anti-inflammatory • Antioxidant • Neuroprotective	Completed clinical trials for ischemic stroke and Alzheimer's disease	DB12749	61361	197
Baicalein	• Trihydroxyflavone • $C_{15}H_{10}O_5$	• Metabolite from *Scutellaria baicalensis* • Prostaglandin antagonist • Inhibitor of arachidonate 12- and 15-lipoxygenase and prolyl oligopeptidase • Free radical scavenger	• Anti-inflammatory • Antioxidant • Neuroprotective	-	-	5281605	67
BLZ945	• Benzothiazole • $C_{20}H_{22}N_4O_3S$	Colony stimulating factor 1 receptor (CSF-1) receptor kinase inhibitor	Antineoplastic	Recruiting for phase II trial in amyotrophic lateral sclerosis	-	46184986	13, 192
BN201	• Peptoid • $C_{25}H_{38}FN_5O_4$	• Crosses the blood-brain barrier by active transport following neuronal stress responses • Promotes OPC and neuronal differentiation • Modulates several kinases in the IGF-1 pathway	Neuroprotective	Completed phase I clinical trial for optic neuritis (NCT03630497)	-	-	184
Bucladesine	• Cell-permeable analogue of cAMP • 3',5'-cyclic purine nucleotide • $C_{18}H_{24}N_5O_8P$	• Bucladesine is a phosphodiesterase-3 inhibitor, which reduces intracellular cAMP catabolism • cAMP is a secondary messenger in signal transduction • cAMP can activate protein kinase A (PKA), which "promotes axonal regeneration, regulates inflammatory responses, and inhibits caspase-3 activity"	• Anti-inflammatory • Anti-apoptotic • Vasodilation	-	DB13242	9687	182

Cordycepin	• Also called 3'-deoxyadenosine • Purine nucleoside antimetabolite and antibiotic • $C_{10}H_{13}N_5O_3$	• Main bioactive ingredient of *Cordyceps militaris* • Crosses the blood-brain barrier using an adenosine transporter due to structural similarity (mimic) • Induces tumor cell apoptosis and blocks proliferation by Inhibiting polyadenylation, activating AMP-activated protein kinase and reducing mTOR signaling	• Anti-inflammatory • Antioxidant • Anti-proliferative • Neuroprotective	In multiple clinical trials for leukemia and lymphoma	DB12156	6303	77
Dapagliflozin	• C-glycosyl compound • $C_{21}H_{25}ClO_6$	• Modulator of lipid and glucose metabolism • Sodium-glucose cotransporter 2 inhibitor	Antihyperglycemic	Type 2 diabetes mellitus	DB06292	9887712	4
Donepezil	• Piperidine derivative • $C_{24}H_{29}NO_3$	Reversible acetylcholinesterase inhibitor	Neurocognitive enhancement	Alzheimer's disease	DB00843	3152	37
Ellagic acid	• Tannic acid derivative • $C_{14}H_6O_8$	• Exact mechanisms unclear • Inhibitor of numerous enzymes • Inhibits the generation of ROS	• Antioxidant • Anti-proliferative	-	DB08846	5281855	22, 159
Epigallocatechin-3-gallate[6]	• Catechin polyphenol • $C_{22}H_{18}O_{11}$	• Most abundant catechin in tea • Binds numerous proteins with high affinity • Exhibits anti-proliferative effects by inhibiting telomerase and DNA methyltransferase • Inhibits MMP-2 and MMP-9 expression • Blocks the activation of epidermal growth factor receptors • ROS scavenging	• Anti-inflammatory • Antioxidant • Antiproliferative	-	DB12116	65064	166
Fluorosamine	• Fluorinated analogue of UDP-N-acetyl-glucosamine (GlcNAc) • Structure reported in article	• Alternative substrate to naturally occurring GlcNAc, a nucleotide sugar and metabolic coenzyme • Interferes with "the enzymatic conversion of naturally occurring UDP-GlcNAc to UDP-N-acetyl-galactosamine by 4-epimerase, which reduces the content of chondroitin sulfate side chains (CSPG precursor)"	Anti-inflammatory	-	-	-	84
Ginkgolide K	• Terpene derivative of ginkgolide B • $C_{20}H_{22}O_9$	• Isolated from *Ginkgo biloba* leaves • Mechanisms mostly unknown • Promotes astrocyte migration and proliferation • Attenuates mitochondrial dysfunction and free radical production	• Neuroprotective • Anti-inflammatory • Antioxidant	-	-	101553595	98
Gli-ANTagonist 61 (GANT61)	• Hexahydropyrimidine derivative • $C_{27}H_{35}N_5$	• Inhibitor of Gli1 and glioma-associated oncogene • Blood-brain barrier permeable	Antineoplastic	-	-	421610	158
Hesperetin	• Flavonoid • $C_{16}H_{14}O_6$	• Lowers cholesterol by inhibiting the activity of acyl-coenzyme A • Upregulates the LDL receptor • Free radical scavenger	• Antioxidant • Anti-inflammatory • Hypolipidemic • Antineoplastic	-	DB01094	72281	10
Icariin	• Glycosyloxyflavone • $C_{33}H_{40}O_{15}$	• Inhibitor of phoshphodiesterase-5 and NF-κB signalling • Dominant active component extracted from the traditional Chinese herb *Epimedium*	• Antioxidant • Anti-inflammatory • Anti-thrombotic	-	DB12052	5318997	215

		• Proposed to induce multiple different effects	• Lipid modulation				
JZL184	• Benzodioxole • $C_{27}H_{24}N_2O_9$	• Selective and irreversible inhibitor of monoacylglycerol lipase, the main enzyme responsible for degrading 2-arachidonoylglycerol • Increases endogenous cannabinoid levels	Cannabinoid-related behavioural effects in mice	-	-	25021165	17
KT182	• Triazole urea derivative • $C_{27}H_{26}N_4O_2$	• Specific inhibitor of the 2-arachidonoylglycerol hydrolytic enzyme, monoacylglycerol lipase ABHD6 • Blood-brain barrier permeable • Modulates endocannabinoid signaling	Neuroregulatory	-	-	53364491	108
L-a-aminoadipate (L-AAA)	• Glutamate homologue • Derived from adipic acid • $C_6H_{11}NO_4$	• Transient astrotoxin • Induces ablation of astrocytes through inhibition of glutamate biosynthesis and uptake • Inhibits signalling between astrocytes and microglia	Gliotoxic	-	-	469	104
Leonurine	• Bioactive alkaloid • Trihydroxybenzoic acid • $C_{14}H_{21}N_3O_5$	• Extracted from *Herba leonuri* • Inhibits cyclooxygenase-2 expression via NF-κB signalling pathways • Reduces microglial and macrophage activation	• Anti-inflammatory • Neuroprotective	-	-	161464	79
Linagliptin	• Dihydropurinedione-based xanthine • $C_{25}H_{28}N_8O_2$	• Competitive and reversible inhibitor of dipeptidyl peptidase 4 • Stimulates the release of insulin from beta cells in the pancreas while inhibiting the release of glucagon • Reduces glycogen catabolism in the liver and increases insulin release in response to glucose	Antihyperglycemic	Type 2 diabetes mellitus	DB08882	10096344	46
Metformin	• Dimethylguanylguanidine • $C_4H_{11}N_5$	• Modulates energy metabolism and glucose levels • Inhibits mitochondrial complex I activity • Activates AMP-activated protein kinase	• Antihyperglycemic • Antioxidant • Anti-inflammatory	Type 2 diabetes mellitus	DB00331	4091	4, 96, 128
Miconazole	• Azole sterane • $C_{18}H_{14}Cl_4N_2O$	• ERK1/2 activator and glucocorticoid receptor antagonist • Inhibits fungal enzymes, causing elevated levels of ROS • Increases intracellular levels of farnesol in yeast	Antifungal	Mucosal yeast infections	DB01110	4189	125, 201
Mitoxantrone[7]	• Anthracenedione antibiotic • $C_{22}H_{28}N_4O_6$	• Intercalates DNA and RNA • Potent inhibitor of topoisomerase II • Inhibits B cell, T cell, and macrophage proliferation and impairs antigen presentation • Reduces the secretion of pro-inflammatory cytokines	• Antineoplastic • Anti-inflammatory	• Acute Lymphocytic Leukemia • Worsening RRMS • SPMS	DB01204	4212	55
Myricetin	• Hexahydroxyflavone • Structurally similar to quercetin • $C_{15}H_{10}O_8$	• Metabolic precursor • Upregulates the Nrf2 signaling pathway • Inhibitor of cyclooxygenase 1	• Antioxidant • Anti-inflammatory • Antiviral • Antineoplastic	-	DB02375	5281672	212
Nimodipine	• Dihydropiridine • $C_{21}H_{26}N_2O_7$	• Selectively binds and blocks L-type voltage-gated calcium channels on vascular smooth muscle cells • Blood-brain barrier permeable	• Neuroprotective • Antihypertensive	Cerebral vasospasms	DB00393	4497	73, 164

Novel/ proprietary compound 22	• Hydantoin core structure with an imidazole moiety • Structure reported in article	• Inhibitor of protein arginine deiminase (PAD) 2 and 4 • PAD2 and PAD4 expression is upregulated during early lesion formation in the CNS • PAD enzymes can hyper-citrullinate structural proteins such as MBP	Anti-inflammatory	-	-	-	163
Omeprazole	• Benzimidazole • $C_{17}H_{19}N_3O_3S$	• Selective and irreversible proton-pump inhibitor • Reduces gastric acid secretion	• Antisecretory • Anti-inflammatory	Gastric ulcers	DB00338	4594	221
PD0325901	• Synthetic aminobenzoic acid derivative • $C_{16}H_{14}F_3IN_2O_4$	• MAPK kinase inhibitor and the phosphorylation and activation of MAPK/ERK • Reduces tumor cell proliferation	Antineoplastic	In multiple trials for various cancers	DB07101	9826528	174
Phenytoin	• Hydantoin derivative • $C_{15}H_{12}N_2O_2$	• Selective sodium-channel inhibitor • Non-sedative antiepileptic agent with a narrow therapeutic index • "Prevents seizures by inhibiting the positive feedback loop that results in neuronal propagation of high frequency action potentials"	• Anticonvulsant • Neuroprotective	Epilepsy	DB00252	1775	149
PLX3397	• Also called Pexidartinib • Pyrrolopyridine • $C_{20}H_{15}ClF_3N_5$	• Inhibitor of colony-stimulating factor 1 receptor (CSF1R) signalling via selective tyrosine kinases • Microglia and inflammatory macrophage depletion	• Anti-inflammatory • Antineoplastic	Tenosynovial giant cell tumor	DB12978	25151352	176
Pregabalin	• Structural derivative of GABA • $C_8H_{17}NO_2$	• Not entirely defined • Binds α2σ subunit of synaptic voltage gated calcium channels • Inhibits the release of numerous neurotransmitters, including glutamate, dopamine and serotonin	• Analgesic/ Antinociceptive • Anticonvulsant	• Neuropathic pain • Epilepsy disorder	DB00230	5486971	38, 70
Proanthocyanidin[8]	• Flavonoid • Oligomeric polymer • $C_{31}H_{28}O_{12}$	• Component of grape seed extract (condensed tannins) • Reduces ROS levels • Protects from arteriosclerosis by inhibiting oxidized LDL binding to the lectin-like oxidized LDL receptor (LOX-1) • Can modulate NF-κB signalling in the hippocampus	• Antioxidant • Anticancer • Cardioprotective • Neuroprotective • Antimicrobial	-	-	108065	188
Quercetin	• Polyphenolic flavonoid • $C_{15}H_{10}O_7$	• Dietary component of fruit and herbs • Specific quinone reductase 2 (QR2) inhibitor	• Antioxidant • Anti-inflammatory	-	DB04216	5280343	4
Resveratrol	• Polyphenolic phytoalexin • $C_{14}H_{12}O_3$	• Blood-brain barrier permeable • Inhibits cyclooxygenase and hydroperoxidase • Suppresses TNF-induced activation of NFκB in HSV infected cells	• Antioxidant • Anti-inflammatory • Cardioprotective • Antiherpetic	In multiple clinical trials for viral, inflammatory and cardiac conditions	DB02709	445154	53
Rifampicin	• Semi-synthetic antibiotic • $C_{43}H_{58}N_4O_{12}$	• Derived from *Streptomyces mediterranei* • Blocks transcription by inhibiting DNA-dependent RNA polymerase activity • Pregnane X receptor agonist	• Antibacterial • Neuroprotective • Anti-inflammatory	Mycobacterial infection and related disease	DB01045	135398735	207
SB203580	• Imidazole derivative • $C_{21}H_{16}FN_3OS$	Inhibitor of p38, Hsp90, mitogen-activated protein kinase and non-specific serine/threonine protein kinase	Neuroprotective	-	-	176155	187

Scutellarin	• Glycosyloxyflavone • $C_{21}H_{18}O_{12}$	• Protects astrocytes from hypoxia by inducing the production of neurotrophins • Proteasome inhibitor	• Neuroprotective • Antineoplastic	Present in some OTC products and stroke drug Breviscapine	DB14364	185617	187
Sephin1	• Guanabenz derivative • $C_8H_9ClN_4$	• Selective inhibitor eIF2α phosphatase, "thereby prolonging the protective integrated stress response" • Unlike guanabenz, Sephin1 retains inhibitor specificity without measurable α2-adrenergic side effects	Neuroprotective	-	-	9561611	30
Sildenafil	• Structure similar to cGMP • $C_{22}H_{30}N_6O_4S$	• Reduces the catabolism of cGMP by inhibiting cGMP specific phosphodiesterase type 5 • Reduces arterial hypertension by increasing blood flow	• Neuroprotective • Antihypertensive	• Erectile dysfunction • Pulmonary hypertension	DB00203	135398744	39
Sodium valproate	• Fatty acid derivative • Sodium 2-propylpentanoate • $C_8H_{15}NaO_2$	• Increases synaptic GABA levels • Inhibits succinic semialdehyde dehydrogenase, that in turn inhibits GABA transaminase, which catabolizes GABA and/ or blocks synaptic reuptake	Anticonvulsant	• Epilepsy • Migraines	DB00313	16760703	55
STRTAW04	Chemical structure not available	• Increases SIRT1 deacetylase activity • Activator of SIRT1 without nonspecific activation of pathways affected by resveratrol • Effects measurable at an order of magnitude lower concentration than resveratrol	• Neuroprotective • Antioxidant	-	-	-	85
Sulfasalazine	• Synthetic salicylic acid derivative • $C_{18}H_{14}N_4O_5S$	• Unclear • Appears to inhibit cyclooxygenase and prostaglandin production • Therapeutic effects considered to be due to the 5-ASA moiety	Anti-inflammatory	• Rheumatological conditions • Inflammatory bowel disease	DB00795	5339	41
Teriflunomide	• Active metabolite of leflunomide • $C_{12}H_9F_3N_2O_2$	• Multiple proposed mechanisms • Targets active adaptive immune cells (T and B) • Non-competitive reversible inhibitor of the mitochondrial enzyme dihydro-orotate dehydrogenase • Proposed to interfere with antigen presentation to T cells and inhibit cytokine secretion	• Immunosuppressive • Antiproliferative	RRMS	DB08880	54684141	142
Triptolide	• Diterpenoid triepoxide • $C_{20}H_{24}O_6$	• Plant metabolite • Inhibitor of pro-inflammatory NF-κB signaling in macrophages	• Anti-inflammatory • Antioxidant • Anticancer	Evaluated in clinical trials for intestinal inflammation and HIV infection	DB12025	107985	160
UCM-03025 (compound 21)	Structure reported in article	• Potent, selective and reversible inhibitor of monoacylglycerol lipase • Reduces 2-AG degradation	Neuroregulatory	-	-	-	48
VP1.15	• 2-[(2,3-Diphenyl-1,2,4-thiadiazol-5(2H)-ylidene) amino] ethanol • $C_{16}H_{15}N_3OS$	• Dual phosphodiesterase (PDE)7 and glycogen synthase kinase (GSK)3 inhibitor • CNS-penetrant	• Anti-inflammatory • Neuroprotective	-	-	46902082	114

VP3.15	• VP1.15 derivative • N-(2-Morpholin-4-ylethyl) -2,3-diphenyl-1,2,4-thiadiazol-5-imine • $C_{20}H_{22}N_4OS$	• Dual phosphodiesterase (PDE)7 and glycogen synthase kinase (GSK)3 inhibitor • Improved safety profile compared to VP1.15 • CNS-penetrant	• Anti-inflammatory • Neuroprotective	-	-	51038980	114
Xyloside[9]	• Glycoside derived from xylose • $C_5H_{10}O_5$	• Inhibitor of CSPG synthesis by competing with endogenous primers for binding of the core of galactosyltransferase in chondrocytes	Metabolic/ biosynthetic	-	DB09419	135191	48

Table S5C. Small molecule hormones, metabolites and vitamins

Name	Structure	Mechanism(s) of action	Biological effect(s)	FDA approved indication(s)	Accession number		Article Number
					DrugBank	PubChem CID	
Acetate	• 2 carbon short-chain fatty acid • $C_2H_3O_2$-	• Metabolic precursor • Modulation of intestinal homeostasis, energy metabolism and immune responses	• Metabolic • Immunomodulatory	• Food additive • Metabolic acidosis	DB14511, DB09395	175	31
Alpha Lipoic Acid (Thioctic acid)	• Vitamin-like dithiol • Micronutrient • $C_8H_{14}O_2S_2$	• ROS scavenging and metal chelation • Enzyme cofactor in energy production and glucose metabolism • Regenerates endogenous antioxidants, vitamins C and E and glutathione	• Antioxidant • Anti-inflammatory • Antihypertensive	Nutritional supplementation	DB00166	864	161
Butyrate	• 4 carbon short-chain fatty acid • $C_4H_7O_2$-	• Metabolic precursor • Produced by commensal intestinal bacteria • Modulation of intestinal homeostasis, energy metabolism, and immune responses	• Metabolic • Immunomodulatory	-	DB03568	104775	31
Creatine monohydrate	• Amino acid derivative • $C_4H_9N_3O_2$	• Intracellular ATP buffering and energy storage • Reversibly dephosphorylated for rapid ATP regeneration at sites with high energy usage • Oligodendrocytes express creatine-synthesizing enzymes	• Cytoprotective • Antioxidant	• Nutritional supplementation • Mitochondrial disorders	DB00148	80116	26
Cyclic phosphatidic acid[10]	• 1-acyl-2,3-glycerophosphate • Unique cyclic phosphate ring structure • $C_{21}H_{39}O_6P$	• Phospholipid mediator • Analog of lysophosphatidic acid (LPA) that binds LPA receptors 1 – 5 • Exhibits neurotrophin-like activity • Inhibits DNA polymerase α	• Antimitogenic • Cellular regulation	-	-	52922109	199
Cytidine-5′-diphospho (CDP)-choline (Citicoline)	• Naturally occurring endogenous nucleoside • $C_{14}H_{26}N_4O_{11}P_2$	• Metabolic intermediate in the biosynthesis of the cell membrane component phosphatidylcholine (lecithin) • "Degradation products cytidine and choline readily cross the blood–brain barrier and enter the various biosynthetic pathways that use CDP-cholin"	• Neuroregulatory • Metabolic • Anti-apoptotic	Approved in Europe for neurological conditions	DB12153	13804	169

		• Promotes acetylcholine, norepinephrine and dopamine production in the CNS					
Ethyl pyruvate (CTI-01)[11]	• Belongs to the family of alpha-keto acids • Ethyl 2-oxopropanoate • $C_5H_8O_3$	• Simple derivative of pyruvate • Inhibits the systemic release of cytokines TNF-alpha and HMGB1 • ROS scavenging	• Anti-inflammatory • Antioxidant	Critical inflammatory conditions	DB05869	12041	68
L-ascorbyl-2-phosphate (As-2P)	• A synthetic, stable form of Vitamin C • $C_6H_{11}O_{10}P$	• Enzyme cofactor and ROS scavenging • Necessary for the development and maintenance of connective tissues and bones • Role in wound healing and Schwann cell-mediated myelination of dorsal root ganglion neurons	Antioxidant	Cosmetic and dermatological product additive	DB11352	54679073	62
Levothyroxine	• Synthetic levoisomer of thyroxine (T4) hormone • $C_{15}H_{11}I_4NO_4$	• De-iodinated to form triiodothyronine (T3) • T3 binds nuclear thyroid hormone receptors and the hormone-receptor complex • T3 regulates expression of genes involved in cellular growth and differentiation and the metabolism of proteins, carbohydrates and lipids • Cardiac stimulatory effect	• Endocrine • Regulatory	Hypothyroidism (deficiency syndromes)	DB00451	5819	140
Melatonin	• Hormone/ biogenic amine • $C_{13}H_{16}N_2O_2$	• Blood-brain barrier permeable pineal hormone that regulates circadian and seasonal rhythms • Free radical scavenging and regulation of apoptotic pathways • "Implicated in the regulation of mood, learning and memory, immune activity, dreaming, fertility and reproduction" • Inhibition of microglial activation	• Endocrine • Antioxidant • Anti-apoptotic	Circadian rhythm disorders	DB01065	896	81, 183
Methylthio-adenosine	• Polyamine pathway nucleoside metabolite • 5'-S-methyl-5'-thioadenosine • $C_{11}H_{15}N_5O_3S$	• Modulates DNA and protein methylation • Involved in the regulation of gene expression, cell signaling, proliferation, differentiation and apoptosis • Needed for the regeneration of adenosine and methionine	• Hepatoprotective • Immunomodulator • Neuroprotective • Antioxidant	-	DB02282	439176	93, 120
Nestorone (Segesterone acetate)	• Synthetic 19-nor-progesterone derivative and steroidal progestin • $C_{23}H_{30}O_4$	• Highly potent and selective progesterone receptor agonist • 100 times more active than progesterone in the reproductive system • Does not bind androgen receptors	• Reproduction • Anti-ovulatory	Contraceptives	DB14583	108059	45
Progesterone	• C21-steroid hormone • $C_{21}H_{30}O_2$	• Binds intracellular and membrane progesterone receptors in the CNS • Allopregnanolone (derivative) is a potent modulator of GABAA receptors involved in the regulation of myelin gene expression in the periphery • Maintenance of pregnancy • Exerts inhibitory effects on estrogens	• Reproduction • Anti-ovulatory • Neuroregulatory	Contraceptives	DB00396	5994	45, 82

Shikimic Acid	• Cyclohexenecarboxylic acid from star anise • Hydrogenated metabolite of the shikimate pathway • $C_7H_{10}O_5$	• Precursor for the synthesis of aromatic compounds in plants and microorganism • Precursor for the synthesis of the neuraminidase inhibitor Oseltamivir (Tamiflu®) and the antibiotic (6S)-6-fluoroshikimic acid	• Anti-influenza • Antioxidant • Anti-inflammatory • Anti-tumor	Shikimic acid derivative in Tamiflu® is approved	-	8742	101
Sobetirome (GC-1)	• Diphenylmethane • $C_{20}H_{24}O_4$	• Selective T3 agonist • "Devoid of the adverse effects associated with hyperthyroidism and unique among thyromimetics for its ability to cross the blood-brain barrier and distribute to the CNS from a systemic dose" • Regulates myelin gene transcription and biochemistry in the CNS via agonism at thyroid receptors (TR) • 10-fold selectivity for TRβ over TRα	• Antilipidemic • Antiatherosclerotic	-	DB07425	9862248	66, 201
T3 hormone (Liothyronine)	• 3,5,3′-triiodothyronine • $C_{15}H_{12}I_3NO_4$	• Increases energy expenditure and carbohydrate and protein metabolism • Stimulates growth, maturation and metabolism of tissues • Involved in myelination and development of synaptic processes by regulating the timing of OPC differentiation and maturation	• Endocrine • Neuroregulatory	Hypothyroidism	DB00279	5920	66, 208, 211
Vitamin D3 (calcitriol and cholecalciferol)	• Lipid-soluble secosteroids • Vitamin D metabolites	• Ingested through diet or produced in the skin upon exposure to ultraviolet irradiation • Cholecalciferol is the endogenous form of vitamin D • Calcitriol is the biologically active form of vitamin D (1,25-dihydroxyvitamin D3) that acts as a calcitrophic hormone • Immune modulation through receptors expressed on macrophages, dendritic cells, B and T cells • Receptor ligation on osteoblasts regulates transcription • Regulator of peripheral calcium and phosphorus homeostasis	• Immunomodulator • Anti-osteoporotic • Antioxidant	• Hypopara-thyroidism • Vitamin D deficiency and rickets	DB00169, DB00136	5280795, 5280453	111, 131, 132, 139, 143, 178
Vitamin K1 (Phylloquinone)	• Fat-soluble dietary form of vitamin K • $C_{31}H_{46}O_2$	• Cofactor in the post-translational carboxylation of proteins required for blood coagulation (Factors II (prothrombin), VII, IX and X) • Metabolites of vitamin K accumulate in the brain	Clotting cofactor	Coagulation disorders	DB01022	5284607	143

Table S5D. Small molecule protonophores

Name	Structure	Mechanism(s) of action	Biological effect(s)	FDA approved indication(s)	Accession number		Article Number
					DrugBank	PubChem CID	
2,4-dinitrophenol (DNP) i.e. MP101	Related to trinitrophenol (picric acid) $C_6H_4N_2O_5$	Uncouples oxidative phosphorylation by allowing protons to leak across the inner mitochondrial membrane and bypass ATP synthase	Metabolic stimulant	-	DB04528	1493	9
DNP Pro-Drug MP201	Related to trinitrophenol (picric acid) $C_6H_4N_2O_5$	Uncouples oxidative phosphorylation by allowing protons to leak across the inner mitochondrial membrane and bypass ATP synthase	Metabolic stimulant	-	-	-	9, 86

Table S5E. Small molecule organic compound mixtures

Name	Formulation	Mechanism(s) of action	Biological effect(s)	FDA approved indication(s)	Accession number		Article Number
					DrugBank	PubChem CID	
Anthocyanins (ANT)	• Phenolic phytonutrients extracted and purified from grape skin • Flavonoid pigments • Composition: malvidin, peonidin, cyanidin, delphidin, petunidin and pelargonidin	• RNS and ROS scavenging • Metabolic precursors • Can suppress immune cell migration and proinflammatory cytokine expression	• Antioxidant • Anti-inflammatory	-	-	145858	24
Cucurbita maxima extract	• Petroleum ether extract of pumpkin seed • Composition: "30% unsaturated fixed oil (linoleic and oleic fatty acids), triterpenoids flavonoids, coumarins, saponins, cucurbitacin, vitamins, minerals notably zinc, phytosterols, amino acid known as cucurbitin… high amount of carotenoid content which include lutein and beta-carotene"	• RNS and ROS scavenging • Metabolic precursors	• Anthelminthic • Antioxidant • Anti-inflammatory	-	-	-	127
Epimedium flavonoids	• Primary component of horny goat weed plant (*Epimedium Sagittatum*) extract • Secondary plant metabolites derived from phenylalanine • Composition[17]: Icariin, epimedin A, B, and C, hexandraise A	• Used in traditional Chinese medicine as a kidney tonic and antirheumatic medicine • Prenylated flavonoids demonstrated to be the main bioactive components • Icariin is a phoshphodiesterase-5 inhibitor and phytoestrogen	• Osteoprotective • Neuroprotective • Cardiovascular • Anti-inflammatory • Reproductive	-	DB12052	5318997	99
Kolaviron[18]	• Biflavonoid complex isolated from seeds of the *Garcinia kola* plant • Composition: Kolaflavonone, garcinia biflavonones 1 and 2	• Prevents lipid peroxidation and protein damage • Inhibits intracellular ROS production	• Anti-inflammatory • Antioxidant • Anti-bacterial/ fungal • Cytoprotective	-	-	155169	136, 137

Polyprenols	• Bioactive long-chain isoprenoid alcohols • Contain a hydroxyl group and a long unsaturated isoprenyl chain • Chain length of natural polyprenols varies from 6 to 40 isoprene units • Isolated from the green verdure of *Picea abies (L.) Karst*	• Precursors to terpenes and steroids • Modified to metabolically active forms via α-saturation and phosphorylation in the liver • Involved in cell wall biosynthesis • Regulators of cell proliferation • ROS scavenging	• Hepatoprotective • Neuroprotective • Antioxidant • Mildly immune-modulatory	Ropren® has completed a phase III clinical trial	-	-	87
Sativex (Nabiximols)	• Combination of phytocannabinoids • Equivalent amounts of Δ9-tetrahydro-cannabinol (Δ9-THC) and cannabidiol (CBD)-botanical drug substance (BDS) • Contains other minor cannabinoids, flavonoids and terpenes from two cannabis plant varieties	• Combination of THC and CBD mechanisms of action • Partial agonists of CB1 and CB2 receptors	• Anti-inflammatory • Antioxidant • Psychoactive (analgesic, euphoric and anticonvulsive)	Approved for spasticity and neuropathic pain in MS by Health Canada	DB14011	44148067	47

Table S5F. Protein biologics

Name	Classification	Structure	Mechanism(s) of action	Biological effect(s)	FDA approved indication(s)	Accession Number			Article Number
						DrugBank	PubChem CID	UniProt	
Anti-EphrinB3	Antibodies	Recombinant Human Ephrin-B3 Fc IgG	• Blockade of EphrinB • EphrinB is a transmembrane signalling protein that negatively regulates the formation of corticospinal tract axons, and is expressed on adult CNS oligodendrocytes	Neuroregenerative	-	-	-	-	175
Anti-Nogo-A	Antibodies	Highly purified mouse monoclonal IgG1 clone 11C7	• Neutralization of Nogo-A • Nogo-A is an inhibitor of neuronal growth and plasticity, and is expressed on oligodendrocytes	Neuroregenerative	Anti-Nogo-A GSK1223249 tested in phase I trial for RRMS (NCT01435993)	-	-	-	72
Anti-SEMA4D	Antibodies	• Mouse monoclonal IgG1 clone 67-2 • Mouse and human reactivity	• Blocking of SEMA4D signals SEMA4D has multiple roles, including: • Axon-guidance factor • Glial activation • Inhibition of OPC migration and differentiation • Regulation of blood-brain barrier tight junctions	• Anti-inflammatory • Anti-proliferation/ cancer • Neuroprotective	Anti-SEMA4D Pepinemab has completed phase I clinical trial for MS (NCT01764737)	-	-	-	171
Elezanumab (ABT-555)	Antibodies	• Fully humanized monoclonal IgG • Human, NHP, rat and mouse reactivity	• Specific for repulsive guidance molecule A (RGMa) • RGMa inhibits axonal growth, myelination and oligodendrocyte regeneration	• Neuroprotective • Neuroregenerative	Ongoing phase II trials for RRMS and PMS (NCT03737851) (NCT03737812)	DB15240	-	-	35
Temelimab (GNbAC1)	Antibodies	Humanized monoclonal IgG4	• Targets multiple sclerosis-associated retrovirus viral envelope protein (HERV-W Env), which is expressed in MS CNS lesions • Reduces HERV-W Env-induced inhibition of OPC differentiation and nitrosative stress • HERV-W Env promotes inflammatory microglial polarization and axonal degeneration	Gliomodulatory	Recruiting for phase IIa trial in RRMS (NCT04480307)	DB15634	-	-	12
Anti-LINGO-1	Antibodies	• Clone 1A7: Human IgG1 monoclonal antibody	• Antagonist of LINGO-1	• Neuroregenerative • Neuroprotective	-	-	-	-	61, 210

		with human and rat reactivity • Clone 3B5: Murine IgG1 monoclonal antibody with human and mouse reactivity	• LINGO-1 is an inhibitor of oligodendrocyte differentiation and axonal regeneration						
Opicinumab (BIIB033)	Antibodies	• Human IgG1 monoclonal antibody • Binds human and mouse LINGO-1	• Antagonist of LINGO-1 • LINGO-1 is an inhibitor of oligodendrocyte differentiation and axonal regeneration	• Neuroregenerative • Neuroprotective	Ongoing phase II trial in RRMS (NCT03222973)	DB14959	-	-	23, 61, 50, 116
HIgM12	Antibodies	Human serum derived IgM12	• Binds neurons and induces neurite extension • Binds gangliosides GD1a and GT1b with high affinity • Increases brainstem NAA concentrations	Neuroprotection	-	-	-	-	194
rHIgM12	Antibodies	Monoclonal IgM expressed from two plasmids encoding the heavy and light chain coding sequences and the human J chain	• Binds neurons and induces neurite extension • Binds gangliosides GD1a and GT1b with high affinity • Increases brainstem NAA concentrations	Neuroprotection	-	-	-	-	196
rHIgM22	Antibodies	Recombinant human IgM with human H and L chains, murine J chain	• Binds to oligodendrocytes and myelin in the CNS • Promotes oligodendrocyte process outgrowth • Increases brainstem NAA concentrations	Remyelination	Completed phase I trial for RRMS (NCT02398461)	-	-	-	36, 43, 122, 195
Erythropoietin (EPO)	Growth and regulatory factors	• Glycoprotein cytokine • 165 amino acids	• Hematopoietic growth factor • Stimulates erythrocyte production • Involved in developmental differentiation of neuronal precursor cells • Induces differentiation of OPCs	• Anti-oxidative • Anti-inflammatory • Anti-apoptotic • Neuroprotective	Anemia	DB00016	-	P07321	150, 168
Fibroblast growth factor 2 (FGF2)	Growth and regulatory factors	• Cell signaling protein • Related to interleukin 1-beta	• Interacts with four cell surface receptor subtypes • Mediator of neurogenesis • Binds to heparin and heparan sulfate	• Angiogenic • Mitogenic	-	-	5486993	P13109	7
Fibroblast growth factor 21 (FGF21)[1]	Growth and regulatory factors	• Hormone/ myokine • 181 amino acid peptide derived from a 209	• Stimulates oxidation of fatty acids and generation of ketone bodies • Inhibitor of lipogenesis	Metabolic and endocrine regulation	PEGylated FGF21 in clinical	DB15365	-	Q9JJN1	94

		amino acid mature protein	• Stimulates glucose uptake in differentiated adipocytes • Crosses the blood-brain barrier		trials for liver disease				
Insulin-like growth factor 1 (IGF-1)	Growth and regulatory factors	• Mitogenic globular polypeptide • 70 amino acids	• Similar to insulin by structure and function, but has greater growth-promoting activity • Signals through the tyrosine kinase type I receptor (IGF-IR) • Acts as a neurotrophin for motor nerves	• Neuroprotective • Tissue growth	IGF-1 deficiency	DB01277	5748425	P08025	69
Leukaemia inhibitory factor (LIF)	Growth and regulatory factors	• IL-6 family cytokine and growth factor • 180 amino acids	• Promotes developmental myelination • Promotes oligodendrocyte maturation after myelin injury • (156) Delivered in poly(lactide-co-glycolide) nanoparticles “targeted using NG2 chondroitin sulphate proteoglycan antibodies to OPCs”	• Neuroregenerative • Immunomodulatory	In clinical trials for infertility	DB06562	-	P09056	110, 156
Macrophage colony-stimulating factor (M-CSF)	Growth and regulatory factors	• Cytokine CSF1 • Three different biologically active dimeric isoforms: proteoglycan, glycoprotein and cell surface protein	• Hematopoietic growth factor • Regulates cell survival, proliferation and differentiation of myeloid cells • Promotes anti-inflammatory microglial phenotype and the release of trophic factors • Regulates the phagocytic activity of microglia	Immunomodulatory	Related drug Sargramostim completed phase II trial for Alzheimer's disease	-	-	P07141	95
Nerve Growth Factor (NGF)	Growth and regulatory factors	• Signalling protein • Endosomal and secreted	• Regulates the growth, maintenance, proliferation and survival of neurons • Involved in allergic inflammatory responses	Neurotrophic	-	DB12620	-	P01139	184
Neuregulin-1 (rhNrg-1β1 peptide)	Growth and regulatory factors	• Recombinant human peptide with active epidermal growth factor-like domain • Multiple trans-membrane and secreted isoforms • Delivered in poly (lactic-co-glycolic) acid nanoparticles	• Cell adhesion molecule • Acts as a neurotrophin by regulating neurotransmission and synaptic plasticity • Involved in the regulation of oligodendrocytes and neurons	Neuroregulatory	Heart failure drug Neucardin fast-tracked for FDA approval	-	-	Q02297	83

Thymosin beta 4	Growth and regulatory factors	• Small peptide • 43 amino acids	Role in actin polymerization, cell motility and organization of the cytoskeleton	• Angiogenesis • Tissue repair	Completed numerous trials for wound healing	DB12003	-	P20065	213
Transforming growth factor-beta1 (TGF-β1)	Growth and regulatory factors	• Highly pleiotropic cytokine • 390 amino acid precursor processed to a mature peptide of 112 amino acids	• Binds TGF-beta Receptors I and II • Produces a signalling cascade that regulates the transcription of multiple genes related to immune function, cell survival and migration	Immunomodulatory (among others)	-	-	-	P04202	65
Tuftsin	Growth and regulatory factors	• Tetrapeptide located in the Fc-domain of the IgG heavy chain • $C_{21}H_{40}N_8O_6$	• Secreted by splenocytes • Stimulates the phagocytic activity of blood polymorphonuclear leukocytes and neutrophils	Immunostimulant	-	-	156080	-	181
Galectin-1	Growth and regulatory factors, Other	• Highly conserved animal lectin • 135 amino acids • Contains a carbohydrate recognition domain (CRD) that binds complex carbohydrates	Modulates cell-cell and cell-glycan interactions by binding beta galactosides	Immunomodulatory (among others)	-	-	-	P16045	154
Ancrod (Viprinex)	Inhibitors and proteases	Thrombin-like serine protease originally isolated from the venom of the Malayan pit viper	• Defibrinogenating agent • Cleaves fibrinogen to small peptides for rapid clearance	Anticoagulant	Thrombosis	DB05099	-	P26324	141
Apamin	Inhibitors and proteases	• Derived from dry bee venom (2-3% apamin peptide) • Neurotoxin • 18 amino acids	• Selectively blocks axonal Kv1.3 potassium channels in the central nervous system, as well as on immune cells and microglia • Blood-brain barrier permeable	• Neuroprotective • Anti-inflammatory	Completed phase II trial for Parkinson's disease	-	-	P01500	118
P110	Inhibitors and proteases	Seven amino acid peptide conjugated to the cell permeating peptide TAT47–57 for intracellular delivery	• Selective mitochondrial Drp1 peptide inhibitor • Hyperactivation of Drp1 causes oxidative stress and oligodendrocyte death	• Antioxidant • Neuroprotective	-	-	-	-	102
Pam2CSK4 (P2C)	Inhibitors and proteases	• Synthetic diacylated lipopeptide • $C_{65}H_{126}N_{10}O_{12}S$	• TLR2 ligand • Repeated administered at low dose induces systemic TLR2 tolerance	• Innate immune response activation (adjuvant-like)	-	-	9989023	-	190
XPro1595	Inhibitors and proteases	• Dominant-negative TNF analogue	• Second generation selective inhibitor of soluble TNF • Blood-brain barrier permeable	Immunosuppressive	Ongoing phase I trial in	-	-	-	80

		• Engineered mutations prevent binding to TNFR1 and TNFR2	• "Exchanges subunits with and thus destroys the native homotrimeric soluble TNF ligand, while fully preserving transmembrane TNF activity"		Alzheimer's disease				
Protamine	Inhibitors and proteases, Other	• Natural cationic polypeptide • Arginine-rich for DNA binding • 49-54 amino acids	• Endogenous function is chromatin condensation in sperm • Used clinically to halt the anticoagulant effects of heparin • Delays the absorption of insulin	• 'Anti-anticoagulation' • Chromatin regulation	Heparin overdose	DB13700	-	P04554	91
TnP peptide	Inhibitors and proteases, Other	• Small stable synthetic peptide derived from fish venom • 13 amino acids	"Systemic and CNS localized effects that result in inhibition of traffic of inflammatory leukocyte to CNS and demyelination"	• Anti-inflammatory • Anti-allergic	-	-	-	-	89
Glatiramer Acetate (GA)	Peptide mimetics and decoys	• A mixture of synthetic polypeptides • Random polymer of alanine, glutamic acid, lysine and tyrosine	• Neurotrophin mimetic • Structurally similar to myelin basic protein	Immunomodulatory	RRMS (Copaxone)	DB05259	3081884	-	42
Plexin-A1 antagonist peptide (MTP-PlexA1)	Peptide mimetics and decoys	• Synthetic mimic peptide • T1240 to K1268 of the transmembrane domain of Plexin-A1	• Transducer of Sema3A inhibiting signals in neurons • Blocks the anti-migratory and anti-differentiation effect of Sema3A in oligodendrocytes	Neuroregulatory	-	-	-	P70206	18
Intracellular Sigma Peptide (ISP)	Peptide mimetics and decoys, Inhibitors and proteases	Peptide mimic of the wedge domain of PTPσ connected to TAT sequence to enable blood-brain barrier crossing	• Inhibitor of proteoglycan receptor protein tyrosine phosphatase sigma, PTPσ • PTPσ is expressed on neural and glial cells in the CNS • PTPσ binds repair inhibitory molecules like CSPGs	Neuroregenerative	NVG-291, a close analog of ISP, is in preparation for clinical trials in spinal cord injury	-	-	B0V2N1	103, 129
TAT-G-G pep	Peptide mimetics and decoys, Inhibitors and proteases	• GluR2NT1-3-2 peptide fused to the cell membrane transduction domain of HIV-1 TAT peptide to enable intracellular delivery	• Blocking of GluR2–GAPDH complex and glutamate receptor-mediated excitotoxicity without interfering with basal neurotransmission • Protects from excitotoxicity induced demyelination, axonal damage, and loss of neurons	Neuroprotective	-	-	-	-	209

Table S5G. Cellular biologics

Cell type	Tissue source	Modifications	Mechanism(s) of action[2,3]	Biological effect(s)	Article Number
Embryonic stem cells	Murine blastocyte	None	• Pluripotent and self-renewing • Can be maintained in an undifferentiated state indefinitely	Cell/ tissue repair and replacement	147
Mesenchymal stem cells	Human autologous bone marrow (RR/SPMS patients)	Culture-expanded	• Multipotent and self-renewing • Cytokine and neurotrophin production • Tissue repair	• Cellular replacement • Neurogenesis • Angiogenesis • Synaptogenesis	49
Mesenchymal stem cells	Canine adipose tissue	None	• Multipotent and self-renewing • Cytokine and neurotrophin production • Tissue repair	• Cellular replacement • Neurogenesis • Angiogenesis • Synaptogenesis	1
Mesenchymal stem cells	Embryonic stem cell line	None	• Multipotent and self-renewing • Cytokine and neurotrophin production • Tissue repair	• Cellular replacement • Neurogenesis • Angiogenesis • Synaptogenesis	78
Mesenchymal stem cells	Human adipose tissue	None	• Multipotent and self-renewing • Cytokine and neurotrophin production • Tissue repair	• Cellular replacement • Neurogenesis • Angiogenesis • Synaptogenesis	54, 153
Mesenchymal stem cells	Human bone marrow (iliac crest)	None	• Multipotent and self-renewing • Cytokine and neurotrophin production • Tissue repair	• Cellular replacement • Neurogenesis • Angiogenesis • Synaptogenesis	109
Mesenchymal stem cells	Human, canine and murine bone marrow	None	• Multipotent and self-renewing • Cytokine and neurotrophin production • Tissue repair	• Cellular replacement • Neurogenesis • Angiogenesis • Synaptogenesis	157
Mesenchymal stem cells	Murine bone marrow	None	• Multipotent and self-renewing • Cytokine and neurotrophin production • Tissue repair	• Cellular replacement • Neurogenesis • Angiogenesis • Synaptogenesis	11, 44, 56

Mesenchymal stem cells	Rat bone marrow	Induced with neurotrophin-3 and retinoic acid in culture	• Multipotent and self-renewing • Cytokine and neurotrophin production • Tissue repair	• Cellular replacement • Neurogenesis • Angiogenesis • Synaptogenesis	100
Mesenchymal stem cells	Rat placental tissue	None	• Multipotent and self-renewing • Cytokine and neurotrophin production • Tissue repair	• Cellular replacement • Neurogenesis • Angiogenesis • Synaptogenesis	78
Mesenchymal stem cells	Murine bone marrow	Stromal cell-derived factor 1α – chemokine preconditioned media	• Multipotent and self-renewing • Cytokine and neurotrophin production • Tissue repair • SDF-1α treatment promotes chemotaxis and cellular homing to the site of injury	• Cellular replacement • Neurogenesis • Angiogenesis • Synaptogenesis	14
Neurotrophic factor-secreting cells	Human adipose tissue-derived mesenchymal cells	Transduced into neurotrophic factor-secreting cells	• Multi lineage cells • Secrete significant amounts of neurotrophic factors	• Cellular replacement • Neurogenesis • Angiogenesis • Synaptogenesis	153
Neural stem cells	Rat brain tissue	None	Differentiation into neural and glial cells	• Cellular replacement • Neurogenesis	51
Neural stem cells	Murine bone marrow	None	Differentiation into neural and glial cells	• Cellular replacement • Neurogenesis	97
Neural stem cells	Murine bone marrow	LINGO-1-Fc-Transduced	Differentiation into neural and glial cells	• Cellular replacement • Neurogenesis	97
Neural stem cells	Murine induced pluripotent stem cell	None	Differentiation into neural and glial cells	• Cellular replacement • Neurogenesis	214
Neural stem cells	Rat brain tissue	Transfected with glial cell line-derived neurotrophic factor (GDNF) gene	Differentiation into neural and glial cells	• Cellular replacement • Neurogenesis	51
Neural precursor cells	Murine neonatal brain	None	Differentiation into neural and glial cells	• Cellular replacement • Neurogenesis	60
Neural precursor cells	hiPSC line 8 (Royan hiPSC8, passage 22)	None	Differentiation into neural and glial cells	• Cellular replacement • Neurogenesis	203
Neural stem cells	Immortalized human NSC line, HB1.F3 (F3), established from primary cultures of a 15-week gestational human fetal brain	None	Differentiation into neural and glial cells	• Cellular replacement • Neurogenesis	8

Oligodendrocyte progenitor cells	Immortalized human NSC line, HB1.F3 (F3), established from primary cultures of a 15-week gestational human fetal brain	F3.olig2 cells made by transduction of F3 cells with Olig2 cDNA	Differentiation into mature myelinating oligodendrocytes	• Cellular replacement • Oligodendrogenesis • Remyelination	8
Oligodendrocyte progenitor cells	Human induced pluripotent stem cell	None	Differentiation into mature myelinating oligodendrocytes	• Cellular replacement • Oligodendrogenesis • Remyelination	180
Oligodendrocyte progenitor cells	Human Wharton's Jelly (umbilical cord) mesenchymal stem cell	None	Differentiation into mature myelinating oligodendrocytes	• Cellular replacement • Oligodendrogenesis • Remyelination	117

Table S5H. RNA biologics

RNA Type	Delivery vehicle	Sequence information	Mechanism(s) of action	Biological effect(s)	Article Number
MicroRNA-146a mimic	Lipid emulsion	• Chemically modified for preferential RISC processing and to reduce degradation in vivo • Fluorescently labeled with CY3	• Upregulation of miRNA-146a expression • miRNA-146a is a negative regulator of genes in the TLR2 pathway • TLR2 signalling is upregulated in MS and inhibits OPC differentiation	• Oligodendrogenesis • Anti-inflammatory	217
Short hairpin RNA (shRNA)	Lentiviral vectors with GFP tag	• LINGO-1 specific shRNA • Sequence not reported	• Silencing of LINGO-1 gene expression • LINGO-1 inhibits OPC differentiation and axonal regeneration	Neuroregenerative	186
Small interfering RNA (siRNA)	Monocationic lipid	4 different sequences combined • CACCCTCTGGATCTACTCCAA • CACCCTCTTTCTCTTCAACAA • AAGGAGCAGGACTCAGAACAA • CTGGTGGATTATAAGCCCAAA	• Silencing of Nogo receptor NgR1 expression • NogoA is known to inhibit myelination and regeneration in the CNS	Neuroregenerative	145, 146
Small interfering RNA (siRNA)	Chitosan nanoparticles	• LINGO-1 specific siRNA • Sequence/ catalogue information not reported	• Silencing of LINGO-1 gene expression • LINGO-1 inhibits OPC differentiation and axonal regeneration	Neuroregenerative	204

Table S5I. Lipid biologics

Name	Structure	Mechanism(s) of action	Biological effect(s)	PubChem CID	Article Number
E6020	• Lipid A mimetic • Phospholipid dimer with hexa-acylated acyclic backbone	• Novel synthetic TLR4 agonist • "Mimics the physiochemical and biological properties of Lipid A moieties in Gram-negative bacteria and activates TLR4 similar to the natural Gram-negative bacteria TLR4 ligand LPS, although the response is attenuated at equimolar doses"	• Immune potentiator • Candidate for vaccine adjuvant	-	33
GD1a ganglioside	Glycosphingolipid with 2 sialic acid residues $C_{79}H_{139}N_3O_{39}$	• Signaling modulator of cell function • Gangliosides can promote OPC maturation by inhibiting fibronectin and integrin interactions	• Cell growth • Apoptosis • Differentiation	102601600	148

Table S5J. Inorganic compounds

Name	Mechanism(s) of action	Biological effect(s)	FDA approved indication(s)	Accession Number		Article Number
				DrugBank	PubChem CID	
Lithium carbonate (Li_2CO_3)	• Not fully elucidated • Inhibits multiple enzymes and interacts with a number of neurotransmitters and receptors • May reduce inositol triphosphate levels by inhibiting inositol phosphatases	• Psychiatric • Mood stabilizer	Bipolar disorder	DB14509	11125	155

Table S5K. Dietary interventions

Intervention	Structure	Method of administration	Mechanism(s) of action	Biological effect(s)	FDA approved indication(s)	Accession Number		Article Number
						DrugBank	PubChem CID	
Cholesterol	Lipid sterol $C_{27}H_{46}O$	Rodent chow	• Precursor for hormones, vitamins and bile acids • Component of cell membranes	• Endocrine • Metabolic	N/A	DB04540	5997	16
Docosahexaenoic acid (DHA)	• Omega-3 fatty acid • 22:6(n-3) • $C_{22}H_{32}O_2$ • (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoic acid	Rodent chow	• A primary structural component of the CNS • Ligand at PPARγ and α • Metabolites of DHA are anti-inflammatory lipid mediators	• Metabolic • Anti-inflammatory	Doconexent supplement	DB03756	445580	28
Eicosapentaenoic acid (EPA)	• Omega-3 fatty acid • 20:5(n-3) • $C_{20}H_{30}O_2$ • (5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenoic acid	Rodent chow or oral gavage	• Main n-3 PUFA in CNS • Precursor for prostaglandin-3 and thromboxane-3 metabolic pathways • EPA derivatives stimulate leukocyte chemotaxis, platelet aggregation and vasoconstriction	• Metabolic • Anti-inflammatory • Anti-thrombotic	Icosapent supplement	DB00159	446284	28, 40
Alternate day fasting	N/A	Restricted access to rodent chow	• Nutrient and calorie restriction • Metabolic effects	• Unclear • Multifactorial • Anti-inflammatory • Cardiovascular	N/A	-	-	128
Fasting mimicking diet (FMD)	N/A	3-day fasting cycles	• Nutrient and calorie restriction • Metabolic effects	• Unclear • Multifactorial • Anti-inflammatory • Cardiovascular	N/A	-	-	32

Table S5L. Physiological interventions

Intervention	Method of administration	Mechanism(s) of action	Biological effect(s)	FDA approved indication(s)	Article Number
Electroacupuncture therapy	Electrical stimulation via stainless steel needles inserted adjacent to the thoracic vertebral canal	• Relief of nociceptive pain and promotion of repair through modulation of serotonergic receptors • Can stimulate the release of β-endorphin and adrenocorticotropic hormone	• Analgesic • Tissue repair	Devices are approved	100, 220
Prolonged electrical stimulation	CNS-implanted stimulation device	• Relief of nociceptive pain and promotion of repair through modulation of serotonergic receptors • Can stimulate the release of β-endorphin and adrenocorticotropic hormone	• Analgesic • Tissue repair	Devices are approved	105
Pulsed focused ultrasound[4]	Transcranial transducer with three different temporal frequency patterns	• Activation of central neural circuits • Stimulation of local cytokine expression • Transient BBB disruption • Heating deep tissue	Tissue engineering and remodelling	Devices are approved	135
High-intensity exercise interval training	Progressive increase in running speed on treadmill, 5 days per week	• Multiple but unclear • Presumed to be anti-inflammatory and/or upregulate growth factor secretion • Induction of neurogenesis and repair	• Neuroregulatory • Anti-inflammatory • Psychological • Metabolic	N/A	124
Low-intensity continuous exercise training	Progressive increase in running speed on treadmill, 5 days per week	• Multiple but unclear • Presumed to be anti-inflammatory and/or upregulate growth factor secretion • Induction of neurogenesis and repair	• Neuroregulatory • Anti-inflammatory • Psychological • Metabolic	N/A	124
Voluntary exercise	Free access to running wheel installed in cage	• Multiple but unclear • Presumed to be anti-inflammatory and/or upregulate growth factor secretion • Induction of neurogenesis and repair	• Neuroregulatory • Anti-inflammatory • Psychological • Metabolic	N/A	76, 107
Environmental enhancement	Housing in a complex environment	Enhances neurogenesis and synaptic plasticity in the hippocampus	• Psychological or cognitive • Neuroregulatory	N/A	3
Socialization	Individual and group housing	Enhances neurogenesis and synaptic plasticity in the hippocampus	• Psychological or cognitive • Neuroregulatory	N/A	106

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