XXIII Encuentro de Cooperación Farma-Biotech

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Maresins as a new treatment for injuries and diseases of the nervous system

UAB
Universitat Autònoma de Barcelona

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MINISTERIO DE CIENCIA E INNOVACIÓN
AGENCIA ESTATAL DE INVESTIGACIÓN

MEDICAMENTOS INNOVADORES
Plataforma Tecnológica Española

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The Team

Overview

Neuroresolving Therapeutics

Mission

To provide **new therapeutic** solutions to **neurodegenerative and neuroinflammatory diseases** that have no cure

Product

First in Class product, a natural lipid, pro-resolving lipid mediator family.

Current status: Non-regulatory **preclinical in vivo experimental** in **Traumatic Spinal Cord Injury (SCI), Amyotrophic Lateral Sclerosis (ALS)** and **Multiple Sclerosis (MS**)

IP: 10 patent applications belonging to two families (US granted, AU, EP, AU, IL, IN, CN, CA, JP)

Scientific Project Leader: Rubèn Lopez Prof in UAB

Researcher in Neuroscience Institute, KOL in CNS diseases and Neuroinflammation

Funding accomplished:

over 900,000€ from **Caixaimpulse** & **Health Research La Caixa Banking Foundation & Fundación Luzón**, first ALS patient association in Spain, **Spanish ministry of Science** and Innovation, **AGAUR**, **UAB** and **Barcelona Activa**

The Institution

Neuroresolving Therapeutics

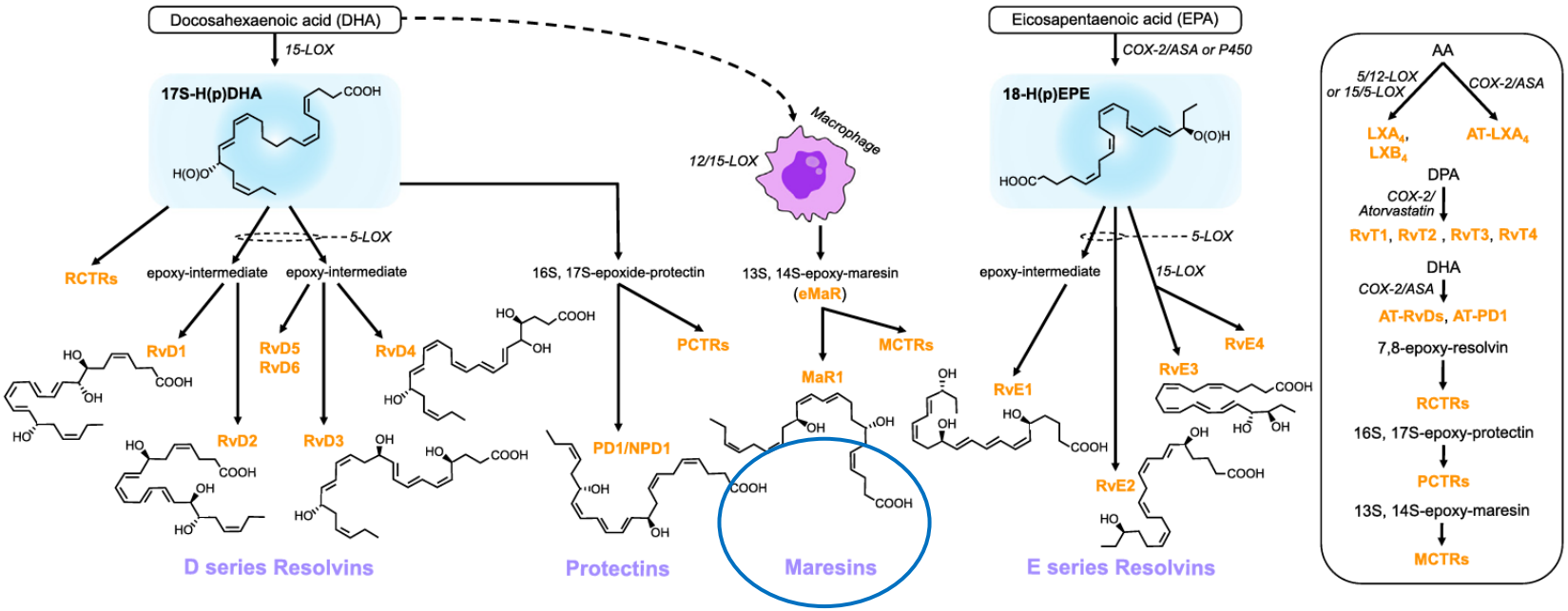
The Universitat Autònoma de Barcelona is located at position 149 in the world ranking and is leading Spanish universities according to the QS World University Rankings 2024,. With regards to Neurosciences the Universitat Autònoma de Barcelona is in the 58th position in the world ranking of the best universities.

Dr. Rubèn Lopéz Vales is Full Professor at the Department of Cell Biology, Physiology and Immunology and Group Leader of the Group of Neuroplasticity and Regeneration. He has published 62 articles in international specialized periodicals and has 3103 citations and an h-index of 35. Dr López Vales is recipient of an Icrea Academia.

https://www.usnews.com/education/best-global-universities/neuroscience-behavior?region=europe

The product

Neuroresolving Therapeutics



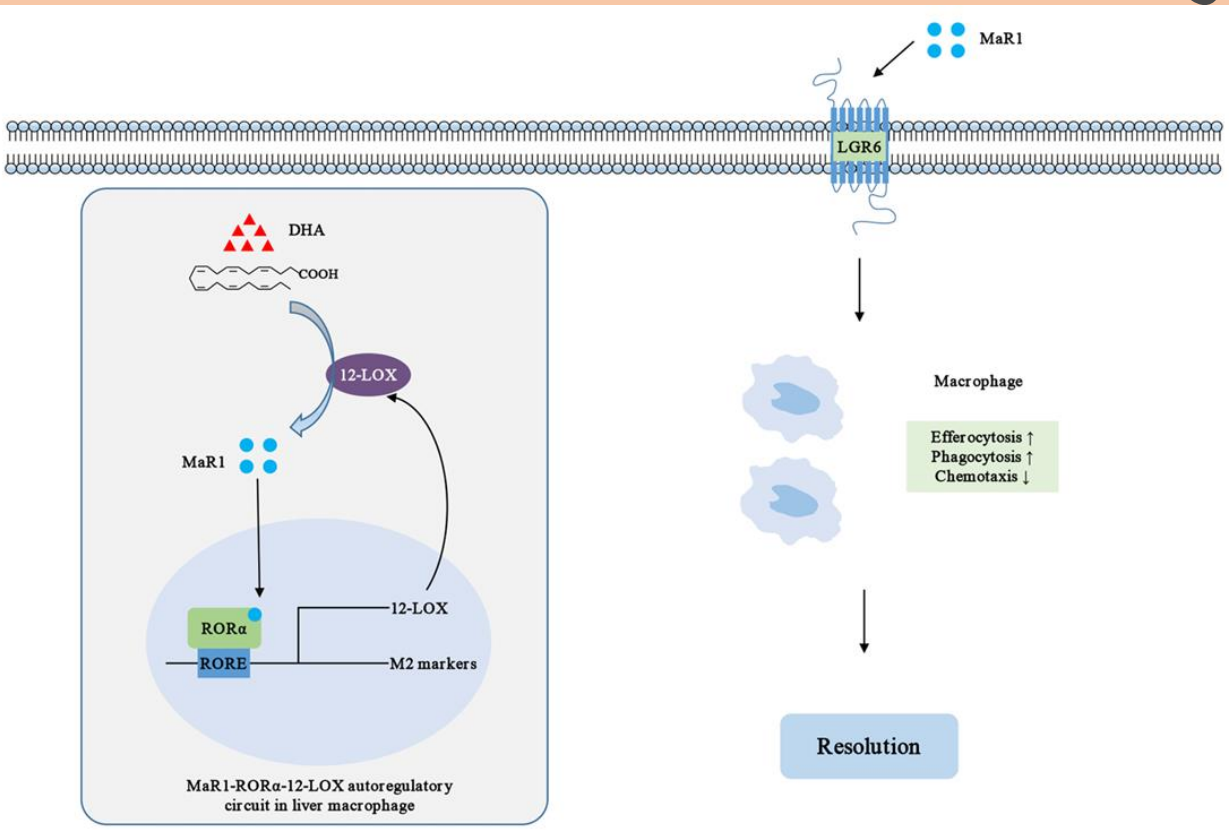
Maresin 1 (MaR1) is a macrophage-derived mediator of inflammation resolution coined from macrophage mediator in resolving inflammation. Maresin 1, and more recently defined maresins, is a 12-lipoxygenase-derived metabolite of the omega-3 fatty acid, docosahexaenoic acid (DHA), that possess potent anti-inflammatory, pro-resolving, protective, and pro-healing properties similar to a variety of other members of the specialized proresolving mediators (SPM) class of polyunsaturated fatty acid (PUFA) metabolites. SPM are dihydroxy, trihydroxy, and epoxy-hydroxy metabolites of long chain PUFA made by certain dioxygenase enzymes viz., cyclooxygenases and lipoxygenases.

The research group of Dr Lopez Vales has shown that the synthesis of SPM is impaired in ALS, MS, SCI mice and/or patients.

Source: https://doi.org/10.1016/j.phrs.2022.106337 ; DOI: 10.1016/j.pharmthera.2021.107879

The Target

Neuroresolving Therapeutics



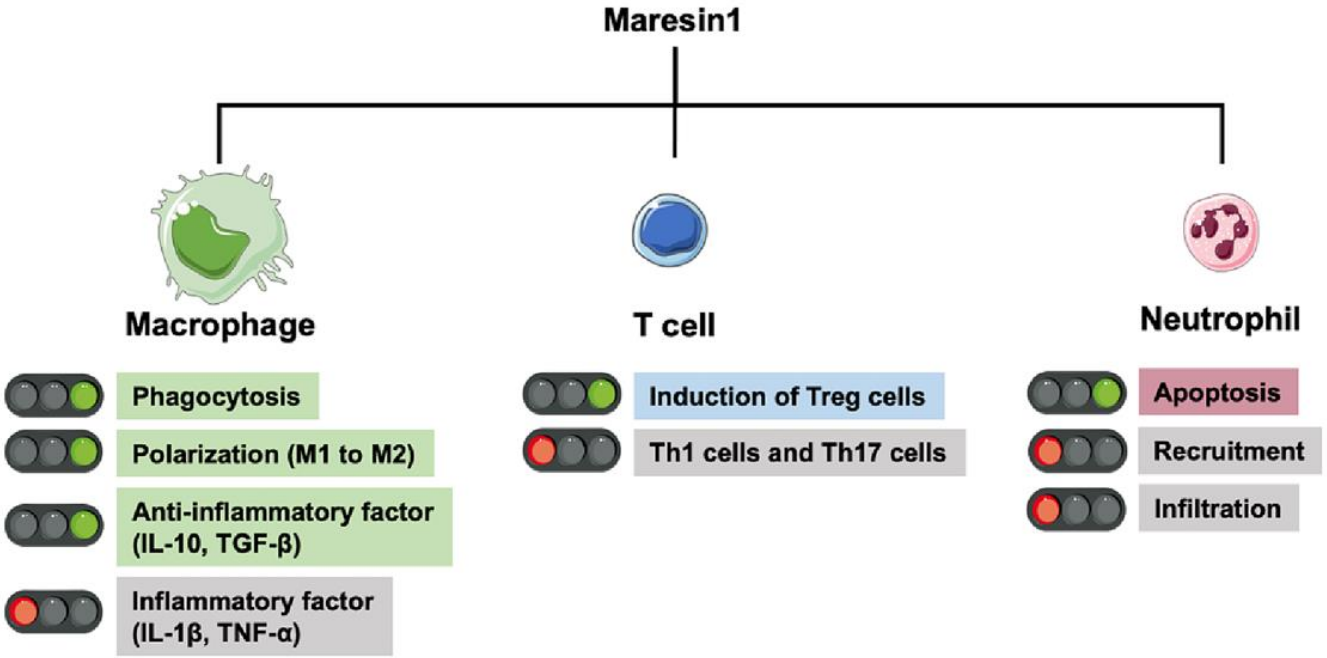
Maresin-1 promotes inflammation resolution via RORα or LGR6. In hepatic macrophages, DHA-derived maresin-1 binds to the nuclear receptor RORα, resulting in increased M2 polarization and 12-LOX expression. Then, 12-LOX promoted DHA metabolism to synthesize more maresin-1. This MaR1-RORα-12-LOX autoregulatory circuit in liver macrophage led to the resolution of NASH. In contrast, maresin- 1 binds to the G-protein couple receptor,, LGR6, leading to increased macrophage phagocytosis and efferocytosis, which promotes inflammation resolution.

DHA, docosahexaenoic acid; LOX, lipoxygenase; MaR1, maresin-1; RORα, retinoic acid-related orphan receptor α; LGR6, leucine-rich repeat domain-containing G protein-coupled receptor 6; NASH, nonalcoholic steatohepatitis.

Source:https://doi.org/10.1016/j.phrs.2022.106337

Innovative mechanism of action

Neuroresolving Therapeutics



Molecular biological roles of maresin-1 (MaR1) in regulating inflammatory cells. MaR1 enhances the phagocytic capacity of macrophages, promotes their polarization toward an M2-like macrophage, and stimulates the production of anti-inflammatory factors. Conversely, MaR1 inhibits the production of inflammatory factors. Additionally, MaR1 increases the induction of Regulatory T cells (Tregs) while decreasing the generation of T Helper Cell 1 (Th1 cells) and T Helper Cell 17 (Th17 cells), thus promoting the resolution of inflammation to some extent. Moreover, MaR1 promotes apoptosis of neutrophils, thereby reducing their recruitment and infiltration. Overall, MaR1 exhibits significant anti-inflammatory and pro-resolving effects.

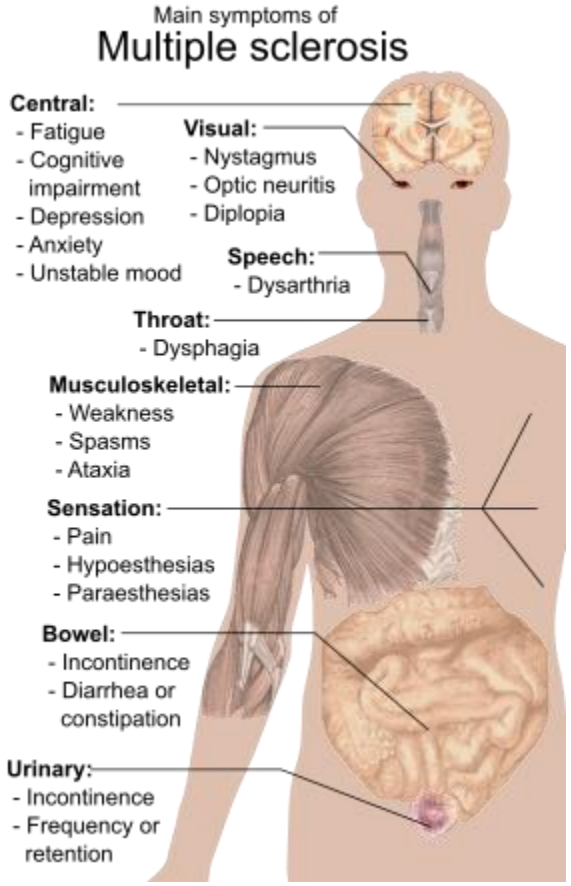
IL-10: interleukin-10; TGF-β: transforming growth factor-β; IL-1: interleukin-1; TNF-α: tumor necrosis factor-α; Th1 cells: T Helper Cell 1; Th17 cells: T Helper Cell 17

Source: DOI: 10.1016/j.intimp.2023.110308

Therapeutic indications: Multiple sclerosis

Neuroresolving Therapeutics

Multiple sclerosis (MS) is an autoimmune degenerative disease in which the insulating covers (myelin sheaths) of nerve cells in the brain and spinal cord are damaged. Associated with this is the inflammation of the loci where the lesions take place. This damage disrupts the ability of parts of the nervous system to transmit signals, resulting in a range of signs and symptoms, including physical, mental, and sometimes psychiatric problems. Specific symptoms can include double vision, visual loss, muscle weakness, and trouble with sensation or coordination. MS takes several forms, with new symptoms either occurring in isolated attacks (relapsing forms) or building up over time (progressive forms). In the relapsing forms of MS, between attacks, symptoms may disappear completely, although some permanent neurological problems often remain, especially as the disease advances.



The global prevalence in 2020 is 35.9 per 100,000 people. The current treatment is based in the use of immunomodulators to diminish the inflammation. First line treatments are Interferons and glatiramer acetate, and second line treatments include fingolimod, teriflunomide, and dimethyl fumarate. The first and second line of treatments cause lymphocytopenia. Third lines of treatments are more selective and for example Ocrelizumab is a humanized anti-CD20 monoclonal antibody that diminished levels of B lymphocytes with out affecting T lymphocytes and hence not causing widespread immunodeficiency.

Source: DOI: 10.1016/j.intimp.2023.110308

Experimental evidence in support of Multiple Sclerosis

Neuroresolving Therapeutics

In the publication Sánchez-Fernández et al. (2022) from Dr. Lopez-Vales' laboratory, it was demonstrated that there is impaired synthesis of SPM in MS mouse (EAE) and in MS patients. Moreover, exogenous administration of MaR1 diminishes the levels of pro-inflammatory cytokines, reduces the infiltration of leukocyte and favors the conversion of macrophages and CD4 cells towards an anti-inflammatory state.

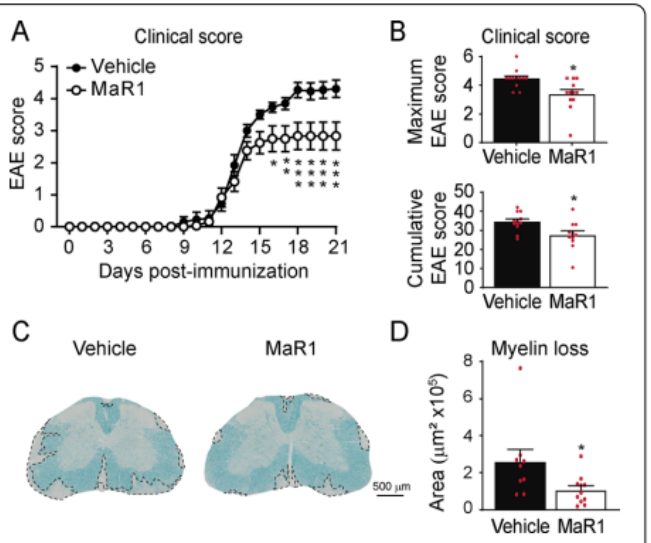


Fig. 10 Effects of MaR1 on neurological deficits and myelin loss in EAE mice. **A**, **B** Graphs showing the clinical score of EAE mice treated with MaR1 or vehicle over disease progression (**A**), as well as the maximum and cumulative EAE score (**B**). **C** Graph showing the quantification of myelin loss in the lumbar spinal cord of MaR1- or vehicle-treated mice at 21 days post-induction. **D** Representative histological spinal cord tissue sections stained with LFB from EAE mice treated with vehicle and MaR1. $*p<0.05$; $**p<0.01$; $***p<0.001$ vs. vehicle. Two-way ANOVA with repeated measures, Bonferroni's post hoc test in A ($n=12$ per group). Unpaired t-test in B ($n=12$ per group) and C ($n=9$ in vehicle and $n=11$ in MaR1). Data were pooled from two different experiments. Data are shown as mean ± SEM

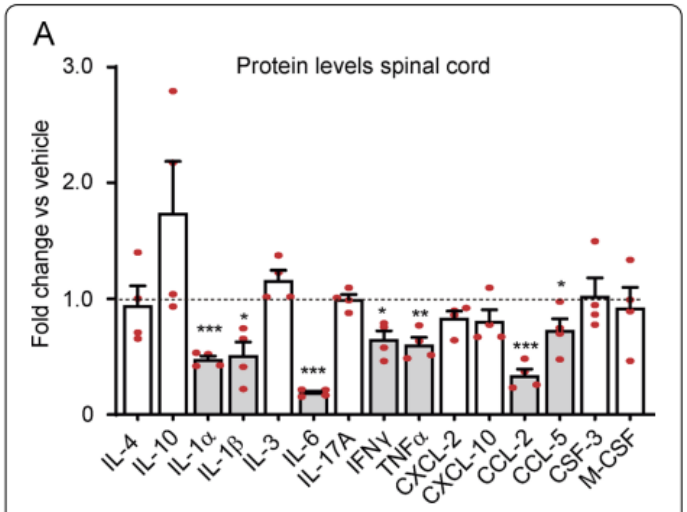


Fig. 6 MaR1 reduces pro-inflammatory cytokines in the spinal cord of EAE mice. Plot showing the fold change in cytokine protein levels of different cytokines in the spinal cord of EAE mice treated with MaR1 relative to those treated with vehicle (dotted line). Grey bars highlight those cytokines that are significantly regulated by MaR1. $*p<0.05$; $**p<0.01$; $***p<0.001$ vs. vehicle. Unpaired *t*-test ($n=4$ per group). Data are shown as mean ± SEM

Importantly, MaR1 confers protection against neurological decline and myelin loss in EAE mice

Overall, these data show that MaR1 is a promising candidate for the treatment of MS

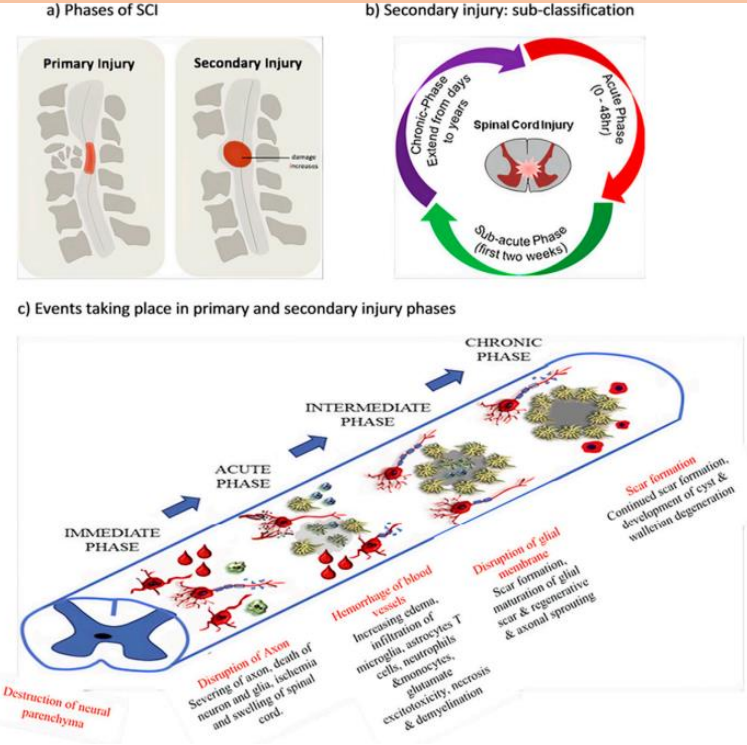
Fuente: Sánchez-Fernández et al. (2022) J of Neuroinflammation (2022) 19:27.

Therapeutic indications: Spinal Cord Injury

Neuroresolving Therapeutics

The global prevalence of spinal cord injury varies from **236 to 1298 per million of population and currently has no treatment.**

Acute SCI commonly occurs due to sudden trauma to the spine and results in fractures and vertebrae dislocation. The initial stage immediately after the injury is known as **primary injury** with features of bone fragments and spinal ligament tearing. Primary injury leads to destruction of neural parenchyma, disruption of axonal network, hemorrhage and disruption of glial membrane. The main determinants for SCI severity are the extent of initial destruction and duration of spinal cord compression. However, there is a second phase of tissue degeneration known as **secondary injury**.



The **secondary injury phase** reflects multi-featured pathological processes following the primary injury phase and lasts for several weeks. Clinical manifestation of secondary injury includes increased cell permeability, apoptotic signaling, ischemia, vascular damage, oedema, excitotoxicity, ionic deregulation, inflammation, lipid peroxidation, free radical formation, demyelination, Wallerian degeneration, fibroglial scar and cyst formation. **Disruption of blood vessels causes hemorrhage in spinal tissues, followed by invasion of monocytes, neutrophils, T and B lymphocytic cells and activation of microglia and astrocytes. This phenomenon is also associated with the release of inflammatory cytokines such as interleukin (IL)-1a, IL-1b, IL-6 and tumor necrosis factor (TNF)-α. This neuroinflammatory response is the main contributor to secondary injury**

Source: doi.org/10.3390/ijms21207533

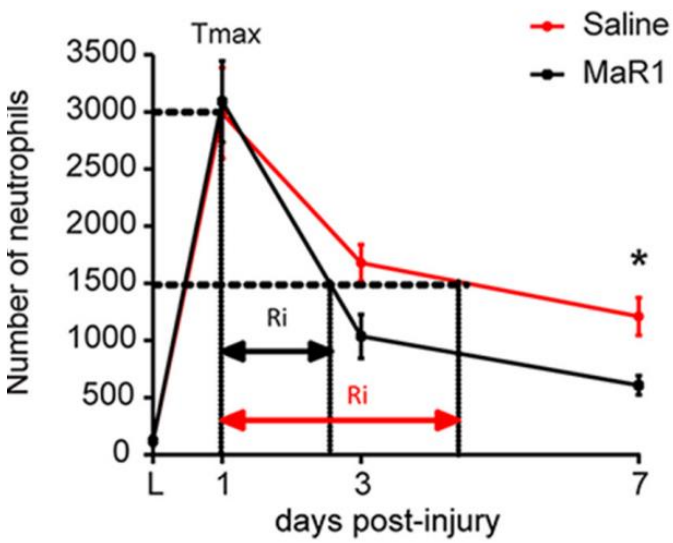
Experimental evidence in support of Spinal Cord Injury

Neuroresolving Therapeutics

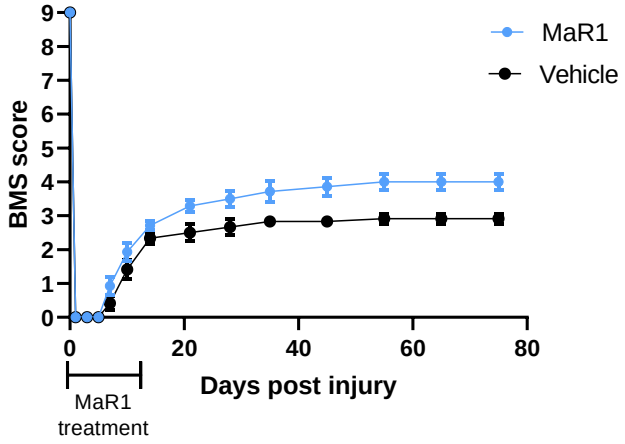
The publication *Francos Quijorna et al* (2017), from the laboratory of **Dr López-Vales' Laboratory,** has shown that the inappropriate biosynthesis of SPM in the lesioned spinal cord hampers the resolution of inflammation and leads to deleterious consequences on neurological outcome in adult female mice. After spinal cord contusion injury in adult female mice, the biosynthesis of SPM is not induced in the lesion site up to 2 weeks after injury. Exogenous administration of MaR1, a highly conserved SPM, propagated inflammatory resolution after SCI, as revealed by accelerated clearance of neutrophils and a reduction in macrophage accumulation at the lesion site. In addition, SPM facilitated several hallmarks of resolution of inflammation, including reduction of proinflammatory cytokines (CXCL1, CXCL2, CCL3, CCL4, IL6, and CSF3), silencing of major inflammatory intracellular signaling cascades (STAT1, STAT3, STAT5, p38, and ERK1/2), redirection of macrophage activation toward a pro-repair phenotype, and increase of the phagocytic engulfment of neutrophils by macrophages. Interestingly, MaR1 administration significantly improved locomotor recovery and mitigated secondary injury progression in a clinically relevant model of SCI. **These findings suggest that proresolution, immunoresolvent therapies such as MaR1 constitute a novel approach to improving neurological recovery after acute SCI**

Source: doi.org/10.3390/ijms21207533

Neutrophil recruitment and resolution indices



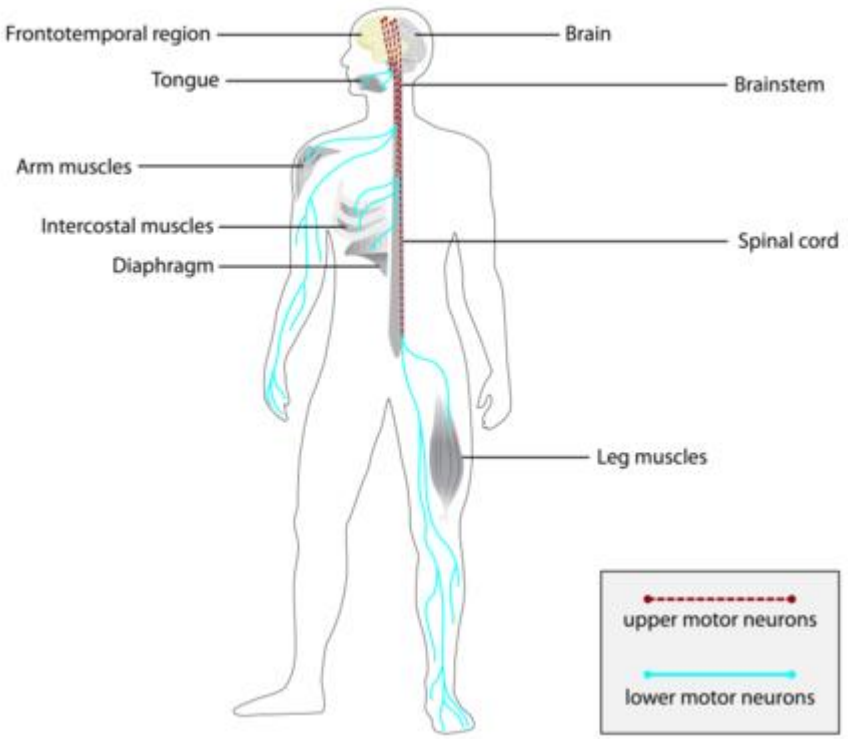
Locomotor recovery



Other indications: Amyotrophic lateral sclerosis (ALS)

Neuroresolving Therapeutics

Amyotrophic lateral sclerosis (**ALS**), also known as **motor neuron disease** (**MND**) or **Lou Gehrig's disease**, is a rare and terminal neurodegenerative disease that results in the progressive loss of motor neurons that control voluntary muscles. ALS is the most common form of the motor neuron diseases. Early symptoms of ALS include stiff muscles, muscle twitches, gradual increasing weakness, and muscle wasting. Limb-onset ALS begins with weakness in the arms or legs, while bulbar-onset ALS begins with difficulty in speaking or swallowing. Around half of people with ALS develop at least mild difficulties with thinking and behavior, and about 15% develop frontotemporal dementia.] Motor neuron loss continues until the abilities to eat, speak, move, or, lastly, breathe are lost.



Most cases of ALS (about 90% to 95%) have no known cause and are known as sporadic ALS. However, both genetic and environmental factors are believed to be involved. The remaining 5% to 10% of cases have a genetic cause, often linked to a history of the disease in the family, and these are known as familial ALS (hereditary). There is no known cure for ALS. The goal of treatment is to slow the disease progression and improve symptoms. Treatments that slow ALS include Riluzole in the EU (extends life by two to three months) and sodium phenylbutyrate/ursodoxicoltaurine in Canada.

Differential features facing the market

Neuroresolving Therapeutics

Anti-inflammatory therapy	Resolution therapy
Reduces infiltration of leukocytes	Stimulates leukocyte clearance
Immunosuppression (high risk of infections)	No immunosuppression (potentiates antibiotic effects)
Significant safety concerns: adverse cardiovascular thrombotic events, including myocardial infarction and stroke, serious gastrointestinal (GI) ulceration, bleeding, and perforation (may be fatal).	No safety concerns as no described side effects
Slows tissue regeneration	Enhances tissue regeneration
Synthetic molecules	Natural molecules
Development of resistance to the drug	No possibility of developing resistance
Normally several off target binding including cytochrome inhibition leading to drug interactions	Normally highly selective compounds
Normally high doses are required mg/kg	High affinty for the receptors lead to low doses (ug/kg)

Overall, the use of resolution therapy has overwhelming advantages over traditional anti-inflammatory therapy

Current status of development

Neuroresolving Therapeutics

Studies performed relevant animal models:

- **Toxicology studies**
  - Mice toxicology study 10d 10x
- **Primary pharmacology** for SCI, ALS and MS relevant animal models
- **Dose-finding studies**
  - Low dose and high dose effectivity studies
  - Dose optimization for oral and intravenous formulation
- **Formulation studies**
  - Stability studies
  - Oral and intravenous GMP-like pre-formulation
- **Comparative studies**
  - Riluzole (goldstandard) vs SPM (ALS)
  - Tecfidera vs SPM (MS)
- **Biomarkers**
  - Human biomarkers in blood and CSF from ALS patients
- **Regulatory preclinical regulatory and Orphan Drug Designation Roadmap ongoing**

IPR protection

Neuroresolving Therapeutics

❖ **WO2018134230A1. Specialized pro-resolving lipid mediators for use in the treatment of neurodegenerative diseases and/or autoimmune diseases. Priority date 18/17/2017**

The present invention relates to a specialized pro-resolving lipid mediator comprising maresins, D-series resolvins, E-series resolvins, protectins or lipoxins, or a combination thereof, for use in the treatment of neurodegenerative diseases and/or autoimmune diseases.

Extended to US, AU, EP, IL, IN, CN, CA, JP (granted in US; IL and AU)

❖ **WO2019016580A1. Maresins for use in the treatment of CNS injuries. Priority date**

The present invention relates to maresins, preferably maresin-1, for use in the treatment of CNS injuries preferably selected from spinal cord injury and traumatic brain injury

Extended to US and CA (granted US)

Risk Assessment

Neuroresolving Therapeutics

- **Lack of efficacy:** MaR1 is an endogenous proinflammatory resolution and so its efficacy has been proven.
- **Poor safety profile**: As the molecule is highly selective for its two targets, does not have off-target bindings, does not inhibit cytochromes and thus, it has a very clean safety profile.
- **Lack of product protection.** Being a natural compound, the molecule can not be patented. However, two patents of use have been obtained which in due course may also be extended. In addition, the orphan drug designation by EMA and FDA will give additional market exclusivity (10 and 7 years respectively). In addition, the EMA gives 8 years of data exclusivity from date of market launch.
- **Development Risk**. MaR1 being an SPM, will be efficacious. The key question is whether it will be more effective than current treatments. Our data show MaR1 has superior efficacy and highly improved safety profile compared to current treatments.
- **Regulatory.** It is unlikely that being an endogenous lipid, MaR1 will face a complex regulatory approval.
- **Lack of financing**. The compound will be licensed/codeveloped with a start up or a pharmaceutical company that can develop then product to Phase I or II. Then the product will be probably licensed again to a larger multinational pharmaceutical company that can carry out the Phase III and regulatory approval and marketing worldwide

Planned studies and funding needs

Neuroresolving Therapeutics

Pre-clinical non-regulatory

SCI

- Dose optimization
- I.V. formulation
- Test i.v. formulation
- Primary, secondary pharmacology
- National patent application
- Orphan drug designation
- SCI in pigs

MS

- Dose optimization
- Oral formulation
- Test oral formulation
- Primary, secondary pharmacology
- Comparative studies
- National patent application

ALS

- Dose optimization
- Oral formulation
- Test oral formulation
- Primary, secondary pharmacology
- Comparative studies
- National patent application
- Orphan drug designation

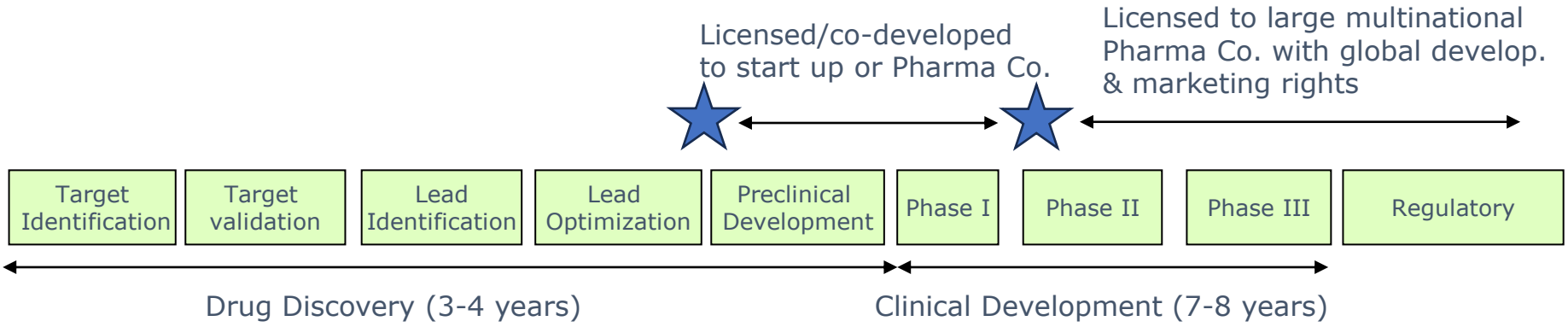
GLP-like toxicology (non GLP)
PK and PD analysis

Done
Not done

Pre-clinical regulatory (2024-2025)

Phase 1 clinical trial (2026-2027)

Partnering opportunities



What are we looking for?

A pharmaceutical company that can license or co-develop with the UAB, MaR1 to Phase I o II, with private and public Funds

The team

Neuroresolving Therapeutics

- **Principal Scientist:**
  - Rubèn Lòpez-Vales, PhD, Neuroscience Institute, UAB
- **Management team**
  - Fermín Goytisolo Gil, PhD, MBA (UAB)
  - Lucas Martín, PhD, (UAB)
  - María Arbulu, (Ph.D), MBA (Independent Consultant)
  - Marc Caro Ph.D (UAB).
- **Collaborators**
  - Mònica Povedano, PhD (Idibell)
  - Jan M Schwab (Wexner Medical Center)
  - Samuel David, (McGill University)
  - Homero Rubbo (Institute Pasteur, Uruguay)

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Want to know more

bit.ly/NeuroResolvingTx