neurofix

Novel therapies for neurological disorders

NFX88

A first in class therapy for neuropathic pain

May 2019

Neurofix

- Founded in 2015
- Offices in Salamanca and Madrid (Spain)
- Currently financed by founders and family offices
- Technology developed at the University of Balearic Islands (Spain)

Improve the life of patients with neurological diseases using rationally designed lipid molecules.

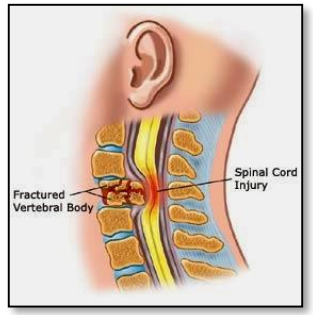
A platform of lipid-derived, first in class therapeutics

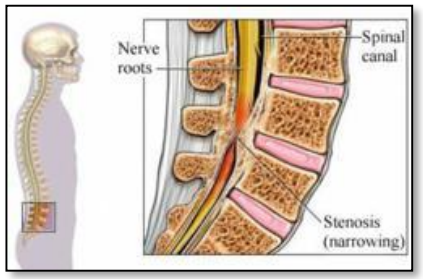
- Lipids are abundant in CNS structures, including the blood brain barrier (a succession of lipid membranes)
- The cell membrane is fundamental for transmission of neural impulses, regulating release and uptake of neurotransmitters and harbouring relevant receptors
- Most inflammation mediators that worsen neurological damage are of lipid nature
- Neurofix develops rationally designed molecules that are lipid-soluble, can readily cross CNS membranes (including the BBB) and interact with, and modulate, relevant cell targets

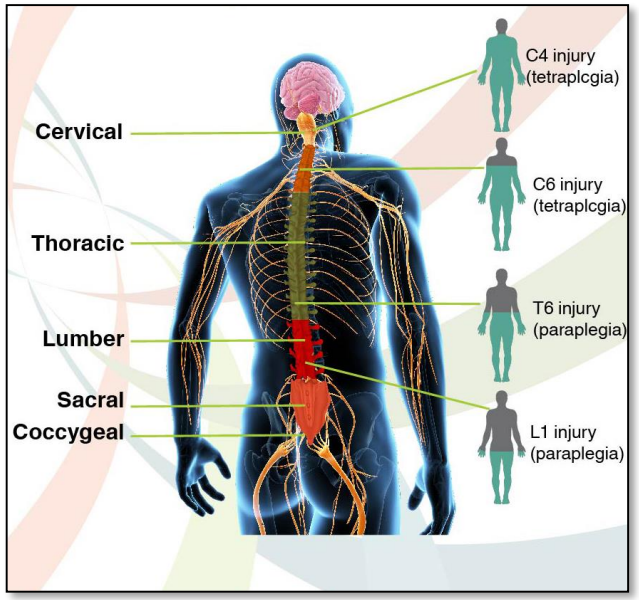
Drug	Indication	R&D	Preclinical	Phase I	Phase II	Phase III
NFX88 (oral 2OH-oleic acid)	Neuropathic pain (SCI)	→	→	→		
NFX81 (iv 2OH-oleic acid - albumin)	Paralysis (SCI)	→	→			
NFX91 (undisclosed)	Sleep disorders	→				

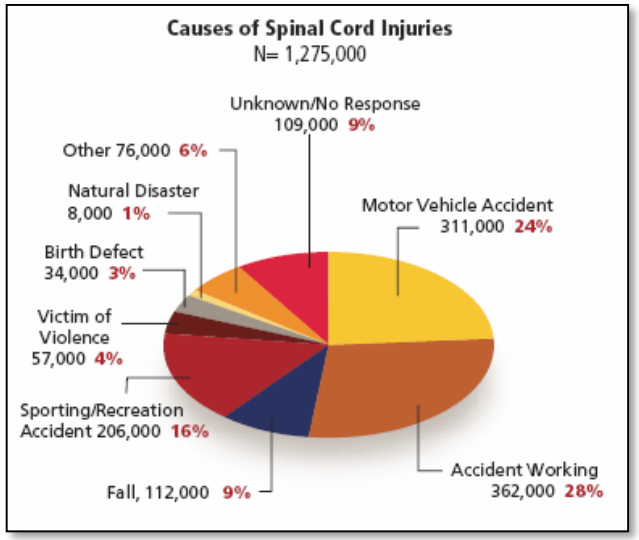
Spinal Cord Injury (SCI)

- Damage to the spinal cord, usually resulting from trauma or from disease or degeneration
- Affects conduction of sensory and motor signals across the site of lesion
- Annual Incidence (Singh, 2014):
  - North America: 25 – 80 / million
  - Europe: 8 – 55 / million
- Prevalence (Singh, 2014):
  - USA: 525 – 906 / million
  - Europe: 250 - 365 / million (Orphan Disease)
- Symptoms depend on the severity of injury and its location on the spinal cord:
  - Partial or complete loss of sensory function
  - Partial or complete loss of motor control of arms, legs and/or body
  - Regulation of bowel or bladder control, breathing, heart rate and blood pressure
  - Chronic pain



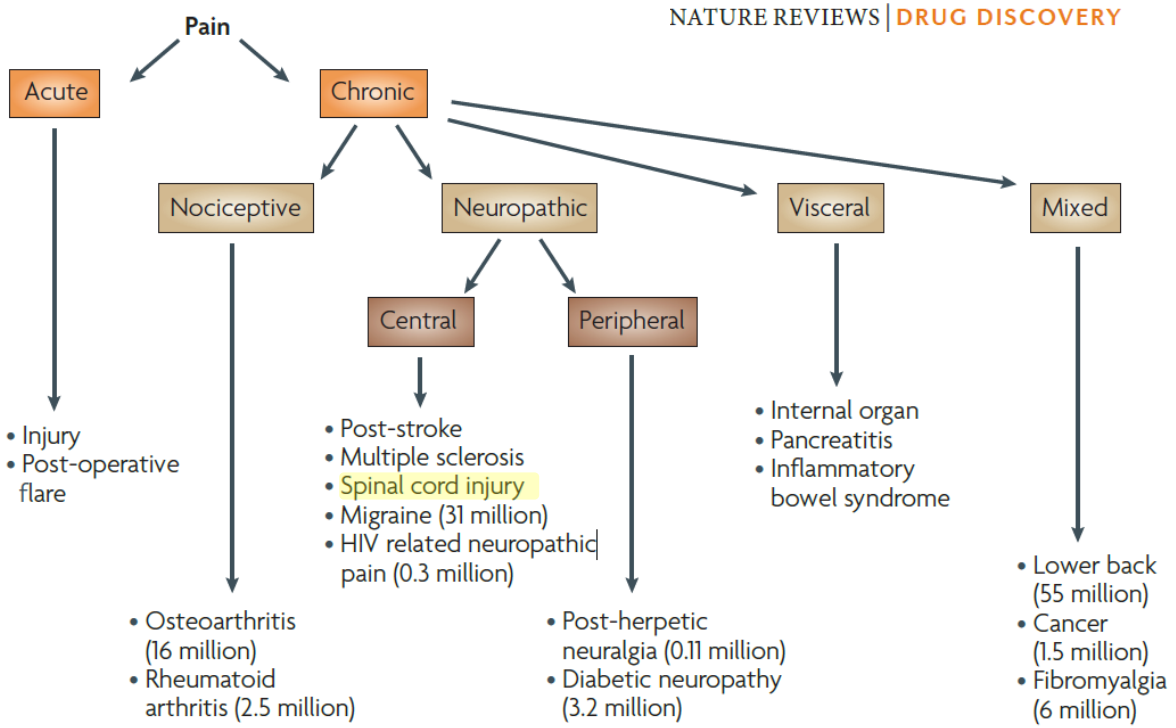






Neuropathic pain (NP)

- A type of chronic pain that is initiated or caused by a primary lesion or dysfunction of the nervous system.
- Post-SCI, NP is broadly attributable to increased neuronal excitability.
- NP is estimated to affect 7%–8% of the population in Europe (Torrance, 2006; Bouhassira 2008), although some estimate suggest that as many as 20% of adults are affected (Reid, 2011)
- In patients with SCI, NP arises within the first few months after injury, is progressive for about 3-5 years before reaching a plateau, and may persist for many years after the acute injury
- NP is usually severe in nature (VAS ≥7), complicates treatment, impacts sleep and mood.
- NP has a substantial negative impact on patient function and quality of life
- 17% of patients with NP have health-related quality of life scores equivalent to "*worse than death*"



Neuropathic pain – current treatments

- The most commonly recommended oral pharmacological agents for chronic pain fall into 3 major categories:
  - Anticonvulsants, which reduce the excitability and abnormal firing in damaged nerves, e.g. Lyrica (Pfizer) and Gabapentin (Pfizer)
  - Antidepressants, e.g. Cymbalta (Eli Lilly)
  - Analgesics
- Pregabalin is the first-line medication and Gabapentin is recommended as the next choice
- Current treatments are inadequate, commonly resulting in a **reduction of only 20-30% in pain intensity**
- In addition, these treatments have **significant side effects**: drowsiness, dizziness, ataxia, fatigue, somnolence, peripheral oedema, weight gain, suicidal thoughts / behaviour

Pain Intensity	Products in Market	2014 Sales ($M)
Severe	Kadian®**	$264
	Avinza®**	$114
	Opana®**	$386
	Nucynta®**	$236
	OxyContin®	$2,466
Moderate	Vicodin®*	$804
	Ultram®*	$184
	BuTrans®	$204
	Suboxone®	$1,115
	Lyrica®	$5,168
	Cymbalta®**	$5,084
	Gabapentin®**	$2,723
Mild	Lidoderm®**	$948
	TOTAL	$19,696

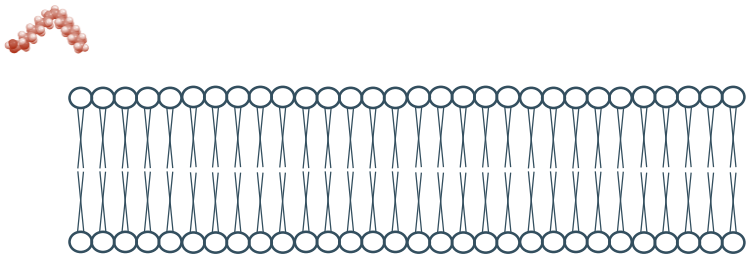
Neuropathic pain - market size / competition

- Neuropathic pain market size: $8.5bn (2017), across 7 major markets (Datamonitor Healthcare)

Product	Mode of action	Company	Status
Pregabalin (Lyrica)	Anti-convulsant (GABA modulator)	Pfizer	Approved
Gabapentin (Neurontin, etc)	Anti-convulsant (GABA modulator)	Pfizer	Approved
Gabapentin (Gralise)	Anti-convulsant (GABA modulator, extended release)	Depomed	Approved
Tapendatol (Nucynta ER)	μ-opioid receptor agonist / noradrenaline reuptake inhibitor	Johnson & Johnson	Approved
Duloxetine (Cymbalta)	Anti depressant (serotonin-norepinephrine reuptake inhibitor)	Eli Lilly	Approved
Lidocaine (Lidoderm)	Transdermal patch	Grünenthal / Teikoku	Approved
Mirogabalin	Anti-convulsant (GABA modulator)	Daiichi Sankyo	Phase III
Gabapentin enacarbil (Horizant)	Anti-convulsant (GABA modulator)	GSK	Phase II
BIIB074 (Vixotrigine)	Nav 1.7 inhibitor	Biogen	Phase II
Cebranopadol	Opioid receptor inhibitor	Grünenthal	Phase II
VX-150	Nav 1.8 inhibitor	Vertex	Phase II
Ralfinamide	Analgesic (inhibitor of sodium channels)	Newron Pharma	Phase II
PL265	Enkephalin-degrading enzyme inhibitor	Pharmaleads	Phase Ib
BIIB095	Nav 1.7 inhibitor	Biogen	Phase I

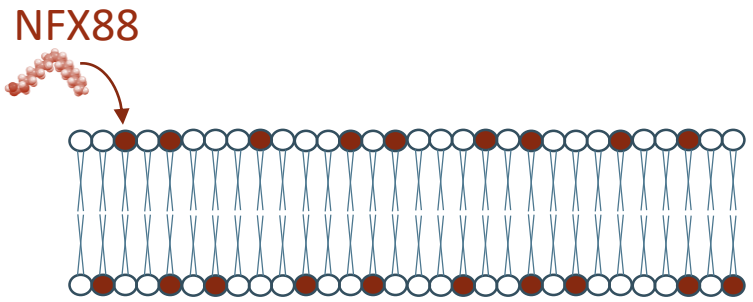
NFX88 is an oleic acid derivative

NFX88

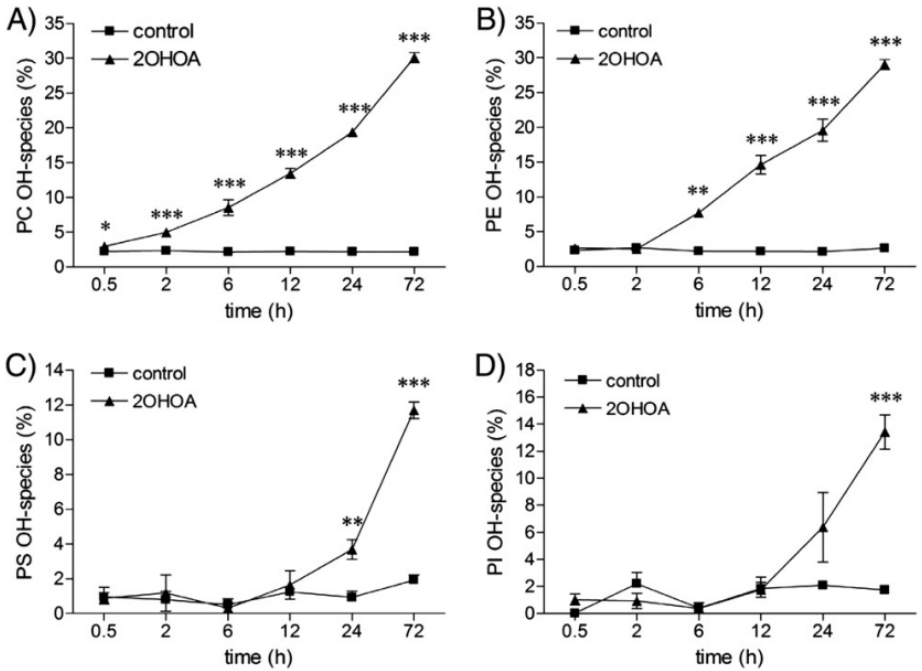


- NFX88 (2-hydroxyoleic acid, 2OHOA) is a derivative of oleic acid (ω-9 monounsaturated fatty acid)
- Hydroxylation of the alpha carbon impairs beta-oxidation (slower metabolism)
- 2OHOA is more potent than oleic acid, in part due to its longer half-life in plasma (confirmed both by preclinical and clinical studies)
- Composition of matter claims granted in EU, USA and other territories (protection up to 2029 / 2034)

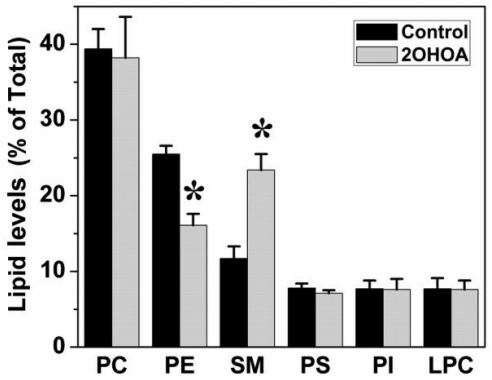
NFX88 induces changes in membrane composition



- NFX88 / 2OHOA is incorporated into the glycerophospholipid fraction of the plasma membrane, particularly PC and PE (Barceló-Coblijn, PNAS 2011; Martín, BBA Biomembranes 2013)
- NFX88 / 2OHOA induces changes in the levels of major lipid species in membranes: phosphatidylethanolamine (PE) and sphingomyelin (Teres, 2012 PNAS)

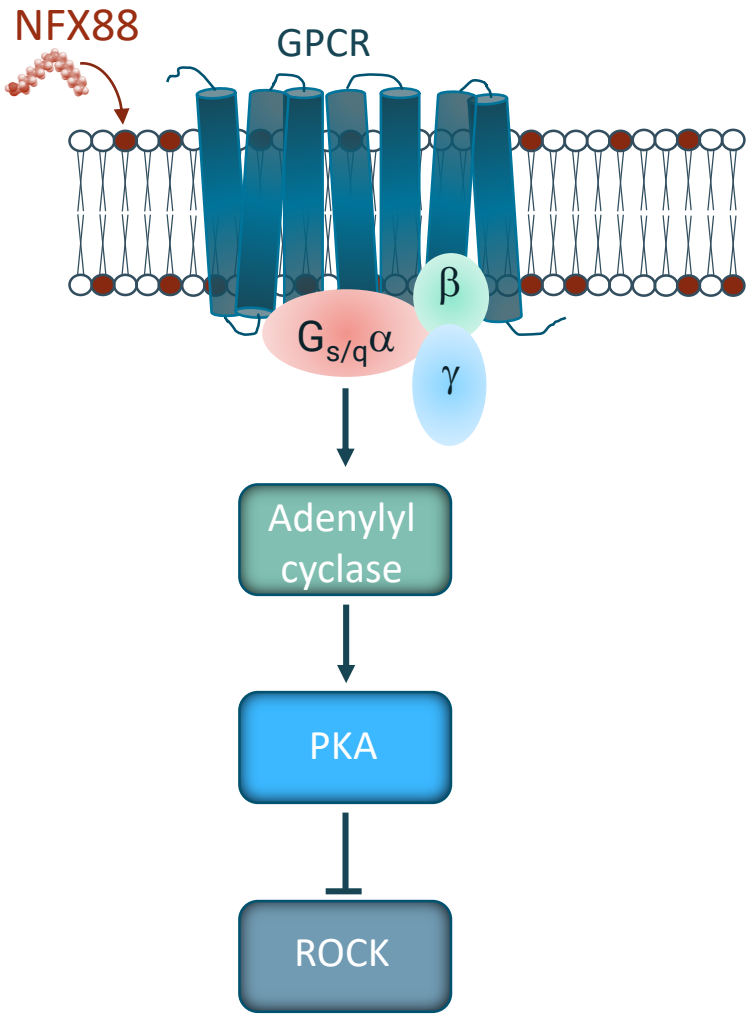


2OHOA is partially incorporated into the phospholipid fraction of U118 glioma cells. (Martín, BBA Biomembranes 2013)

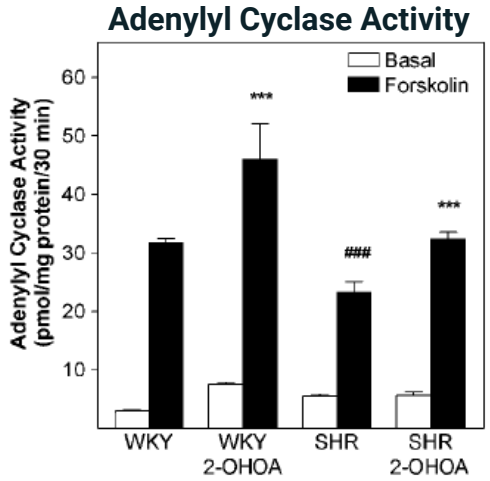


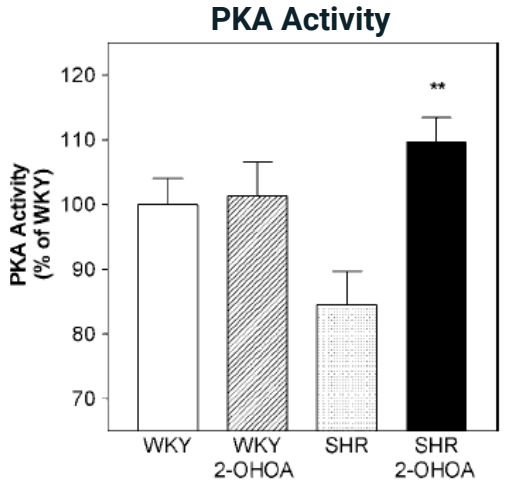
2OHOA induces changes in the membrane lipid composition of SF767 glioma cells after 72h. (Teres, 2012 PNAS)

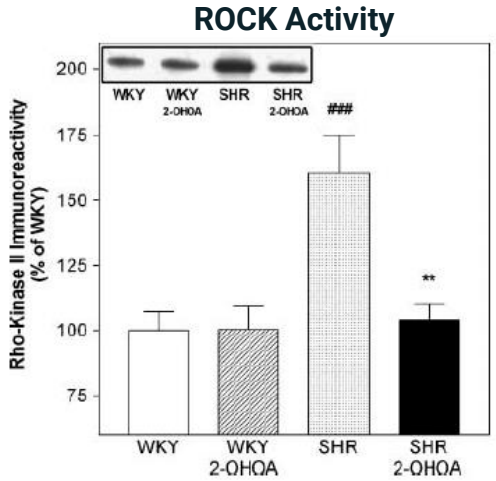
NFX88 modulates GPCR signalling



- Modification in membrane composition / structure induced by NFX88 / 2OHOC leads to modulation of the activity of GPCRs ($G_s\alpha$ and $G_q\alpha$) and downstream effectors such as Adenylyl Cyclase, PKA and Rho kinase (Alemany, 2006 J Lipid Res)





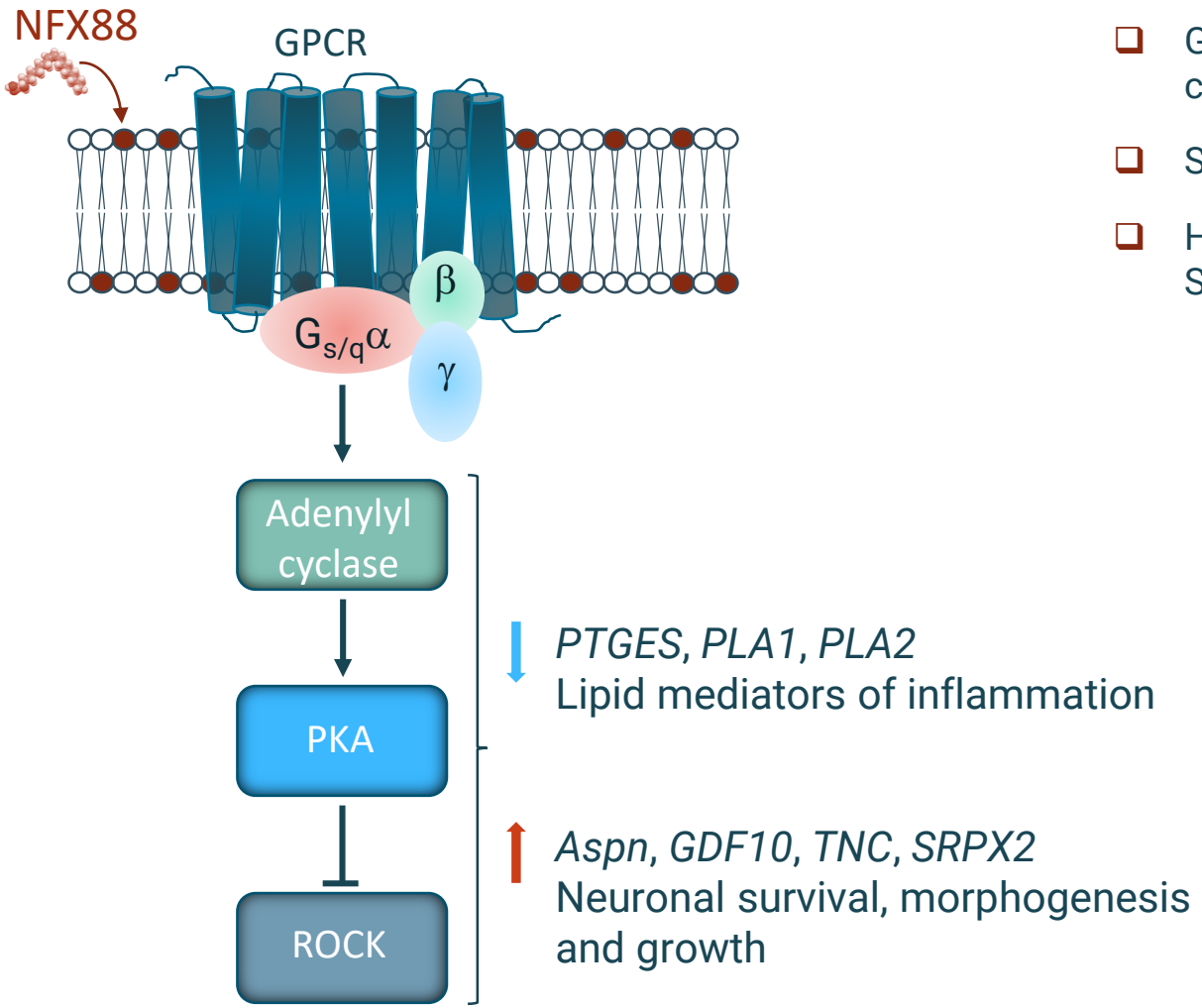


Effect of 2-OHOA treatment (600 mg/kg every 12 h) for 7 days on Adenylyl Cyclase activity, PKA activity and Rho kinase II protein levels in aortas from SHR (Spontaneously Hypertensive) and WKY (Wistar Kyoto) rats.

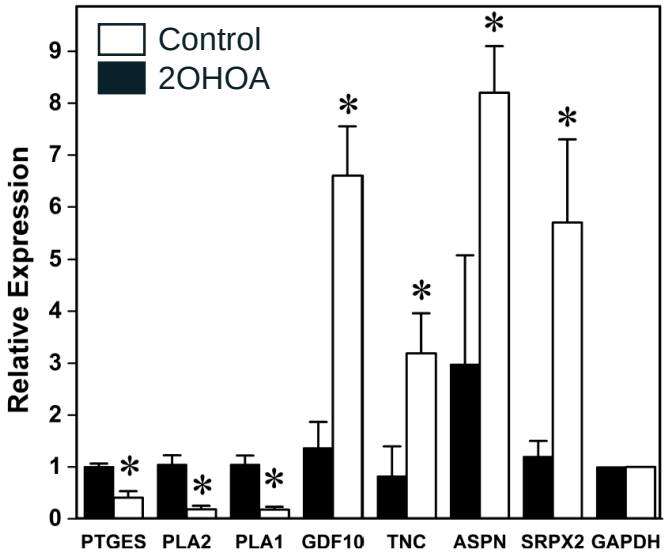
AC activities were determined in the absence and presence of forskolin (10 mM).

Columns represent means of 5-7, 4 and 8-11 animals per group, respectively.

NFX88 downregulates genes involved in inflammation and upregulates genes involved in neuronal growth

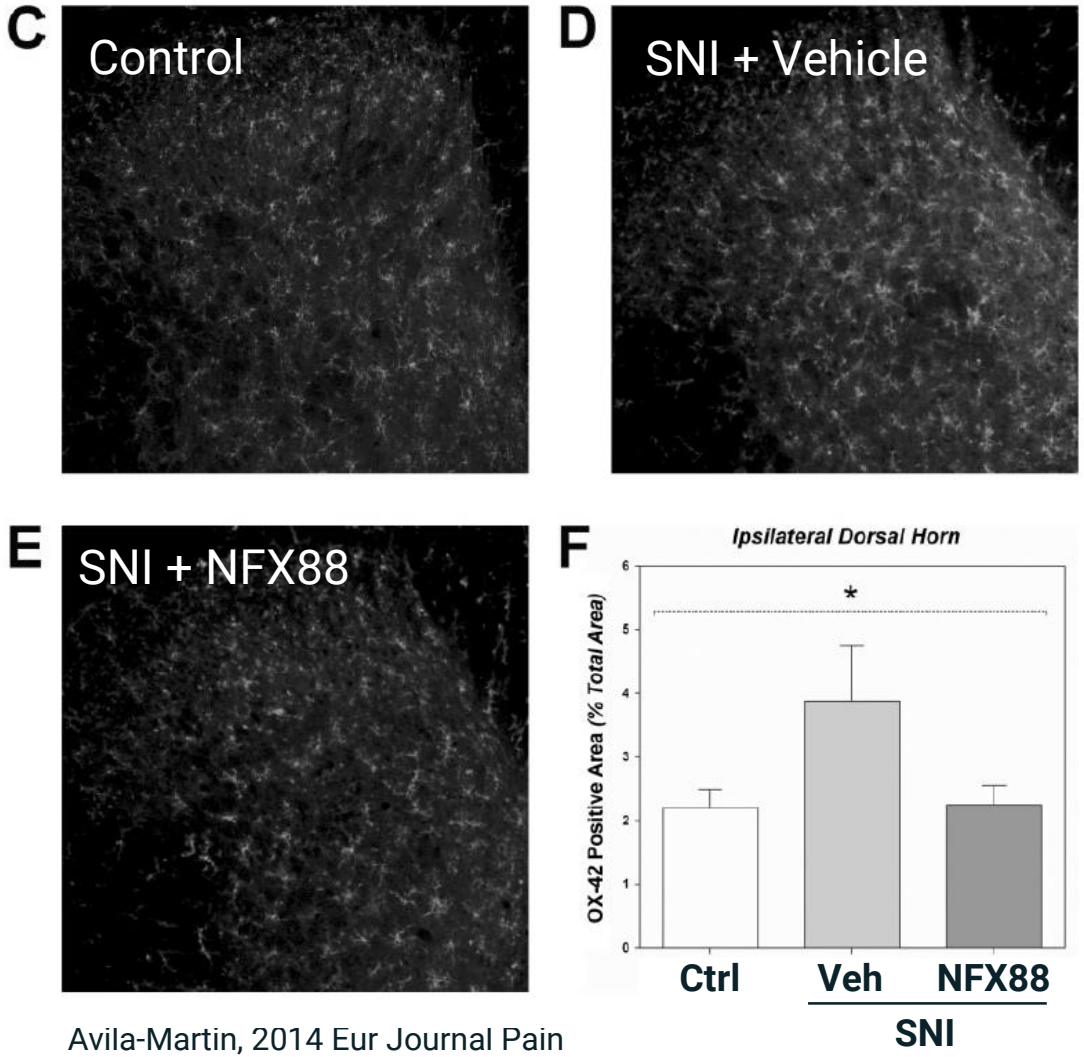


- Gene expression was profiled in the spinal cord of rats 7 days after T9 contusion (Ávila-Martin, 2017 PLoS ONE)
- SCI significantly altered the expression of around 4000 genes
- However, only 41 genes were altered by NFX88 treatment in animals with SCI:
  - 20 genes were significantly upregulated (**3 genes > 4-fold**)
  - 21 genes were significantly downregulated (**3 genes < 4-fold**)



Levels of the mRNA species were quantified by qRT-PCR in the spinal cord of SCI rats 7 days after contusion treated with saline or 2OHOA. Relative expression was calculated from 4 animals using triplicate technical samples, with respect to the expression of the housekeeping gene *GAPDH*. *p<0.01.

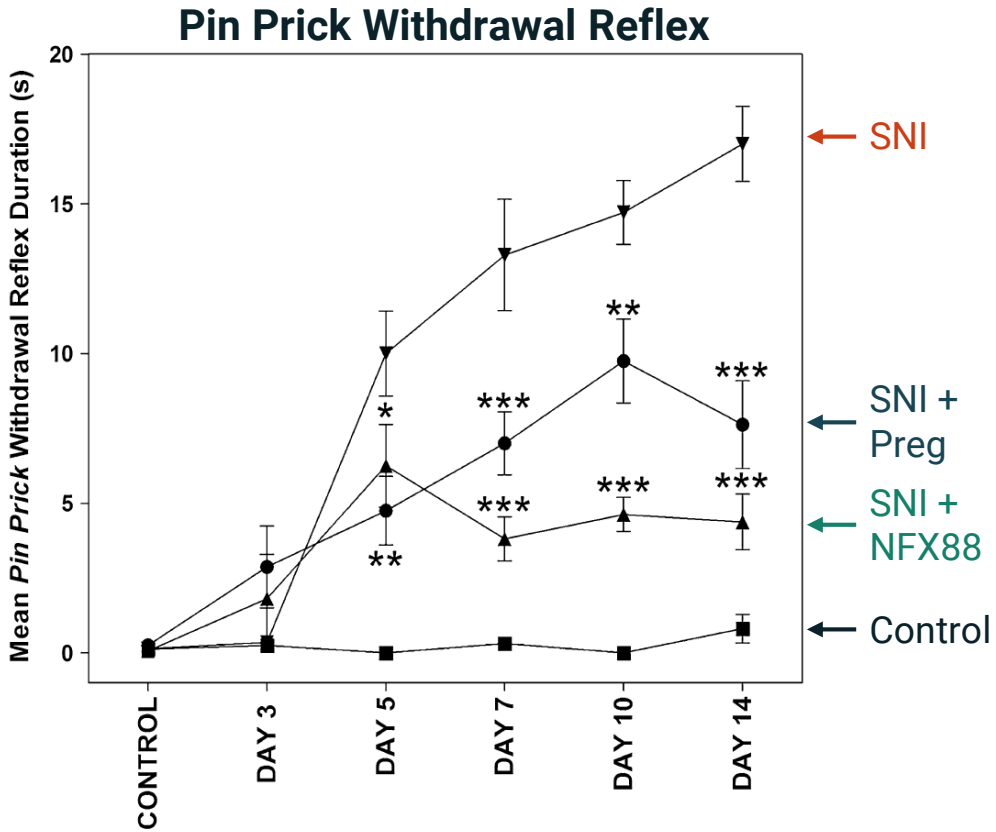
NFX88 reduces microglia reactivy induced by Spare Nerve Injury in rats

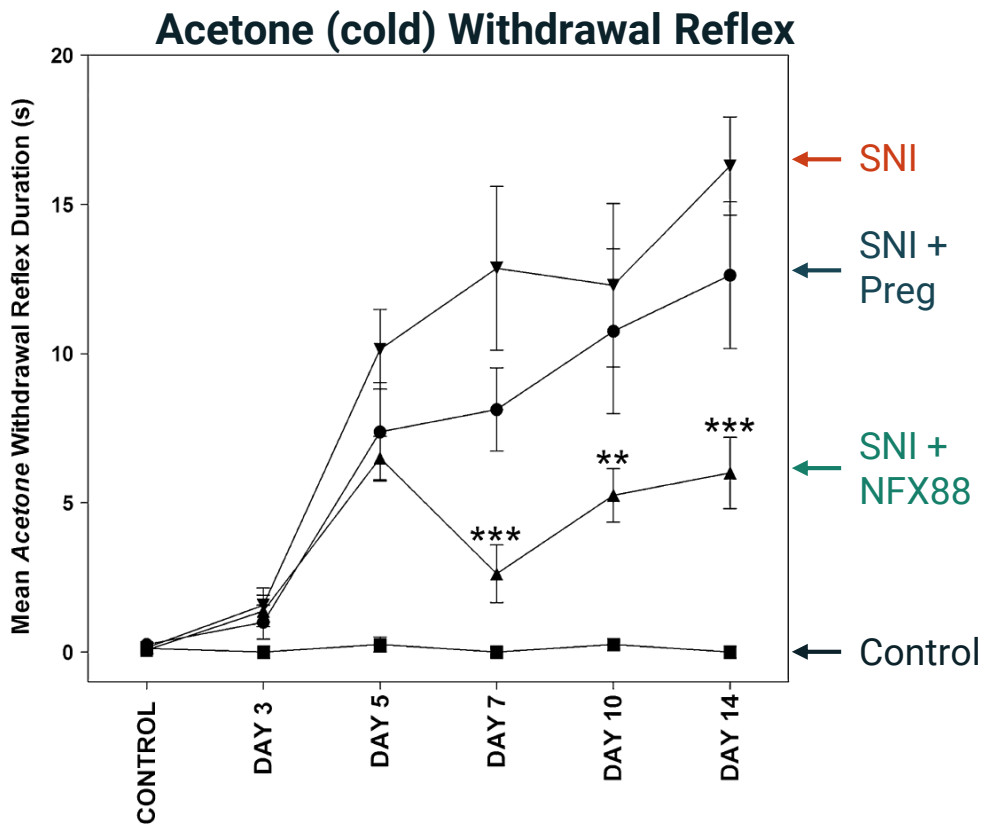


Avila-Martin, 2014 Eur Journal Pain

- Microglia are a type of macrophages found in the brain and spinal cord
- Spare Nerve Injury (SNI) elicits microglia cell activation within the spinal dorsal horn and contributes to the development of mechanical and thermal reflex hypersensitivity
- Wistar rats with spare nerve injury (SNI) display an increase in microglial reactivity L4–L5 dorsal horn ipsilateral to the SNI
- Treatment with NFX88 leads to a decrease in the OX-42/CD11b-positive area (a marker of microglia vs macrophages) within the dorsal horn.

NFX88 is more efficacious than pregabalin in a rat model of neuropathic pain





Ávila-Martin, 2014 Eur Journal Pain

- Wistar rats with spare nerve injury (SNI) have increased withdrawal reflex duration to pin prick / acetone stimulation
- Intrathecal administration of NFX88 has an antinociceptive effect on the duration of the withdrawal reflex
- NFX88 dose of 400 mg/kg (p.o.), according to the FDA is equivalent to 60 mg/kg / 4 g per day (p.o.) in humans

Phase I study of safety and tolerability of 2OHOA / NFX88

- Open label, non-randomized, first-in-man study evaluating the safety, pharmacokinetics and pharmacodynamics of daily, oral treatment with 2OHOA / NFX88 (NCT01792310)
- Dose escalation following a standard “3+3” design to determine safety and tolerability, followed by two expanded safety cohorts at the maximum tolerated dose (MTD)
- Population: patients with advanced solid tumours
- Coordinating investigator: Professor Johann de Bono (The Institute of Cancer Research, UK)
- Study Centres:
  - The Royal Marsden Hospital (UK)
  - Northern Centre for Cancer Care (UK)
  - Vall d'Hebron Institute of Oncology (Spain)
  - Oncology Institute Gipuzkoa (Spain)
  - Clínica IMQ Zorrotzaurre (Spain)

Phase I study of safety and tolerability of 2OHOA / NFX88

Treatment Cohort	Total Daily Dose	Dosing Regimen	Number of Patients Treated	DLT evaluable	DLTs
Dose escalation – 01	0.5 g	b.i.d.	3	3	0
Dose escalation - 02	1 g	b.i.d.	4	4	0
Dose escalation - 03	2 g	b.i.d.	3	3	0
Dose escalation - 04	4 g	b.i.d.	4	3	0
Dose escalation - 05	8 g	b.i.d.	3	3	0
Dose escalation - 06	12 g	t.i.d.	8	6	1
Dose escalation - 07	16 g	b.i.d.	7	6	3
Expanded safety cohort (Glioma)	12 g	t.i.d.	12	*NA*	*NA*
Expanded safety cohort (other solid tumors)	12 g	t.i.d.	10	*NA*	*NA*

- 54 patients have received NFX88 treatment for more than 129 months (~185 cycles).
- NFX88 was generally well-tolerated, apart from some anticipated gastrointestinal effects (mainly grade 1 or 2 diarrhoea, nausea and vomiting)
- 21 serious adverse events (SAEs) recorded: 3 were considered “unlikely to be related” and 18 were considered “not related” to the study drug
- Dose-limiting toxicity (DLTs) were Grade 2 or 3 gastrointestinal adverse events (e.g. diarrhoea)
- Based on these results, the maximum tolerated dose (**MTD**) of NFX88 has been defined as **12 g/day**

NFX88 – Phase IIa proof of concept study (starting Q2 2019)

Study Parameter	Details
Overall Design	Multicentric, Randomized, Double Blind, Parallel Group
Population	Complete or incomplete spinal cord injury (C4-T12) patients with neuropathic pain, under pregabalin treatment; average pain score > 4 (VAS scale)
Primary Objective	Evaluate safety and tolerability of NFX88 treatment over 90 days.
Secondary Objective	Evaluate therapeutic efficacy of NFX88 treatment through the analysis of validated pain measurement scales: • Patient Global Impression Change (PGIC) – **global patient condition** • PainDETECT questionnaire (PD-Q) – **likelihood of neuropathic pain** • Visual Analogue Scale (VAS) – **pain intensity**
Arms	Control Arm *1) Pregabalin (150-300 mg/day)* + Placebo (15 patients) Experimental Arms 2) *Pregabalin (150-300 mg/day)* + 1.05 g/day NFX88 (15 patients) 3) *Pregabalin (150-300 mg/day)* + 2.10 g/day NFX88 (15 patients) 4) *Pregabalin (150-300 mg/day)* + 4.20 g/day NFX88 (15 patients)
Duration of Treatment	90 days (plus 30 days follow up)
Expected completion	Q2 2020

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Dr. Sebastián Salvador
A Coruña University Hospital

Dr. Francisco Javier Medel
Vall d'Hebron University Hospital (Barcelona)

Dr. Miguel David Membrilla
Virgen de las Nieves University Hospital (Granada)

Neurofix / NFX88: future steps

- Further elucidate mechanism of action of NFX88 (in rat models of NP, cell lines and human samples)
- Identify response biomarkers:
  - Currently NP assessment is based on subjective virtual scales and questionnaires
  - Use lipidomic, proteomic and genomic approaches in parallel with MoA elucidation

- Spinal cord injury is an orphan disease → Neurofix applied for EMA "Orphan Drug Designation"
- Prepare Phase IIb study (formulation, CRO, study design):
  - Arm 1: placebo
  - Arm 2: Pregabalin
  - Arm 3: NFX88 (Phase IIa dose)
  - Arm 4: Pregabalin + NFX88 (Phase IIa dose)
  - 40 – 60 patients per arm

- Business development: search collaboration partner
- Non-dilutive funding (H2020)
- Raise capital to fund Phase IIb study

Business development: recent licensing / M&A deals in the neuropathic pain space

Licensor / Acquiree	Licensee / Acquirer	Year	Target	Stage	Financial details
Covergence Pharmaceuticals	Biogen	2015	CNV1014802 (Nav 1.7 inhibitor) for neuropathic pain)	Phase II	$200m upfront Up to $475m in milestones
Chromocell	Astellas	2015	License to CC8464 (Nav 1.7 inhibitor) for neuropathic pain	Phase I ready	$15m upfront Up to $500m in milestones
Spinifex Pharmaceutical	Novartis	2015	EMA401 (angiotensin II type 2 antagonist) for chronic pain, particularly neuropathic pain	Phase IIb ready	$200m upfront Undisclosed milestones

Neurofix - Leadership team

Miguel Ángel Ávila

Chief Executive Officer

- Engineer and R&D manager (GESTIDI certification)
- Previously managed and coordinated 11 national and 2 FP7 projects at R&D companies Oblanca and Apointech

Cláudio Santos

Chief Business Officer

- BSc and PhD in Biology
- Previous roles as technology transfer manager (Cancer Research Technology, UK), Investment Associate (Sixth Element Capital, UK) and CBO (Bioncotech Therapeutics, Spain)

Álvaro Sanz

Manager ("CFO")

- Graduate in Business Administration
- Over 20 years of experience in SME business administration
- Responsible for administration, financial control and accountancy

Daniel Bermejo

Clinical Trial

- BSc and MRes in Biology
- Previous experience in data and project management and clinical development at Farmalider Group, Fina Biotech, PharmaMar and Sermes

Dr. Ignácio Galicia

Clinical Advisor

- Clinical Pharmacologist / MD
- Director of Clinical Research at Institute Fundación Teófilo Hernando
- Previously leader of Clinical Research at Hospital La Paz and Director of the Clinical Trial Unit at Hospital Gómez Ulla

Pablo Escribá

Scientific Advisor

- Professor at University of Illes Balears
- Over 30 years of biomedical research experience
- Author of 6 patents licenced to biotech companies and over 100 scientific publications

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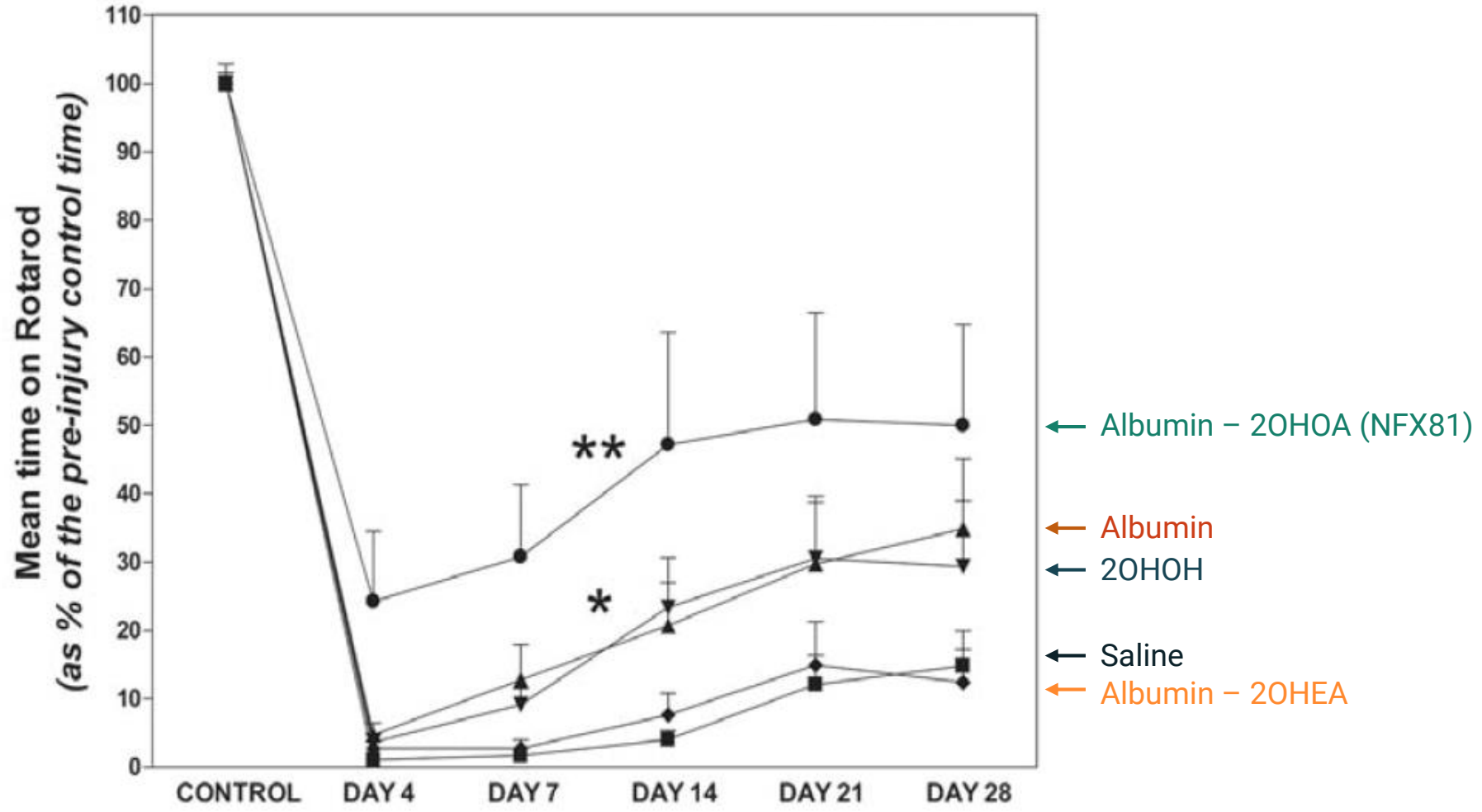
NFX88: Intelectual Property

Territory	Application Number	Status	Filing date	Key claim
WO	PCT/ES2009/070561		04/12/2009	
EP	14195436	Granted		Claim 1: Compound selected from: (…) **α-hydroxy- cis-Δ9-octadecenoic acid** (…), or salts thereof, for use (…) prevention and/or **treatment of pain in humans** or animals.
US	14/664,351	Granted		Claim 1: A method for the therapeutic **treatment of nerve fibre lesions in humans** and mammals, comprising the administration to said human or mammal of a therapeutically effective amount of **α-hydroxy-cis-Δ9-octadecenoic acid** (…)
US	15/645,524	Pending		
JP	201-539060	Granted		
BR	PI0922870-5	Pending		
CN	200980156029.6	Granted		
CA	2745052	Granted		
AU	2009326993	Granted		
IL	213354	Granted		

NFX88: function of genes regulated in a rat model of SCI

Gene	Function
Aspn	▪ Associated with development of the CNS ▪ May play in neural damage recovery after SCI
GDF10	▪ Member of BMG and TGF-α superfamily (involved in anti-inflammatory activity and in alleviating nerve injury-induced neuropathic pain in rats) ▪ Also involved in axonal sprouting and neuron functional recovery after stroke.
TNC	▪ Regulation of proliferation of both oligodendrocyte precursor cells and astrocytes. ▪ Present in central nervous system injuries and gliomas
SRPX2	▪ May play in re-establishing vascularization and recovery from synapse loss. ▪ Mutations have been linked to neurological syndromes with altered neuronal migration.
PTGES	▪ Induced by proinflammatory cytokine IL-1B. ▪ Knock-out mice studies suggest role in mediating acute pain during inflammatory responses.
PLA1 / PLA2	▪ Produce lysophospholipids and fatty acids, such as arachidonic acid, a well-known inflammatory mediator that causes hyperalgesia. ▪ PLA1 plays a relevant role in the turnover of a lipid that regulates localization of signalling proteins to defined synaptic areas. ▪ PLA2 induction after SCI or intrathecal PLA2 injection can cause axon demyelination and focal hemorrhagic pathology. ▪ Inhibition of PLA2 by NFX88 may contribute to reduced inflammation, nociception and cell death in the area of SCI.

NFX81 (Albumin-2OHOA) promotes early recovery of motor function in rats following T9 spinal cord injury



Longitudinal analysis of the mean time spent on the rotarod by Wistar rats following SCI-inducing contusion. Treatment was delivered by intrathecal administration. (Ávila-Martin, 2011 PLoS ONE)