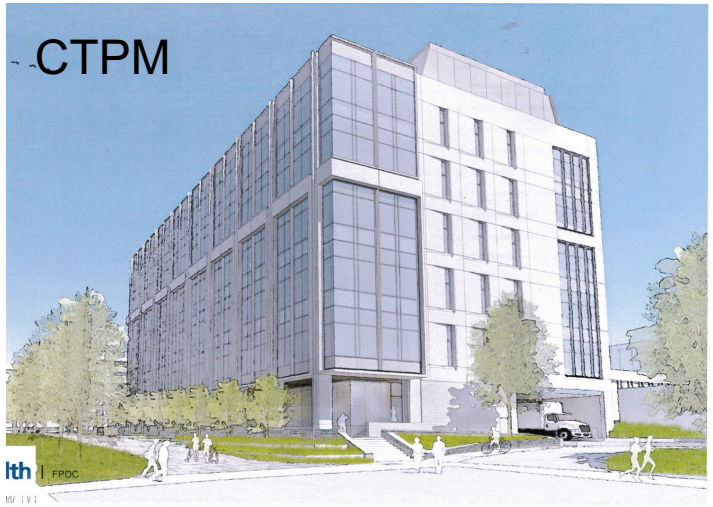
May 16, 2024, Denver

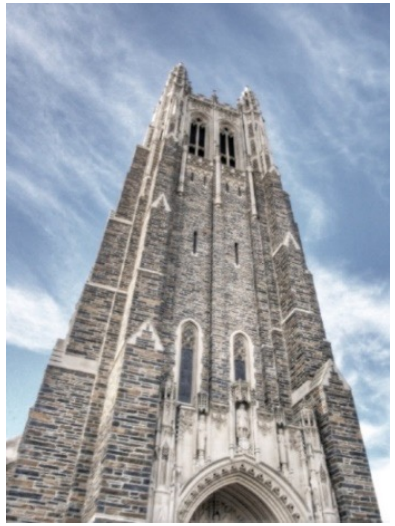
15th Annual Gold Lab Symposium: Pain, Culture, and Intelligence

CTPM
Center for Translational Pain Medicine
Overcoming Pain Together



Using Molecular Pathways of Omega-3 Fatty Acids to Block Inflammatory and Neuropathic Pain:

SPMs in Pain



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Professor of Cell Biology and Neurobiology
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Disclosure

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Editorial board service

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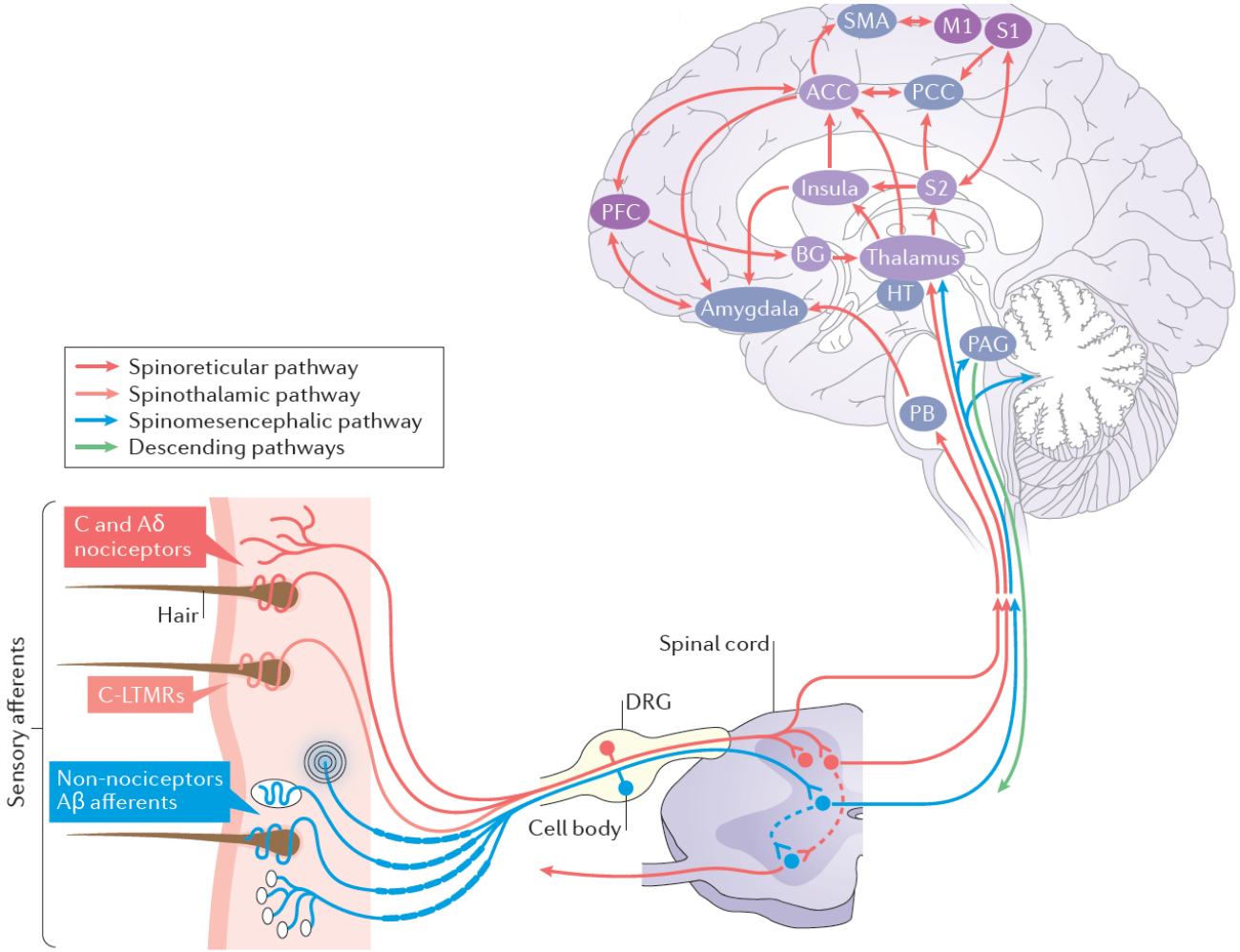
Journal of Pain: Associate Editor
Journal of Neuroscience: Associate Editor
Neuroscience Bulletin: Co-Chief Editor
Physiological Reviews: Associate Editor

Pain pathway



Kuner and Flor, *Nat Rev Neurosci,* 2017

Chronic Pain

Inflammatory pain - arthritis
Neuropathic pain - nerve injury
Cancer pain - tumor

- **Over 100 million Americans**
- **Financial cost of is $635 billion**
- **Co-morbidity: associated with depression, anxiety, insomnia.**
- **Global chronic pain epidemic**
  Opioid use disorder epidemic

Different Types of Inflammation

Roles of inflammation, neurogenic inflammation, and neuroinflammation in pain.
Matsuda M, Huh Y, Ji RR. J Anesth. 2019 Feb;33(1):131-139. doi:

Inflammation: Injury to peripheral tissue, systemic response

Neuroinflammation: Local inflammation in the PNS and CNS

Neurogenic inflammation: Activation of nerve fibers and involvement of neuropeptides

Matsuda M, Huh Y, Ji RR. J Anesth. 2019

Neuroinflammation

Inflammation in the PNS and CNS

Features:

- Infiltration of immune cells
- **Activation of glial cells (microglia, astrocytes, SGCs)**
- Production of immune & glial mediators
  (cytokines & chemokines)

Neuroinflammation causes neurological and psychiatric diseases (AD, PD, MS, depression)

Neuroinflammation is a driving force of chronic pain

Neuroinflammation drives central sensitization and widespread pain

Ji et al., Nat. Rev. Drug Discovery, 2014; Anesthesiology, 2018

Inflammation, inflammatory mediators, and Pain

5 **cardinal signs of inflammation**

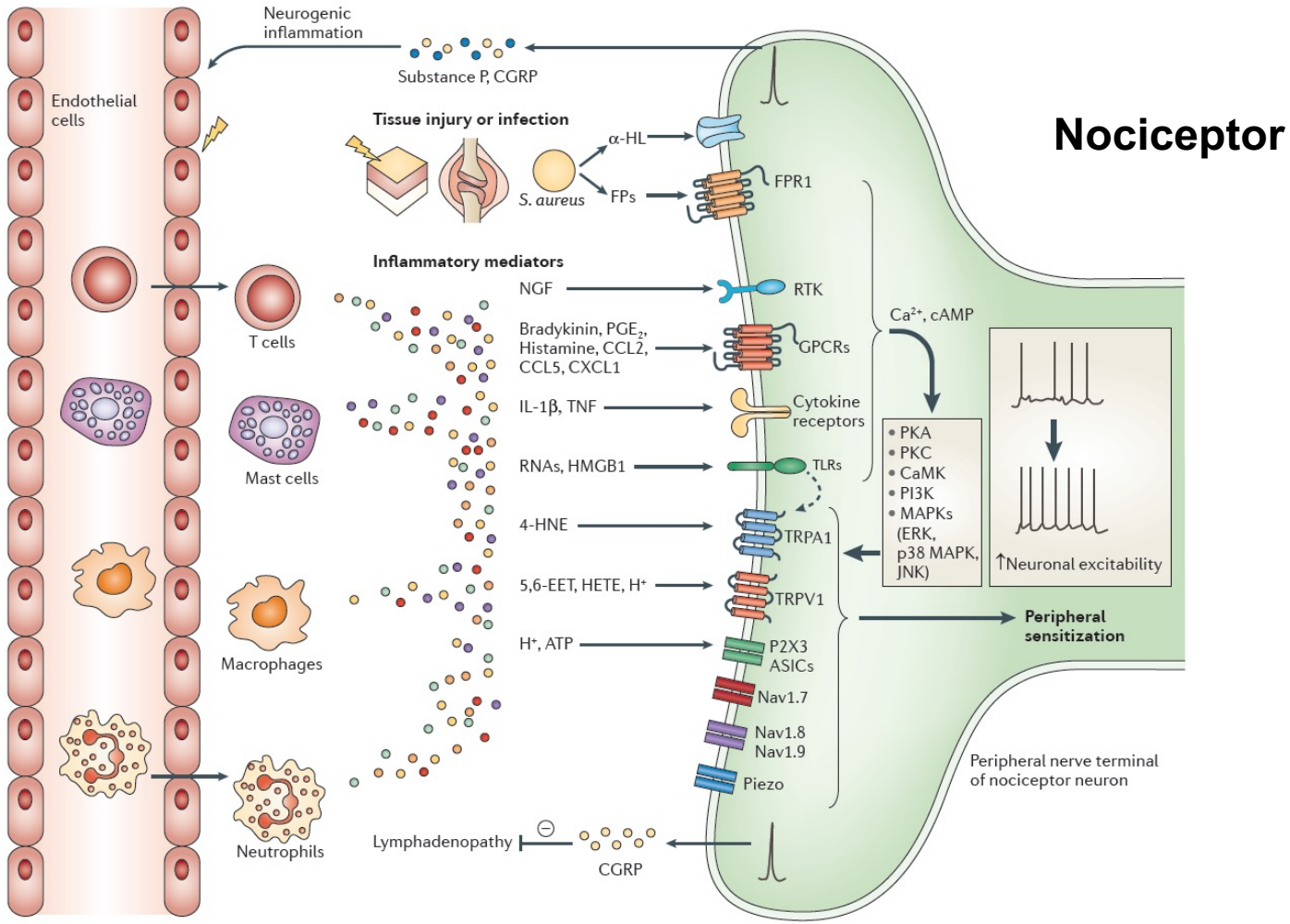
- Rubor (redness)
- Calor (increased heat)
- Tumor (swelling)
- Dolor (pain)
- Functio laesa (loss of function)

Inflammatory mediators

Pro-inflammatory
(Pronociceptive)

Anti-inflammatory
(Anti-nociceptive)

SPMs / Omega-3 Fatty acids
Anti-inflammatory
Pro-resolution
Anti-nociceptive



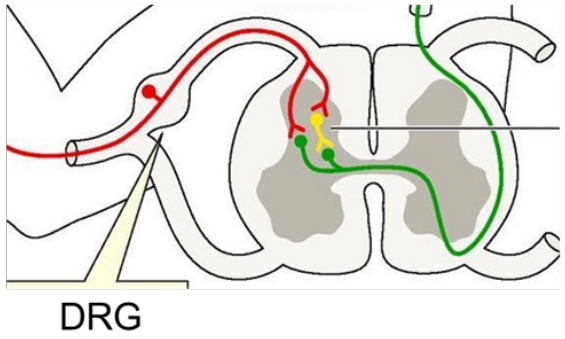
2. Immune modulation

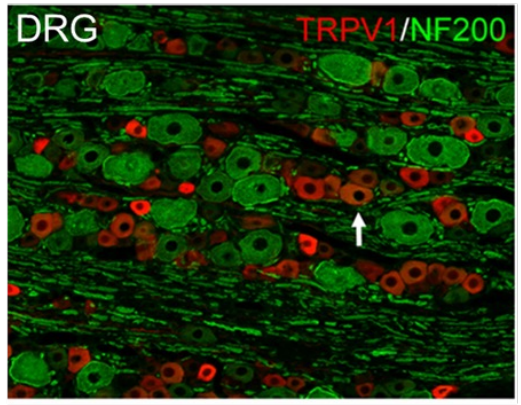
1. Neuromodulation

One stone, two birds

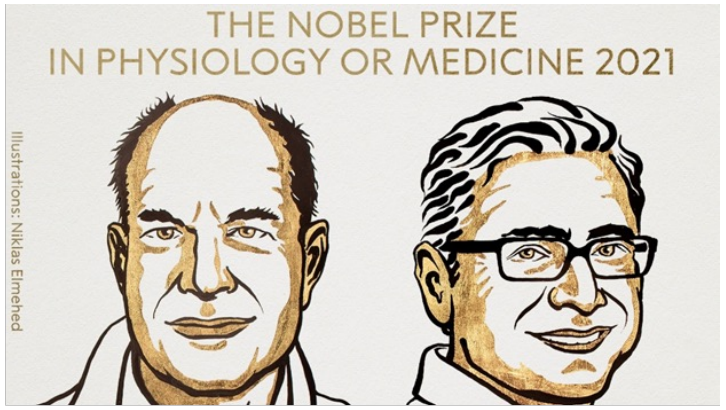
Ji et al., *Nat Rev Drug Discov.*, 2014

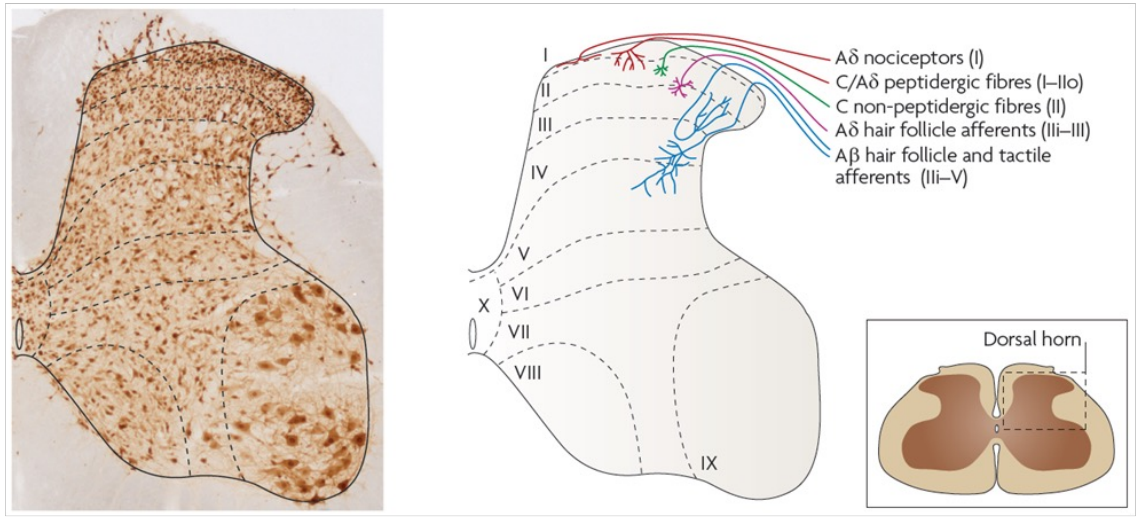
Primary sensory neurons, spinal cord, pain sensors

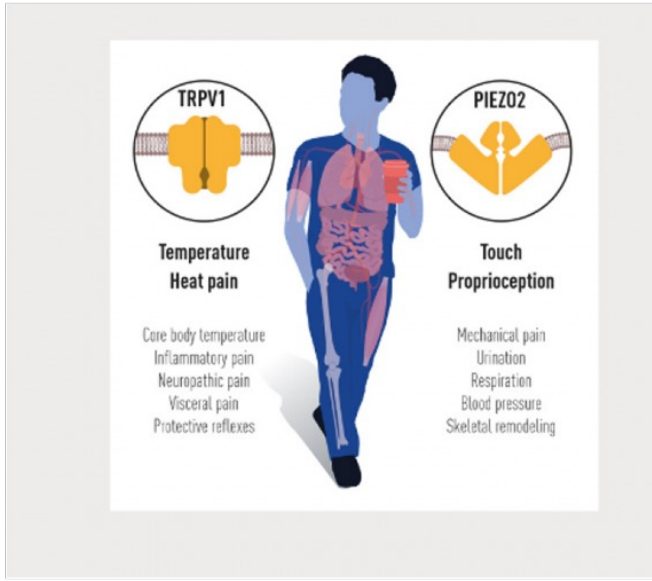




Capsaicin



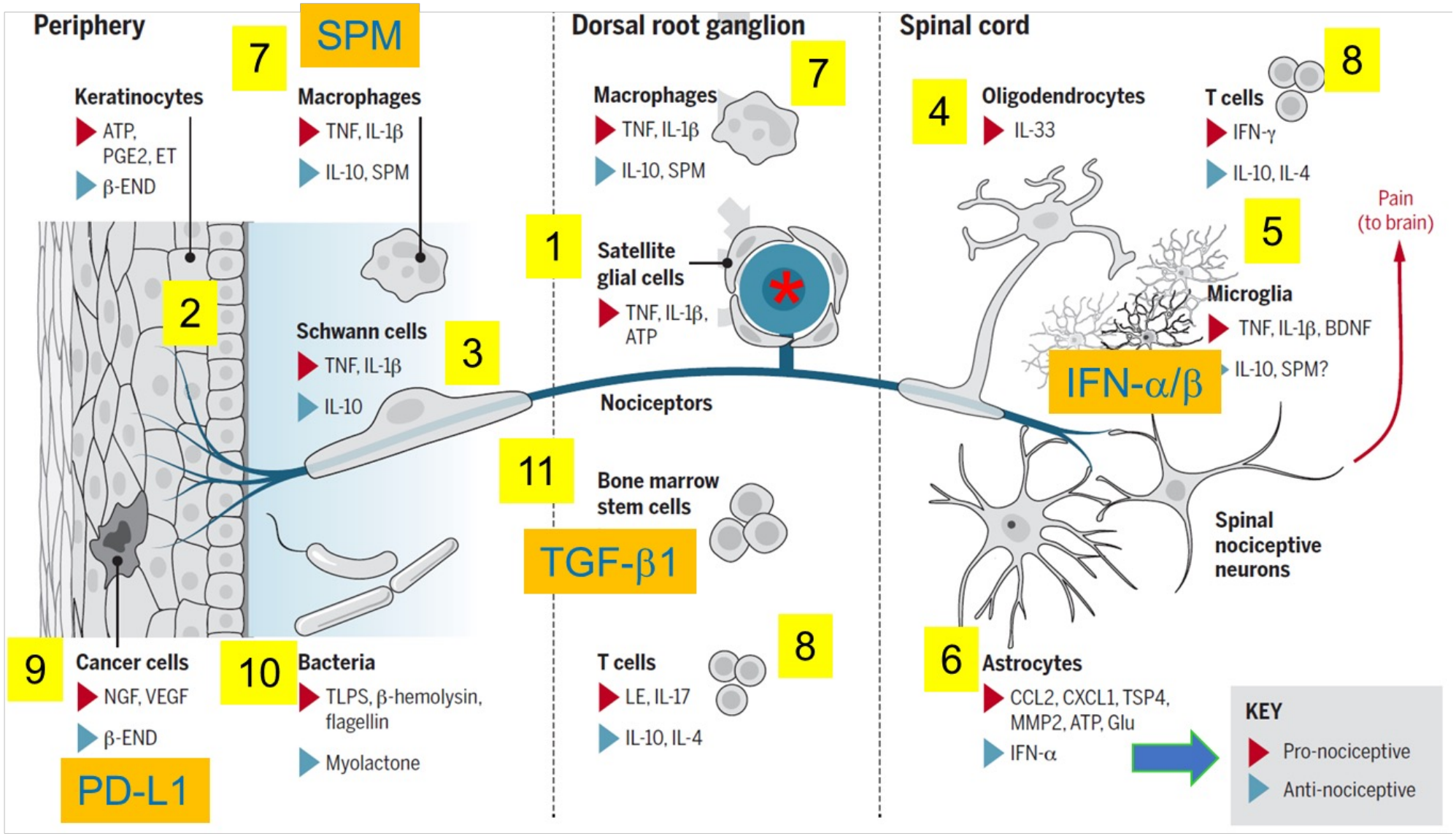




Todd, *Nat Neurosci Rev,* 2010

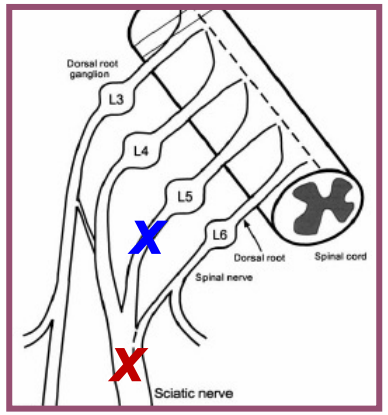
Pain sensors TRPV1 and PIEZO2 are activated by inflammatory mediators

Cell biology of pain

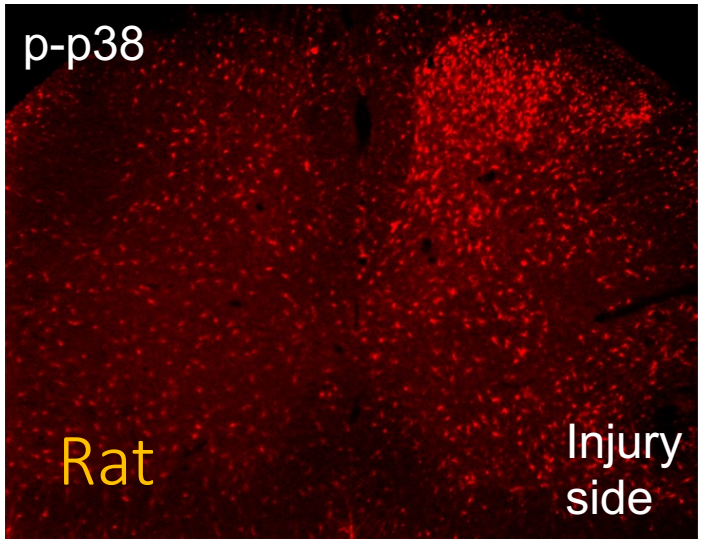


Ji et al., *Science*, 2016

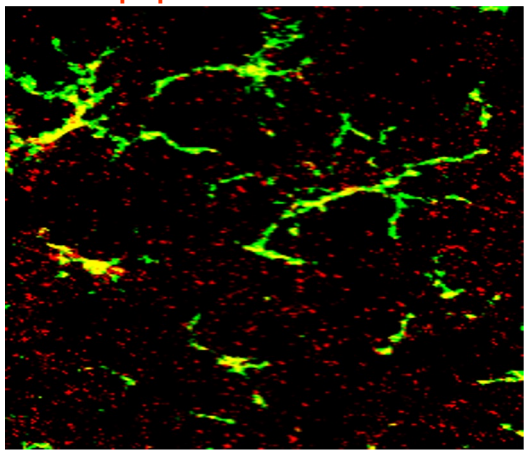
Microglial signaling in chronic pain



Spinal nerve ligation (SNL)
Nerve injury



p-p38 / CD11b



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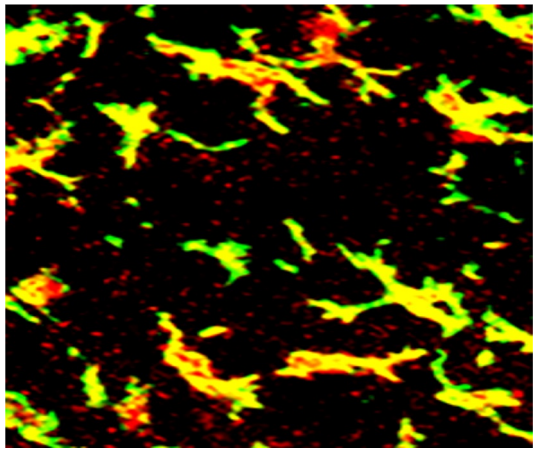
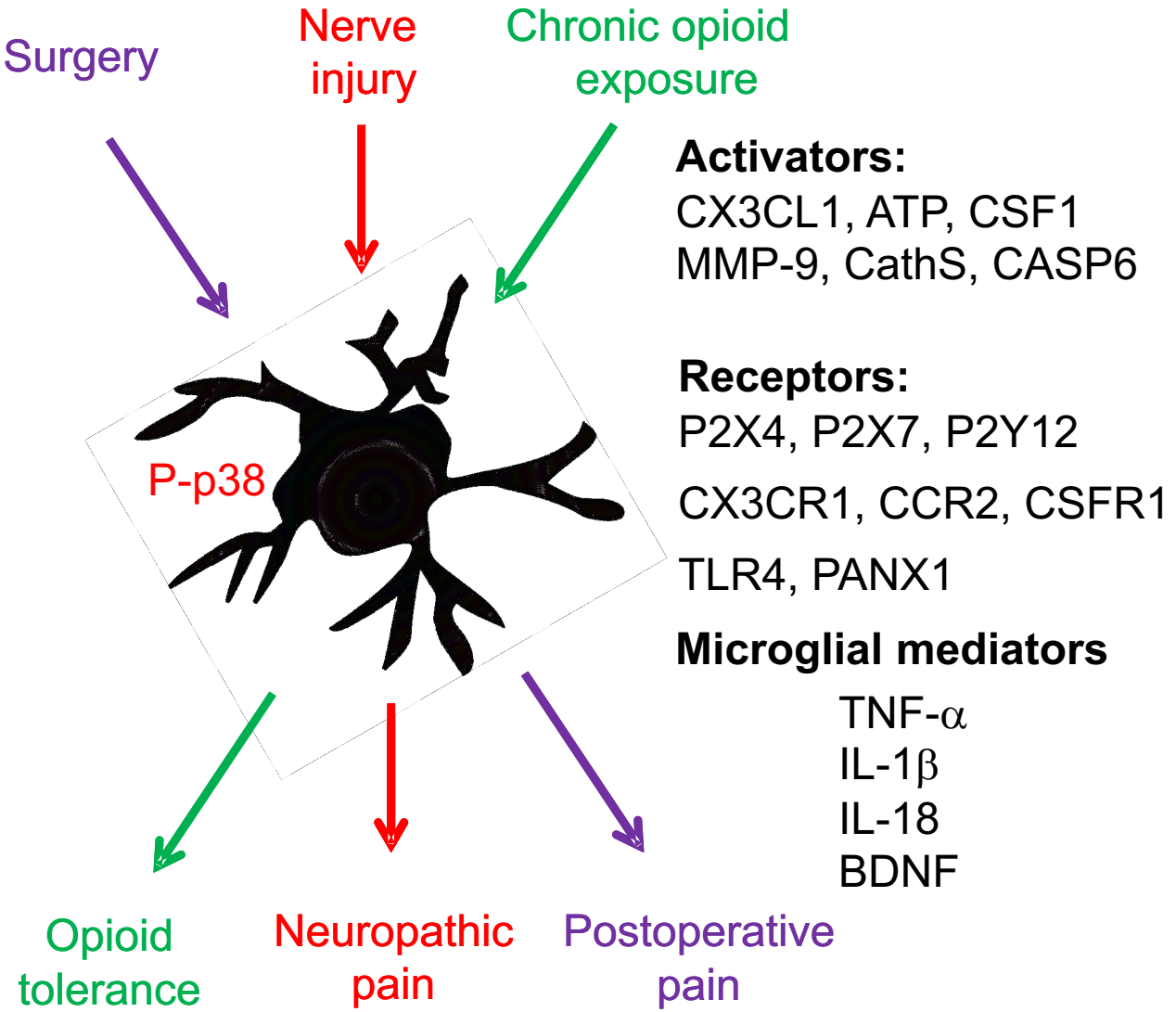


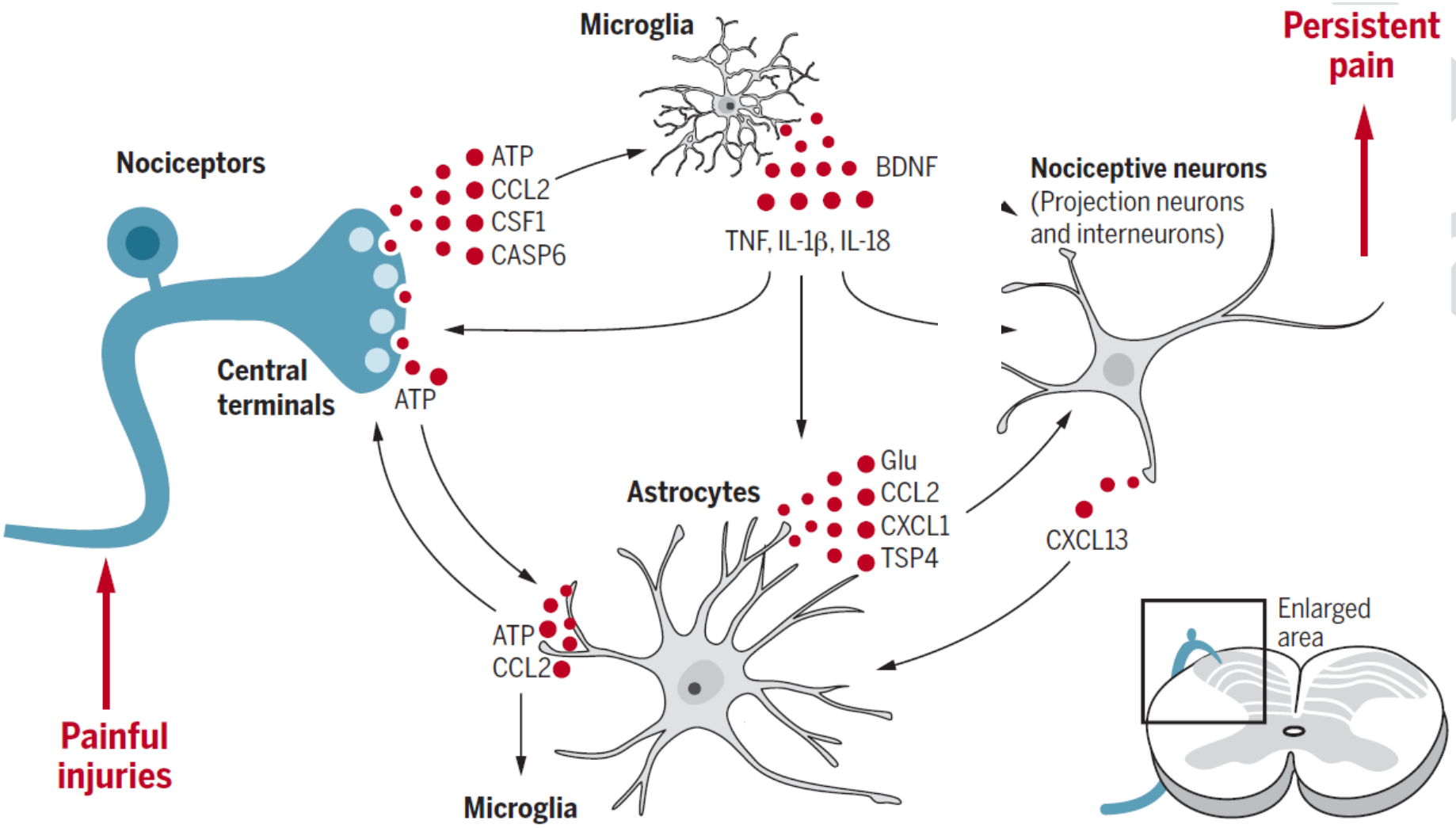


Activators:
CX3CL1, ATP, CSF1
MMP-9, CathS, CASP6

Receptors:
P2X4, P2X7, P2Y12
CX3CR1, CCR2, CSFR1
TLR4, PANX1

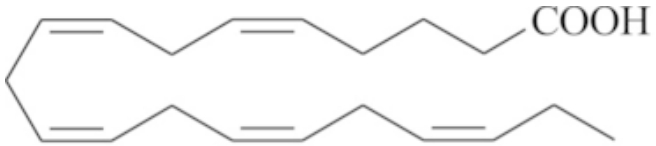
Microglial mediators
TNF-α
IL-1β
IL-18
BDNF

Neuron-glial and glia-glial interactions in chronic pain

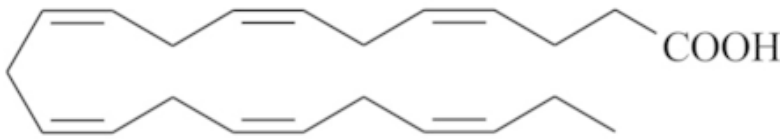


Ji et al., *Science*, 2016

Fish oil / Omega-3 EPA/DHA



EPA Eicosapentaenoic acid
(EPA, $C_{20}H_{30}O_2$)



Docosahexaenoic acid
(DHA, $C_{22}H_{32}O_2$) **DHA**

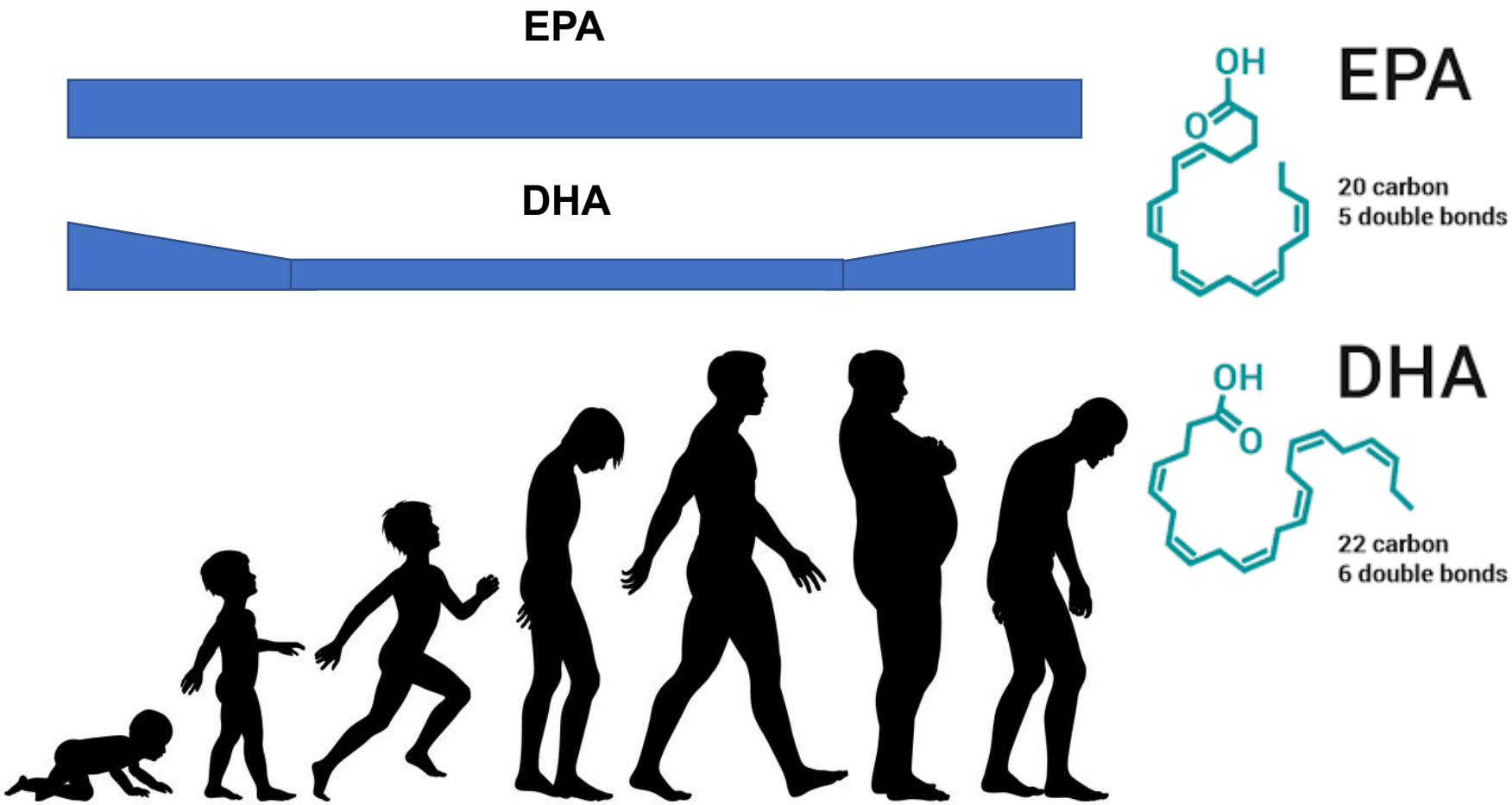
360 mg Omega-3 / Softgel
180 mg EPA
120 mg DHA

Benefits

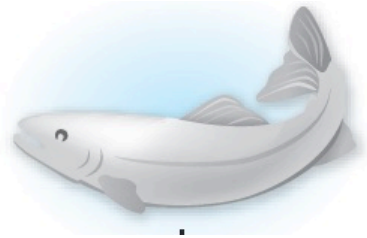
- Joint and bone
- Mental health
- Cholesterol levels
- Eye health
- Skin health
- Heart health
- Healthy blood glucose
- Energy and endurance
- **Pain relief**

Fish oil / Omega-3 EPA/DHA

EPA levels are under constant demand and DHA deficiency in adolescents and adults correlates with mental issues.



How does fish oil modulate pain?



Direct effects

Dietary essentially fat

↓

Omega-3 polyunsaturated fatty acids

↓

Docosahexaenoic acid (DHA) | Eicosapentaenoic acid (EPA)

↓

GPR40 / long-chain free fatty acid receptor 1 (FFAR1)

↓

Anti-inflammation and analgesia (weak effects)

Fish oil, SPM, and pain

Dietary essentially fat

↓

Omega-3 polyunsaturated fatty acids

↓ ↓

Docosahexaenoic acid (DHA) | Eicosapentaenoic acid (EPA)

↓

SPMs (specialized pro-resolving mediators)

↓

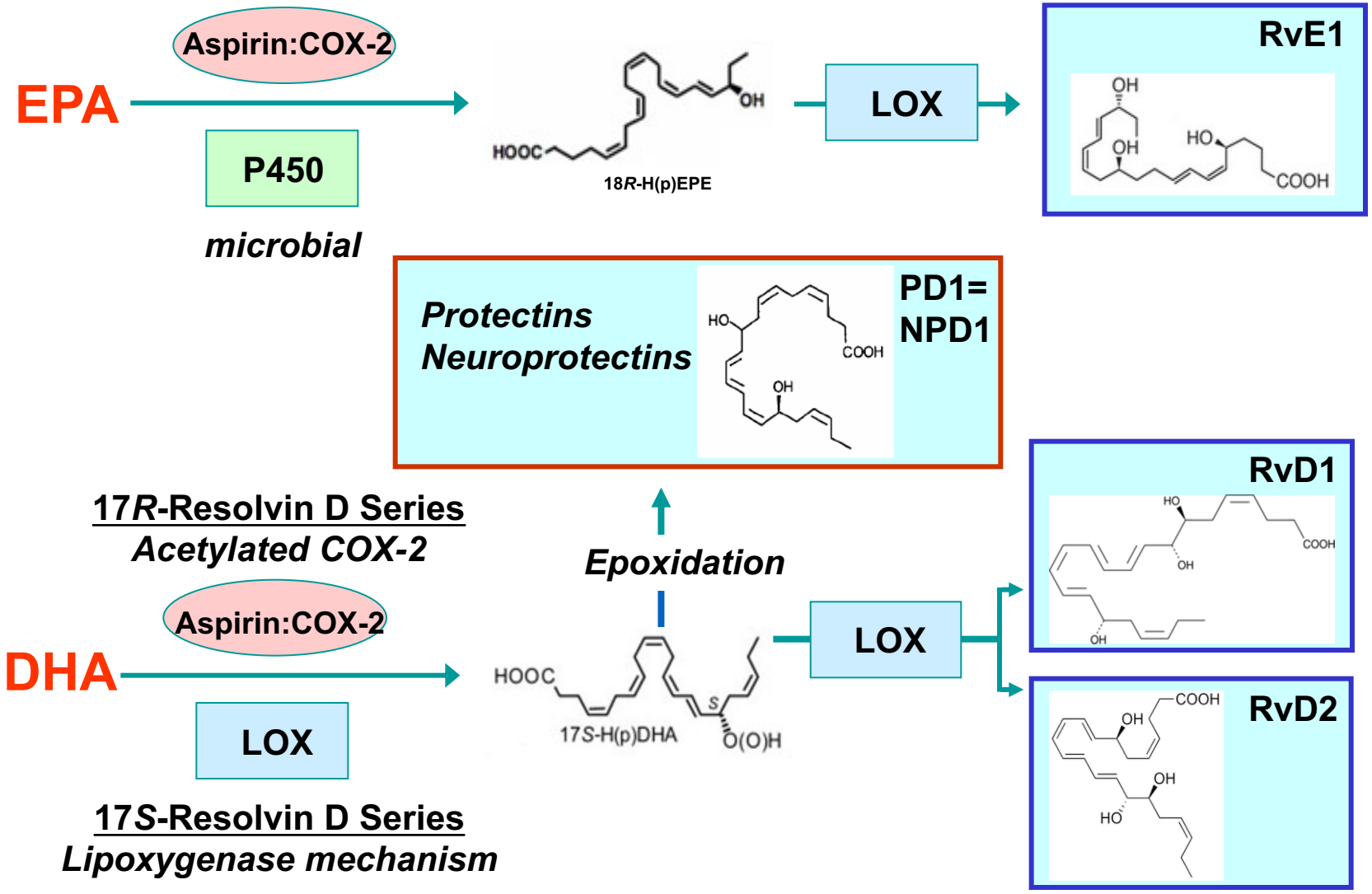
Anti-inflammation, pro-resolution, analgesia (potent effects)

Indirect effects

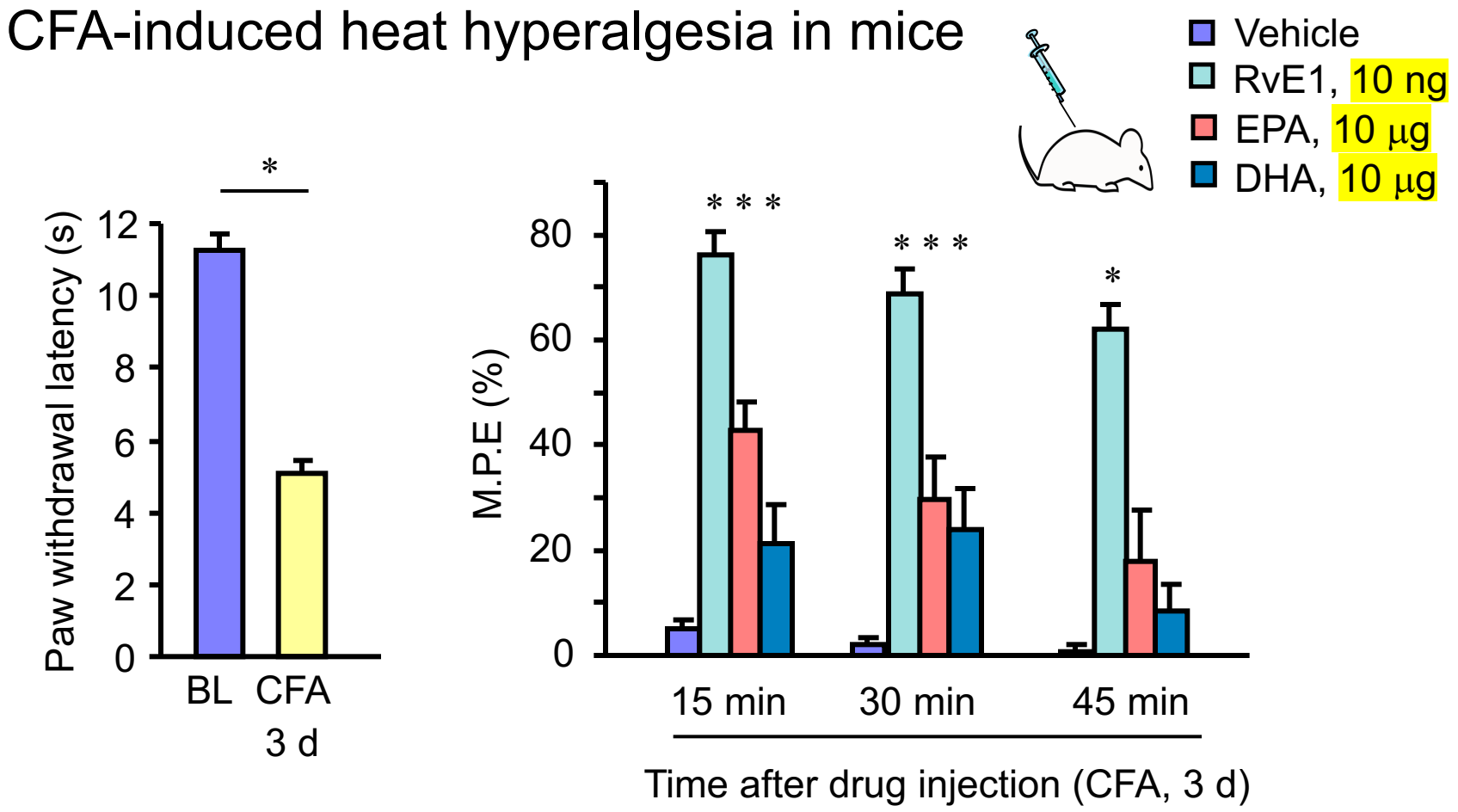
Cayman CHEMICAL

Biosynthesis of SPMs resolvins and protectins

during resolution phase of inflammation

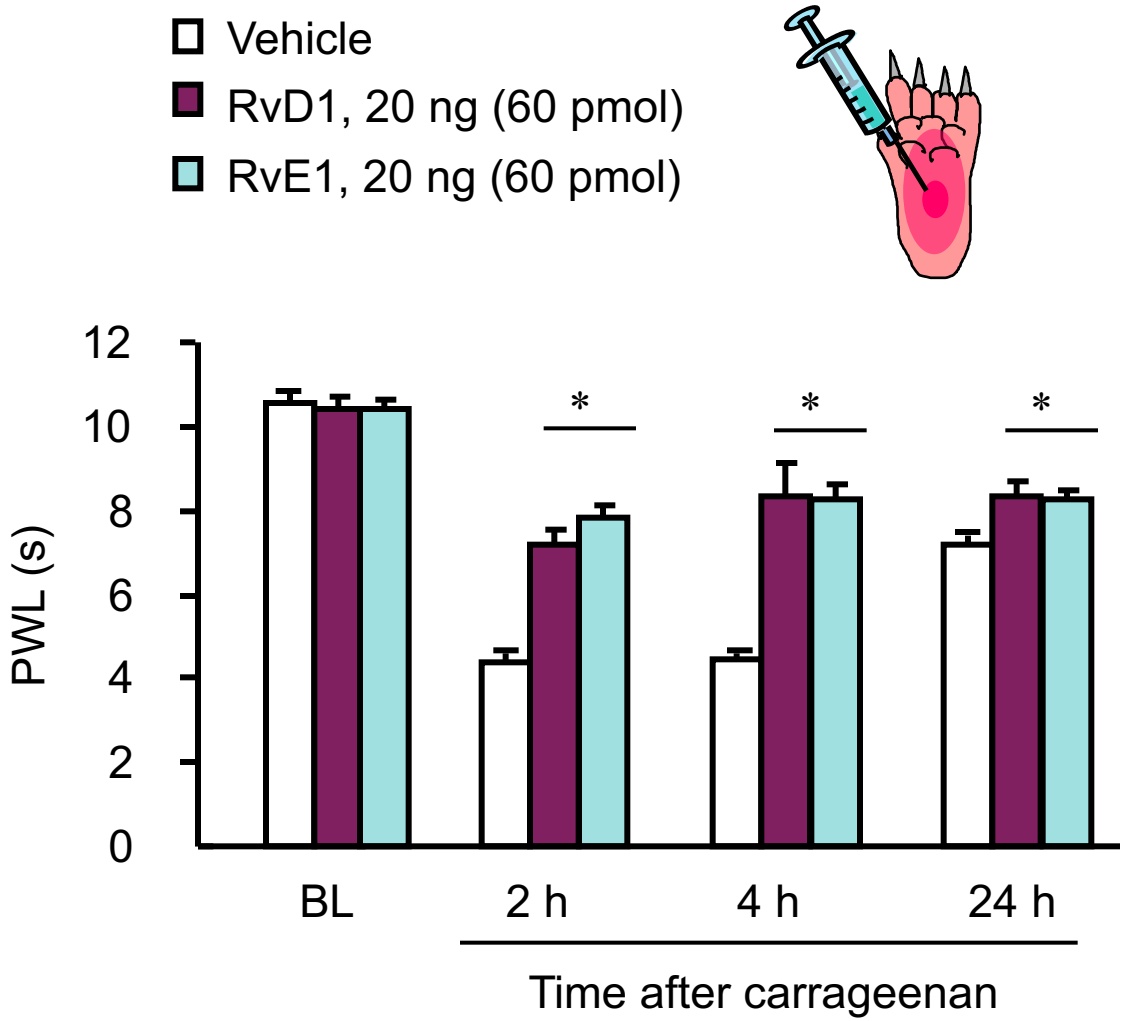


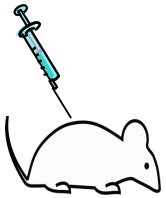
Comparison of analgesic efficacy of resolvin and fish oil in inflammatory pain



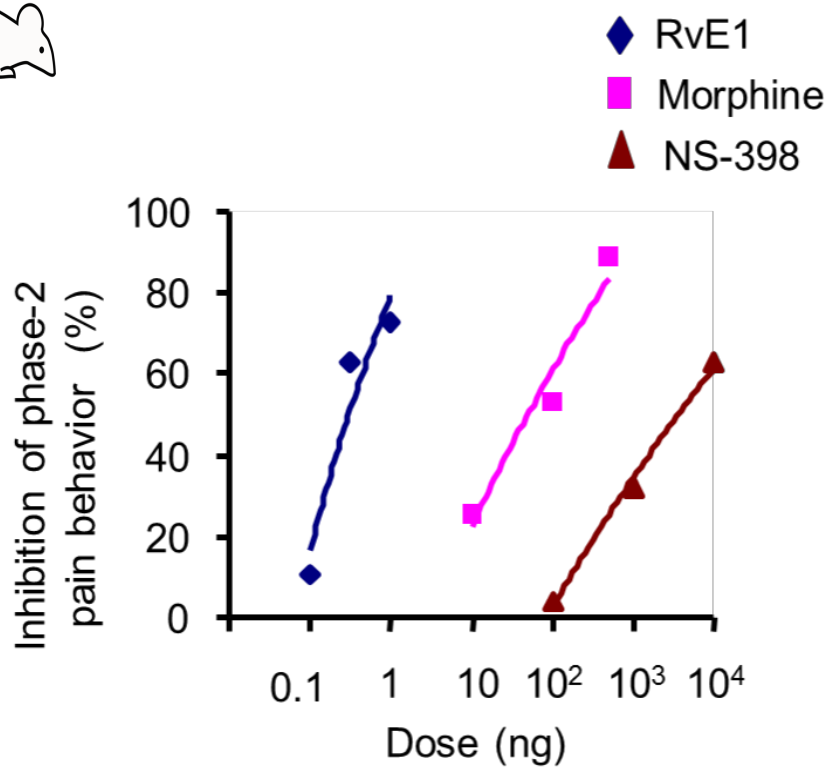
Xu et al., 2010; Nature Medicine

Resolvins potently inhibits inflammatory pain





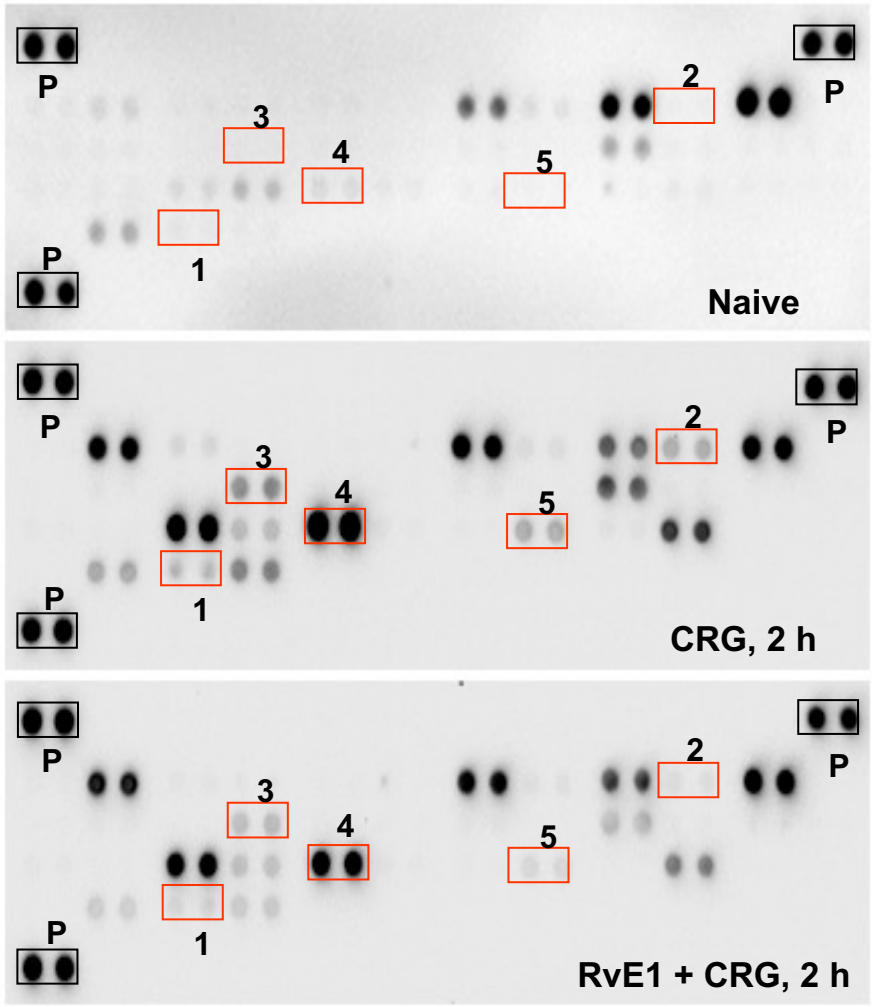
Formalin-induced 2nd-phase pain



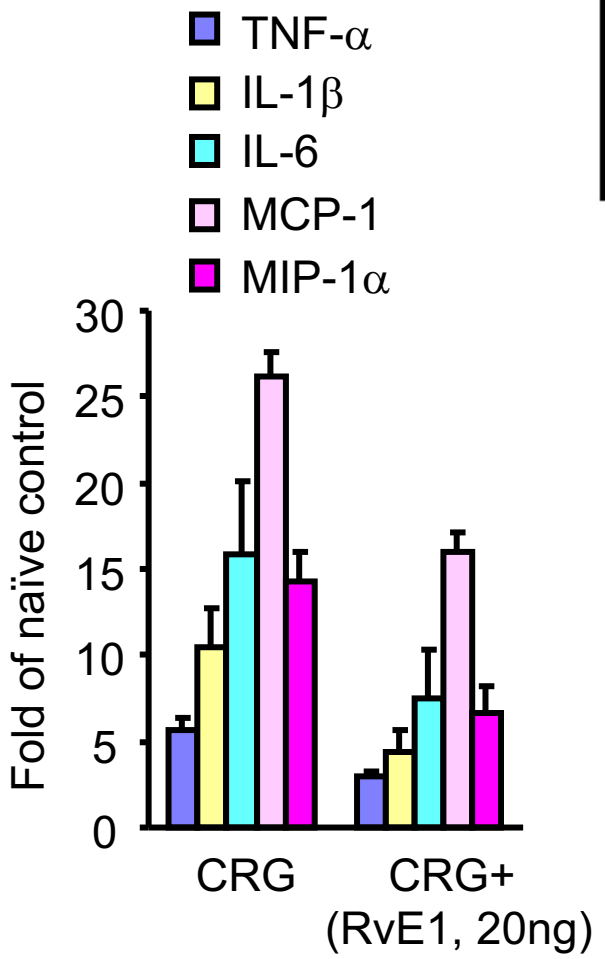
Xu et al., *Nat Med*, 2010

RvE1 inhibits inflammation and neuroinflammation

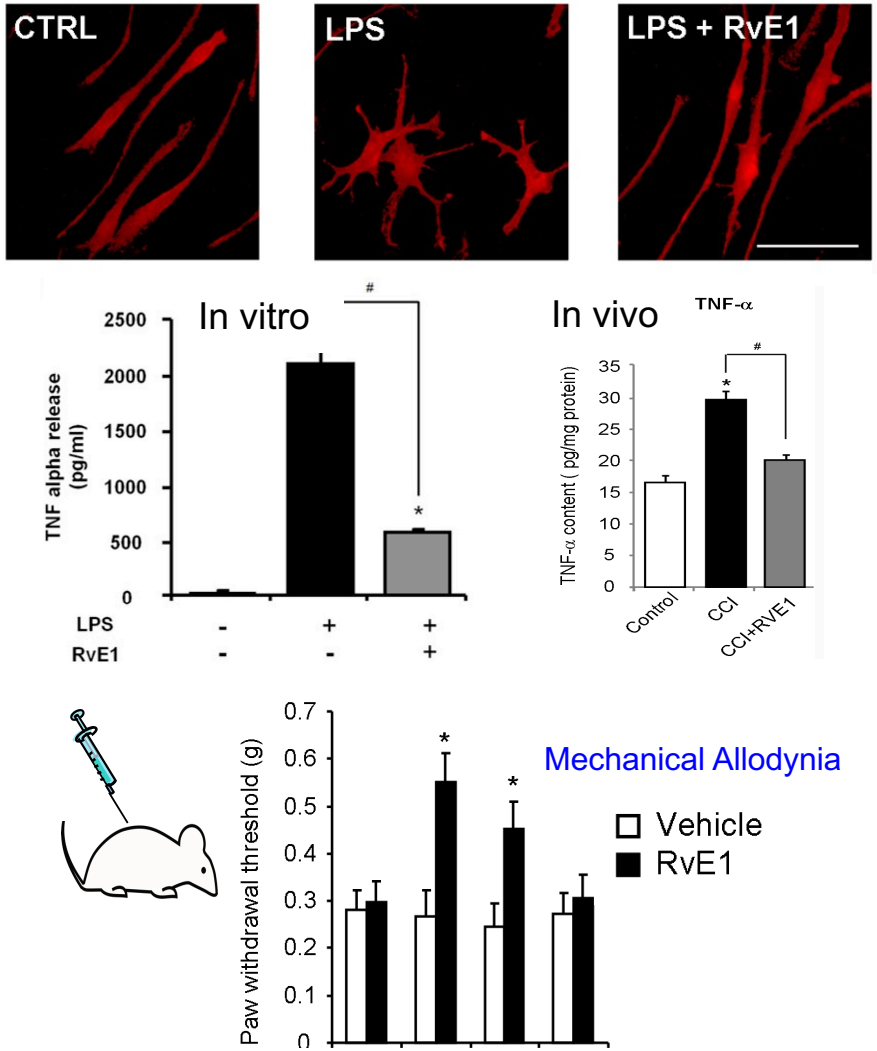
Hind paw inflammation



Cytokine array



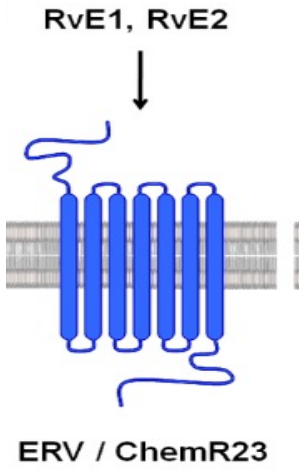
Microglial activation

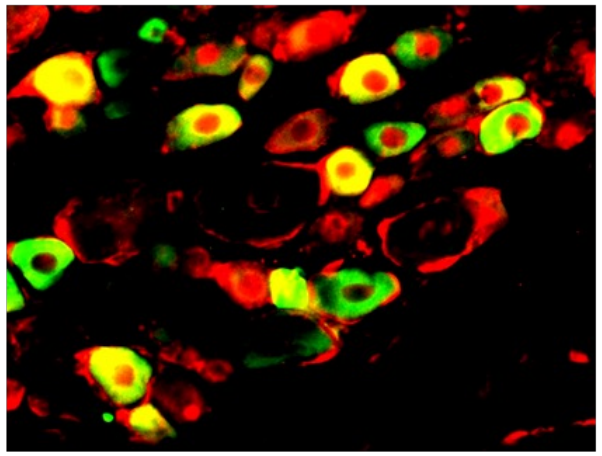


Xu et al., *Nat Med*. 2010

Xu et al., *J Neuroimmune Pharmacol*. 2013

RvE1 inhibits TRPV1 signaling in DRG and spinal cord neurons and acts as a neuromodulator





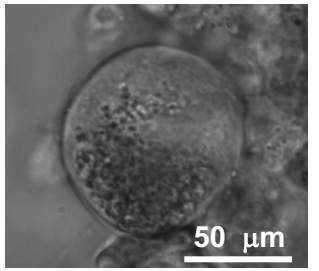
TRPV1 / ChemR23

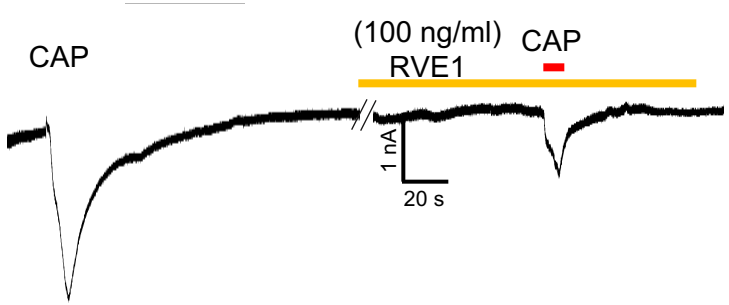
Mouse

TRPV1 current

Capsaicin RvE1 (1 ng/ml)

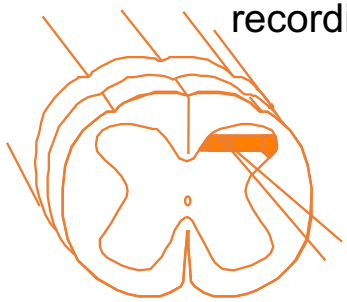
Human

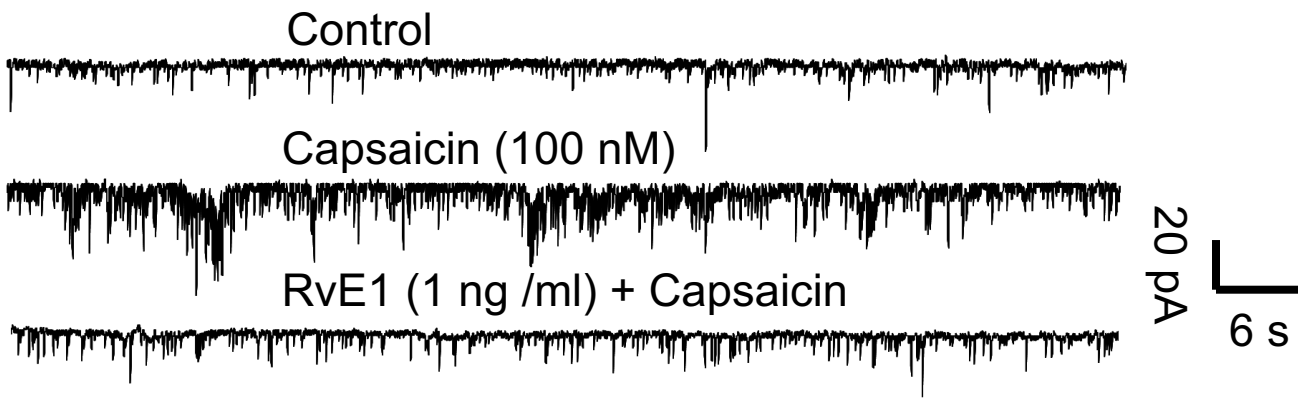




Mouse sEPSC

Patch clamp recording





Xu et al., 2010; *Nature Medicine*

Resolvins, fish oil, and inflammatory pain

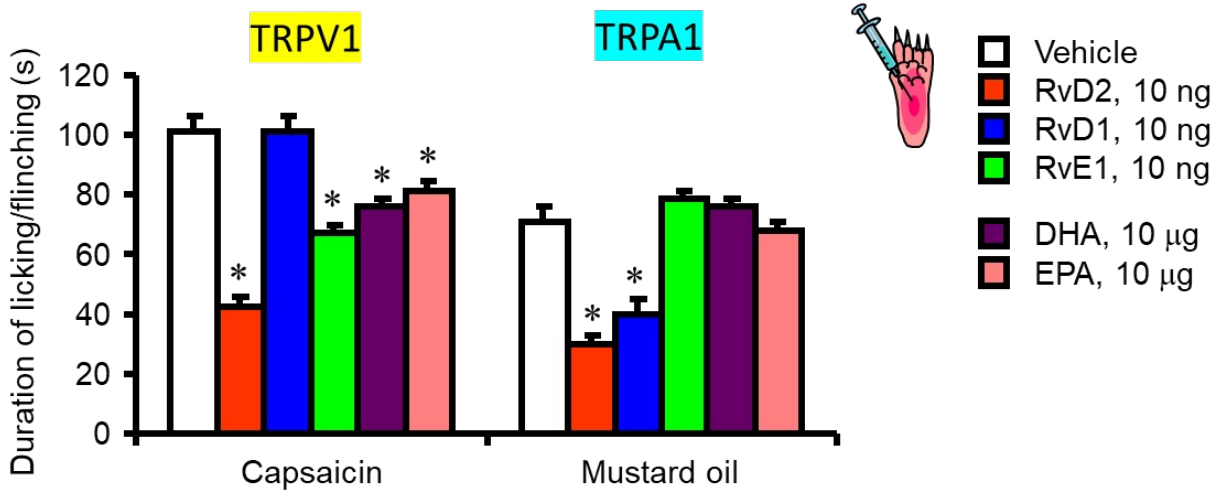


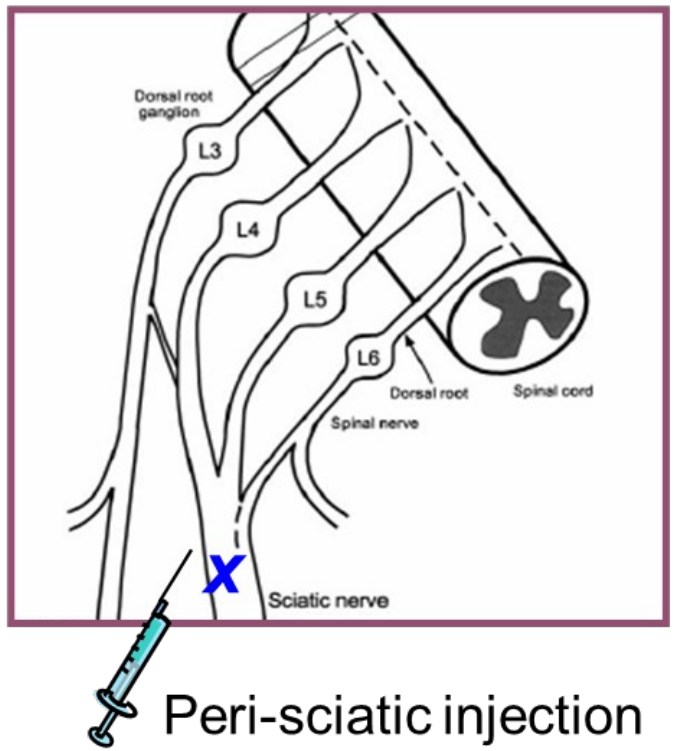
Table 1. IC_{50} for inhibition of TRPV1 and TRPA1 currents by RvD2, RvD1, RvE1, and their fatty acid precursors in DRG neurons

Inhibitors	Molecular weight	TRPV1 IC_{50} (nM)	TRPA1 IC_{50} (nM)
RvE1	350.4	1.0 ± 0.1	>28.5
RvD1	376.5	>26.6	8.5 ± 0.1
RvD2	376.5	0.1 ± 0.01	2.1 ± 0.5
DHA	328.5	1200.0 ± 20.0	>304,000.0
EPA	302.5	224.0 ± 10.0	>330,578.0

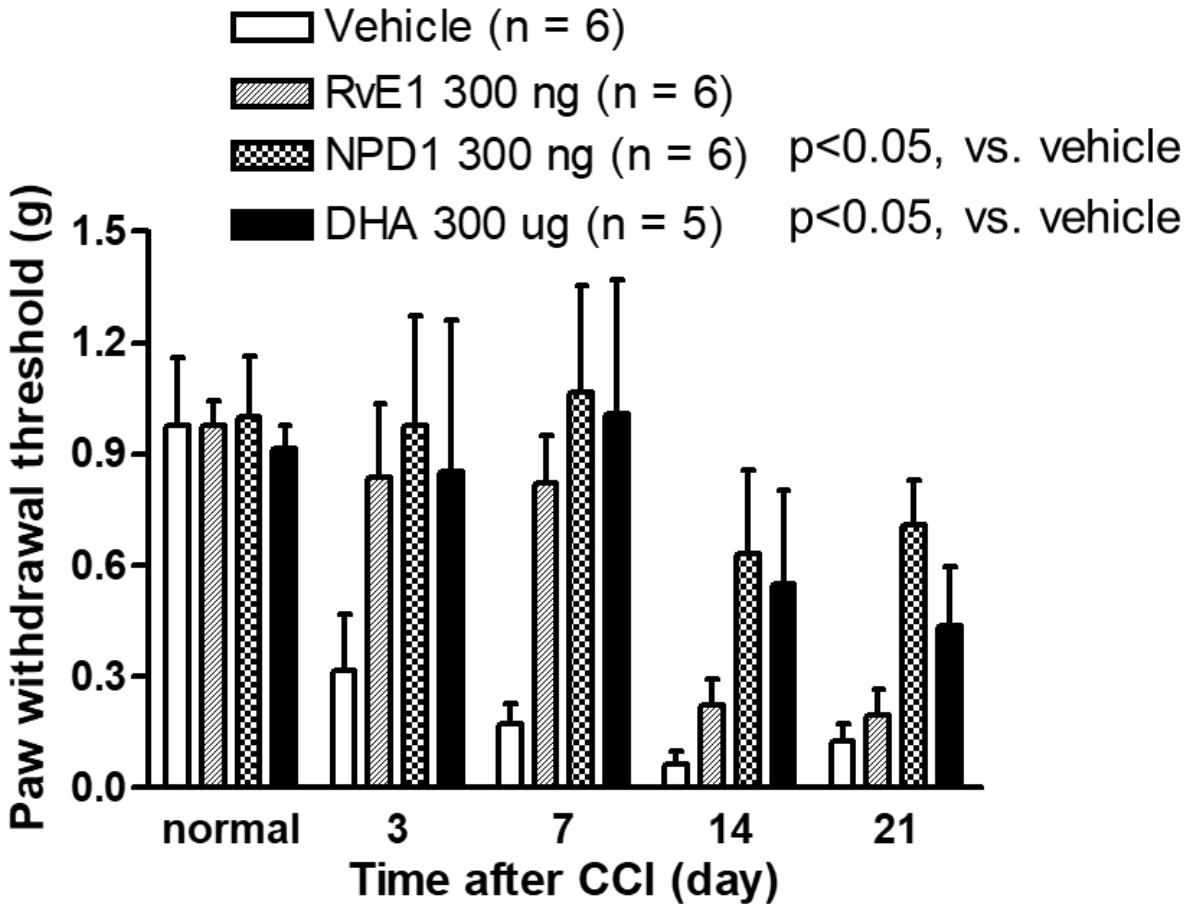
TRPV1 and TRPA1 currents were induced by capsaicin (100 nM) and AITC (300 μM), respectively.

Park et al., J Neurosci, 2011

Pre-treatment of DHA and NPD1 protects neuropathic pain in mice after nerve trauma

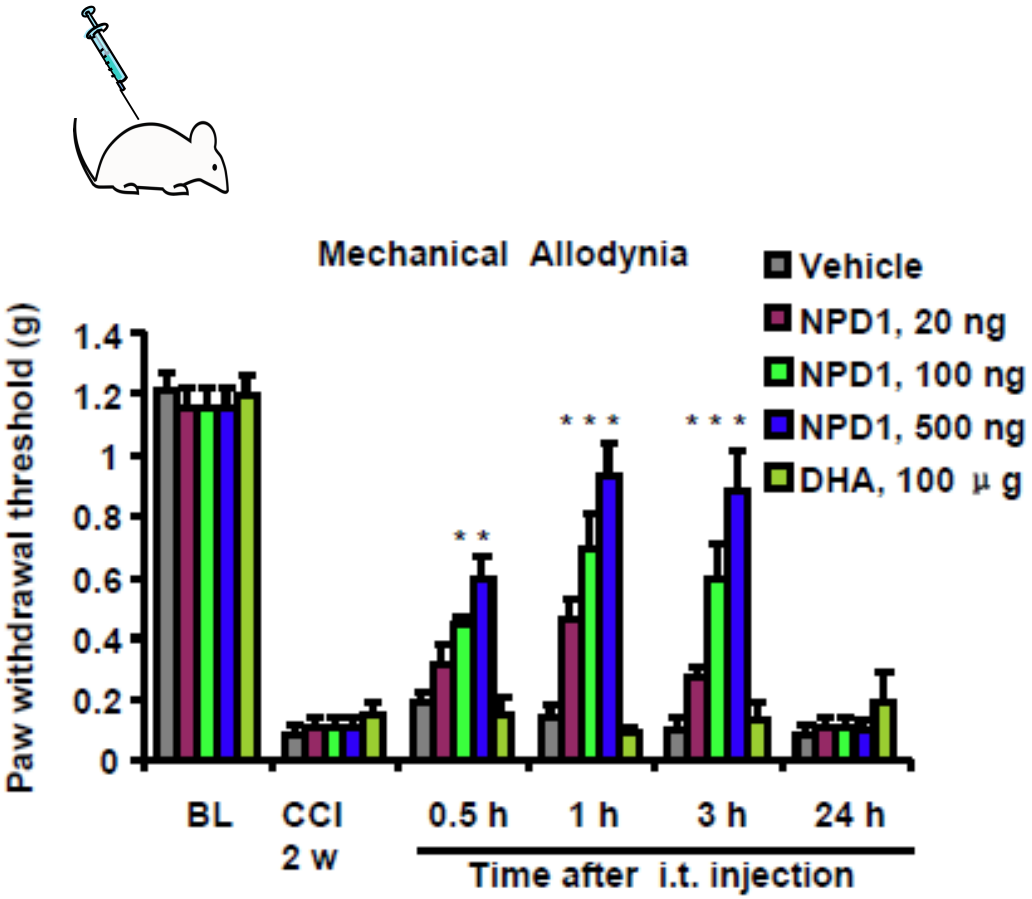


CCI: Chronic Constriction Injury

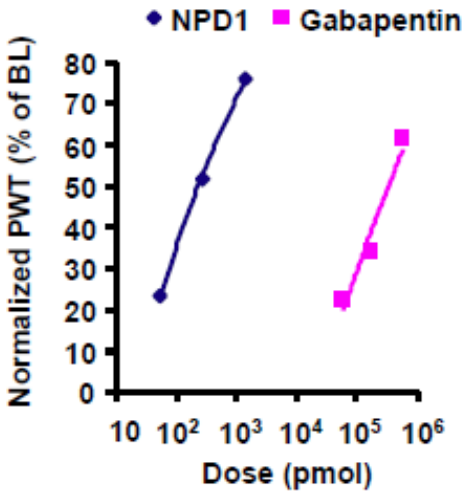


Xu et al., *Annals of Neurology,* 2013

Post-treatment of NPD1 and gabapentin, but not DHA, attenuates established neuropathic pain



Comparison with gabapentin



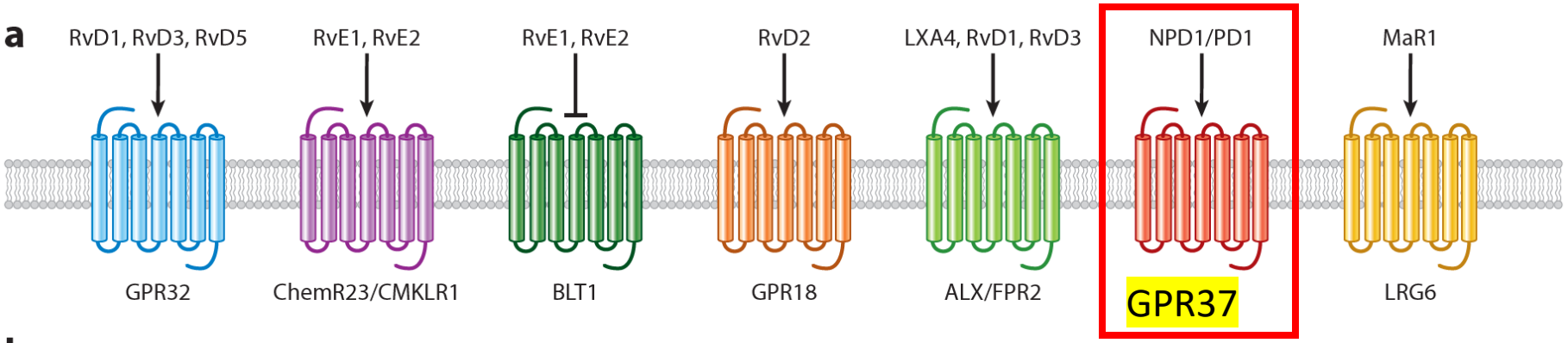
Xu et al., *Annals of Neurology*, 2013

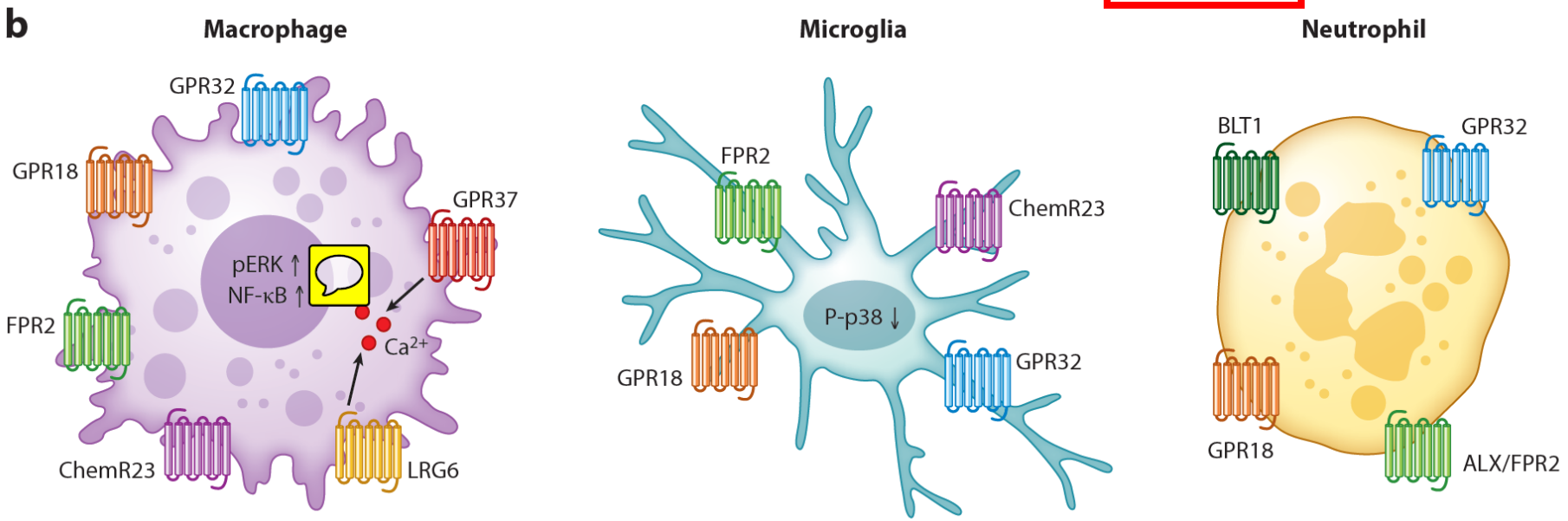
SPMs as Resolution Pharmacology for the Control of Pain and Itch

Pain/itch models	SPMs	Species/Route	Effects	References
Inflammatory pain				
Capsaicin (TRPV1)	RvE1, RvD2/D3, MaR1, NPD1	mice, IPL	Spontaneous pain ↓	55, 58, 59
Mustard oil (TPA1)	RvD1, RvD2	mice, IPL	Spontaneous pain ↓	57, 58,
Formalin	RvE1, NPD1, RvD5	mice, IT	Spontaneous pain ↓	55, 59, 84
Carrageenan	RvD1, RvE1, LXA4, LXB4	mice/rats IT, IV	Heat and mechanical pain ↓	55, 68
CFA	RvD1, RvD2, RvE1, NPD1	mice, IT	Heat hyperalgesia ↓	55, 58, 59
Visceral pain	RvD2	mice, rats, IP	Visceral pain ↓	60
Bladder pain	RvD2	rats, IT,	Mechanical pain ↓	71
Low back pain	LXA4, MaR1	rats, IT	Mechanical pain ↓	72, 73
Vulvodynia	MaR1	mice, topical	Mechanical pain ↓	65
Osteoarthris	17(R)-HDHA, AT-RvD1	rats / IP	Spontaneous & mechanical pain ↓	61
Rheumatoid arthritis	MaR1, AT-RvD1	mice/rats, IP	Mechanical pain ↓	63, 64
Neuropathic pain				
Nerve injury (CCI)	RvE1, MaR1, NPD1	mice, IT	Mechanical and heat pain ↓	83, 87, 88
Spinal cord injury	LXA4	mice, IT	Mechanical allodynia ↓	86
Chemotherapy	RvD1, RvD2, MaR1	mice, IT	Mechanical allodynia ↓	84
Diabetic neuropathy	3-oxa-PD1n-3 DPA	mice, IT	Mechanical allodynia ↓	85
Post-operative pain				
Muscle retraction	RvD1, RvE1	rats, IT	Mechanical allodynia ↓	78
Thoracotomy	RvD1, RvD2	rats, IT	Mechanical and nocifensive pain ↓	79
Tibial bone fracture	RvD1, RvD2, MaR1	mice, IV, IT	Mechanical pain ↓	46
Cancer pain				
Oral cancer pain	RvD2	mice, IP,	Mechanical $ spontaneous pain ↓	96
Bone cancer pain	RvD1, RvE1	mice, IT	Mechanical and thermal pain ↓	95
Dermatitis and itch				
Eczema	LXA4	human, topic	Infantile eczema severely ↓	128
Psoriasiform itch	RvD3	mice, topic	scratching ↓	124
Cancer itch	3-oxa-PD1n-3 DPA	mice, IT	scratching ↓	85

Ji, Annu. Rev. Pharmacol. Toxicol. 2023

SPM receptors and signaling





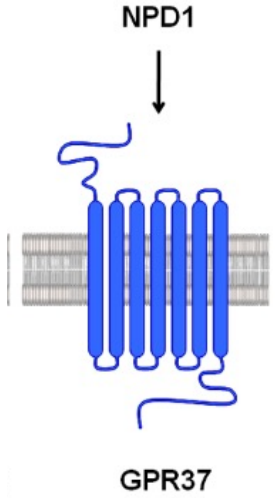
⬆Phagocytosis (RvE1, RvD1, NPD1, MaR1)
⬆Ca^{2+} (NPD1, MaR1)
⬆pERK/pAKT (RvE1, NPD1)
⬆IL-10, TGF-β (RvE1, NPD1)
⬇IL-1β, IL-6 (RvE1, NPD1)

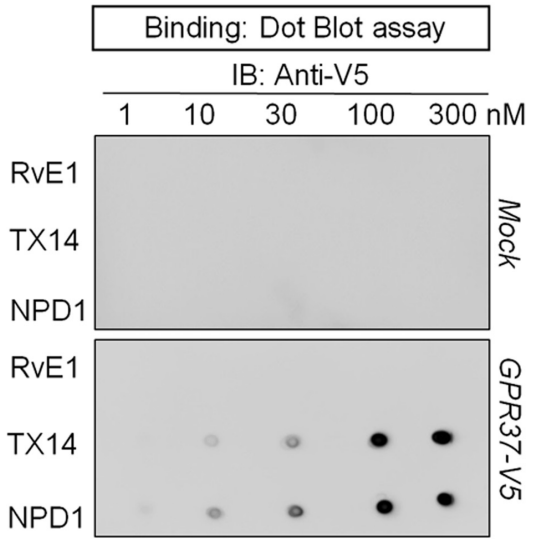
⬇TNF (RvE1, NPD1, LXA4)
⬇P-p38 (RvE1)

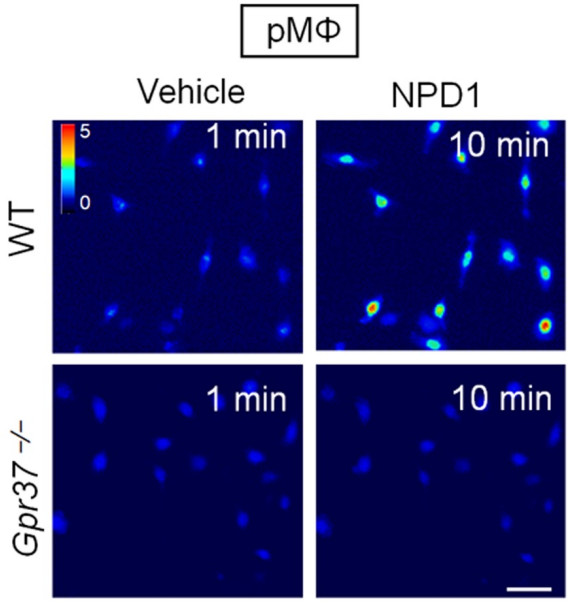
⬇LTB4 functions (RvE1, LXA4)
⬇NF-κB activation (RvE1, RvD1)
⬇Infiltration (RvD1/D2, RvE1)

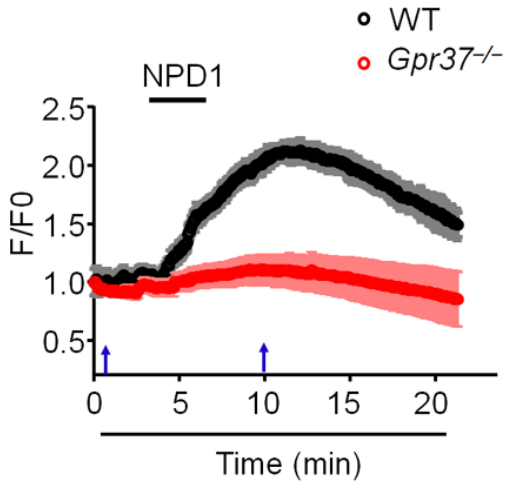
Ji, Annu. Rev. Pharmacol. Toxicol. 2023

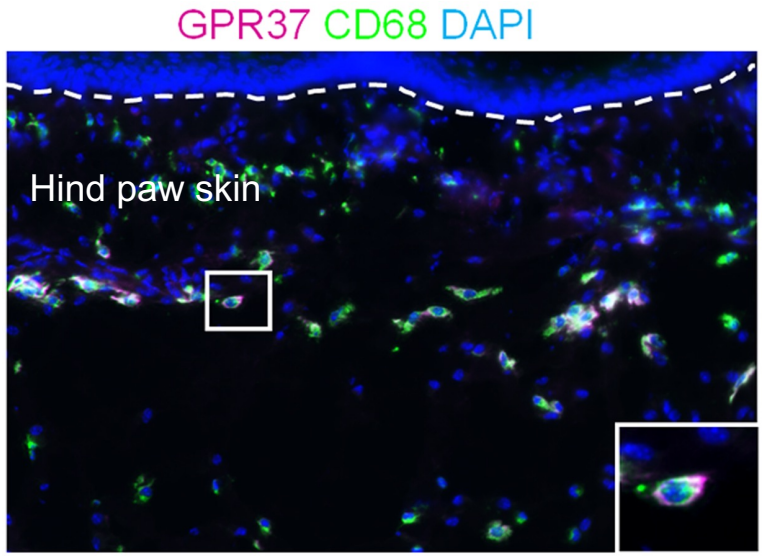
GPR37 is a possible receptor for NPD1 in macrophages

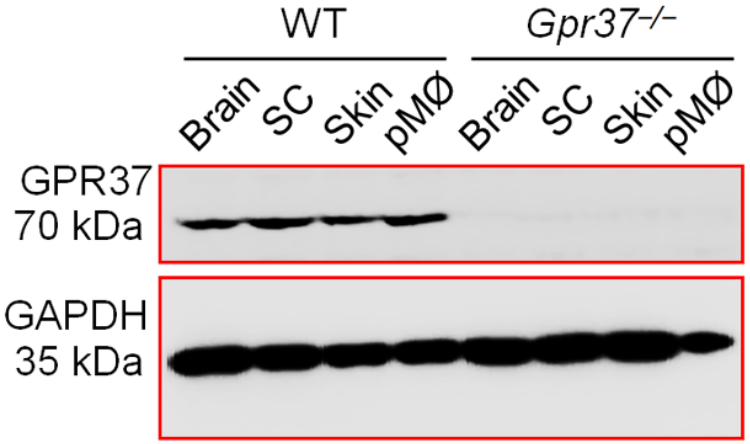






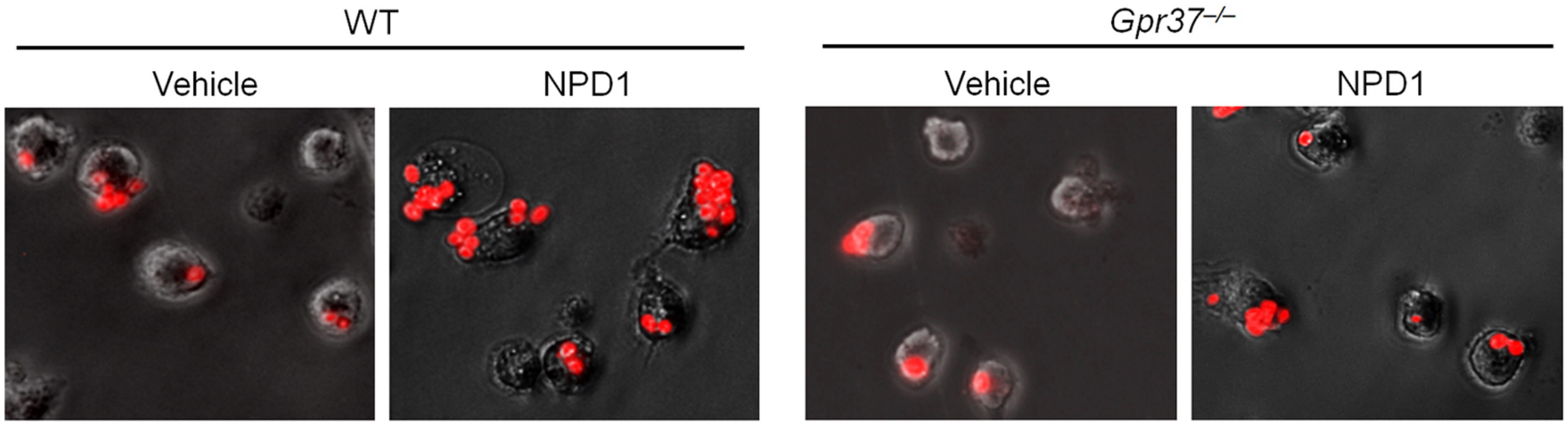






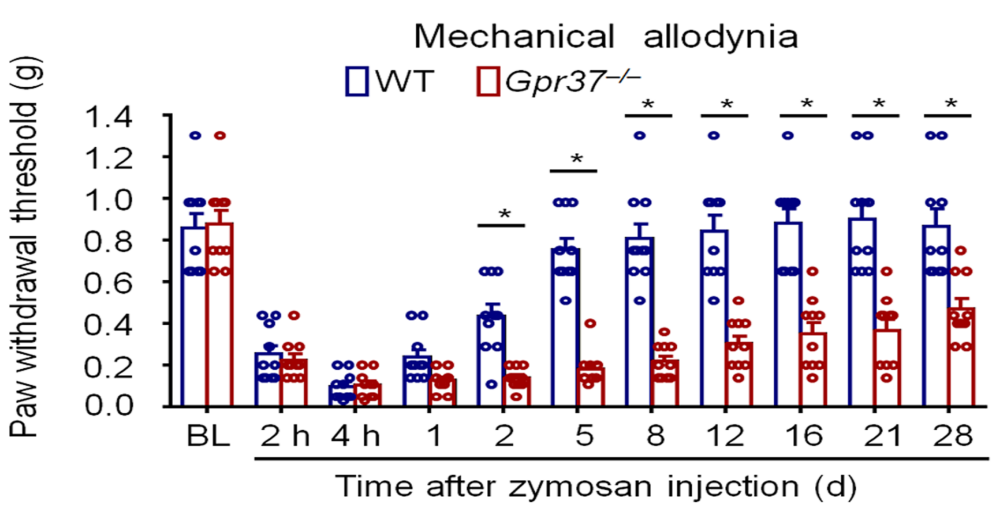
Bang et al., *JCI,* 2018

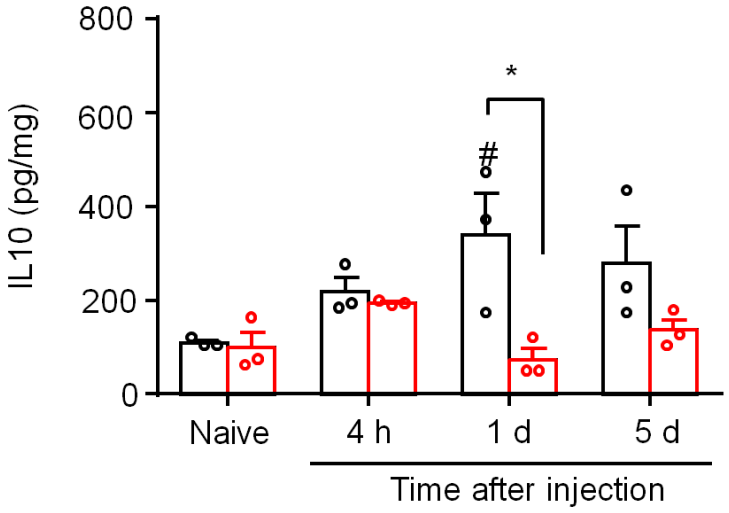
NPD1 induces macrophage phagocytosis via GPR37



Zymosan particles-pH sensitive

GPR37 regulates the resolution of inflammatory pain





Bang et al., *JCI*, 2018

nature COMMUNICATIONS

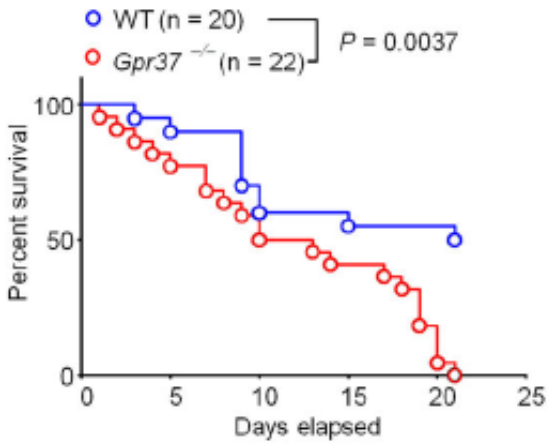
ARTICLE

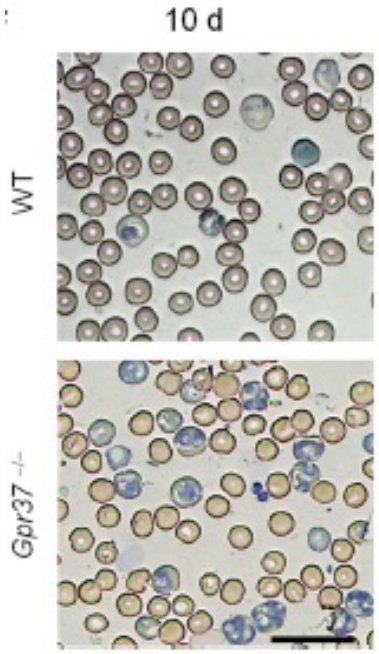
https://doi.org/10.1038/s41467-021-21940-8 OPEN

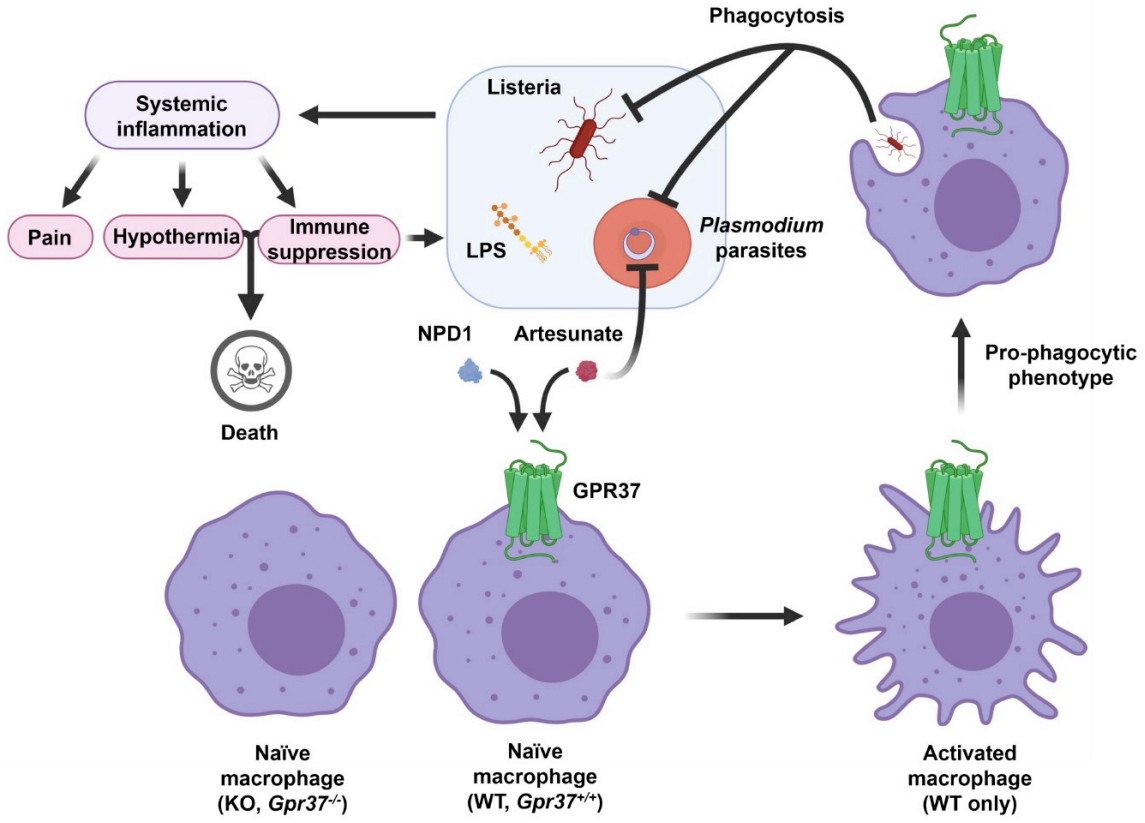
Check for updates

Activation of GPR37 in macrophages confers protection against infection-induced sepsis and pain-like behaviour in mice

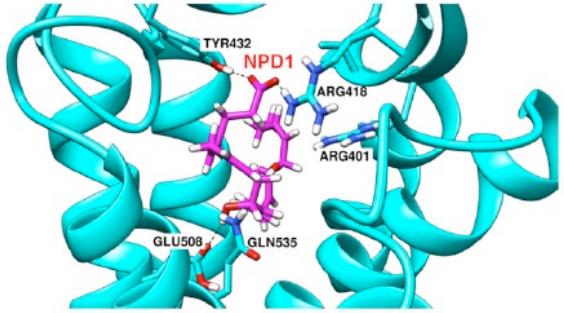
Sangsu Bang[1,5], Christopher R. Donnelly[1,5], Xin Luo[1,5], Maria Toro-Moreno[2,5], Xueshu Tao[1], Zilong Wang[1], Sharat Chandra[1], Andrey V. Bortsov[1], Emily R. Derbyshire[2] & Ru-Rong Ji[1,3,4]✉



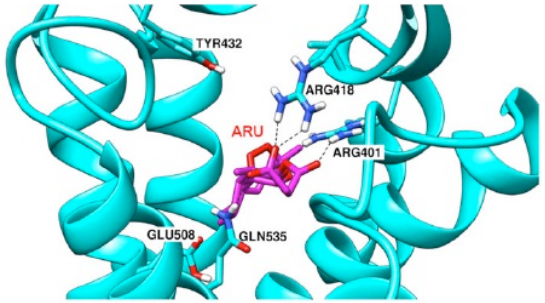




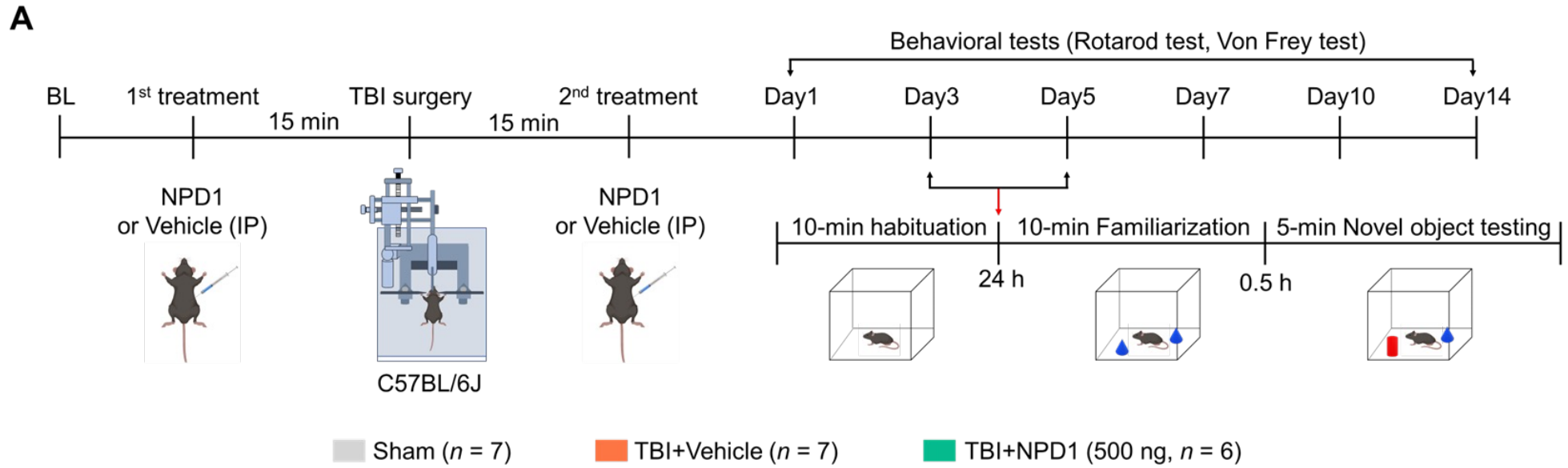
Neuroprotectin D1 (NPD1)

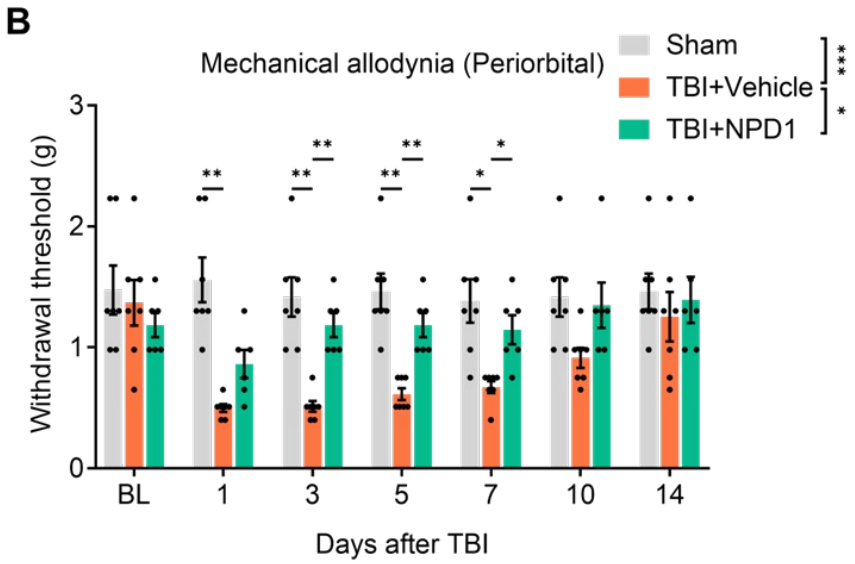


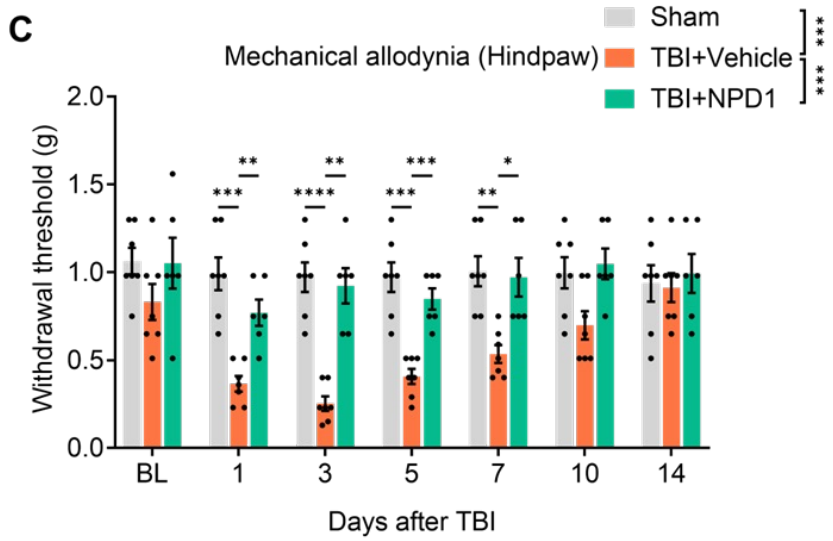
Artisunate (ARU)



NPD1 and neuropathic pain after traumatic brain injury (TBI)

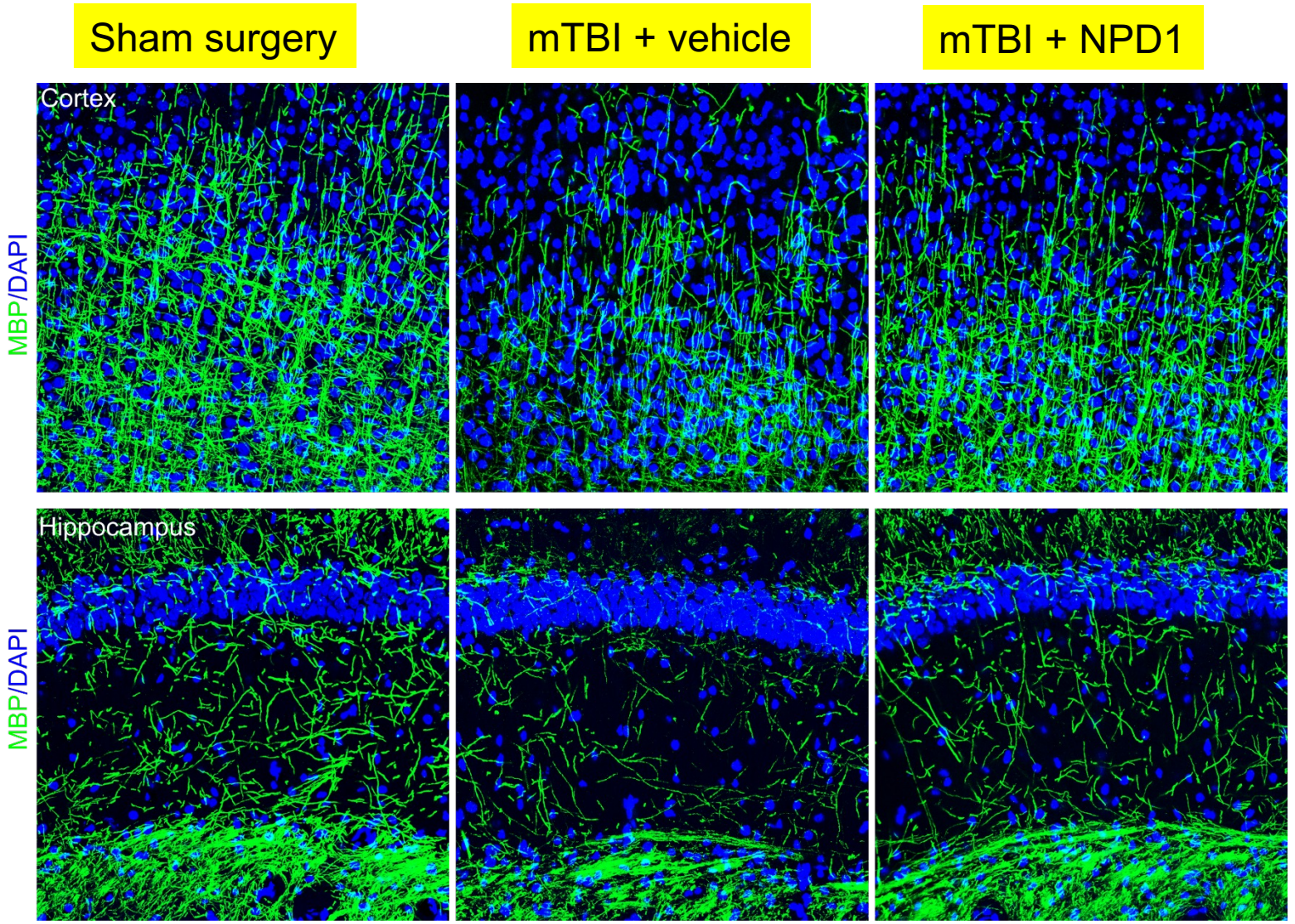






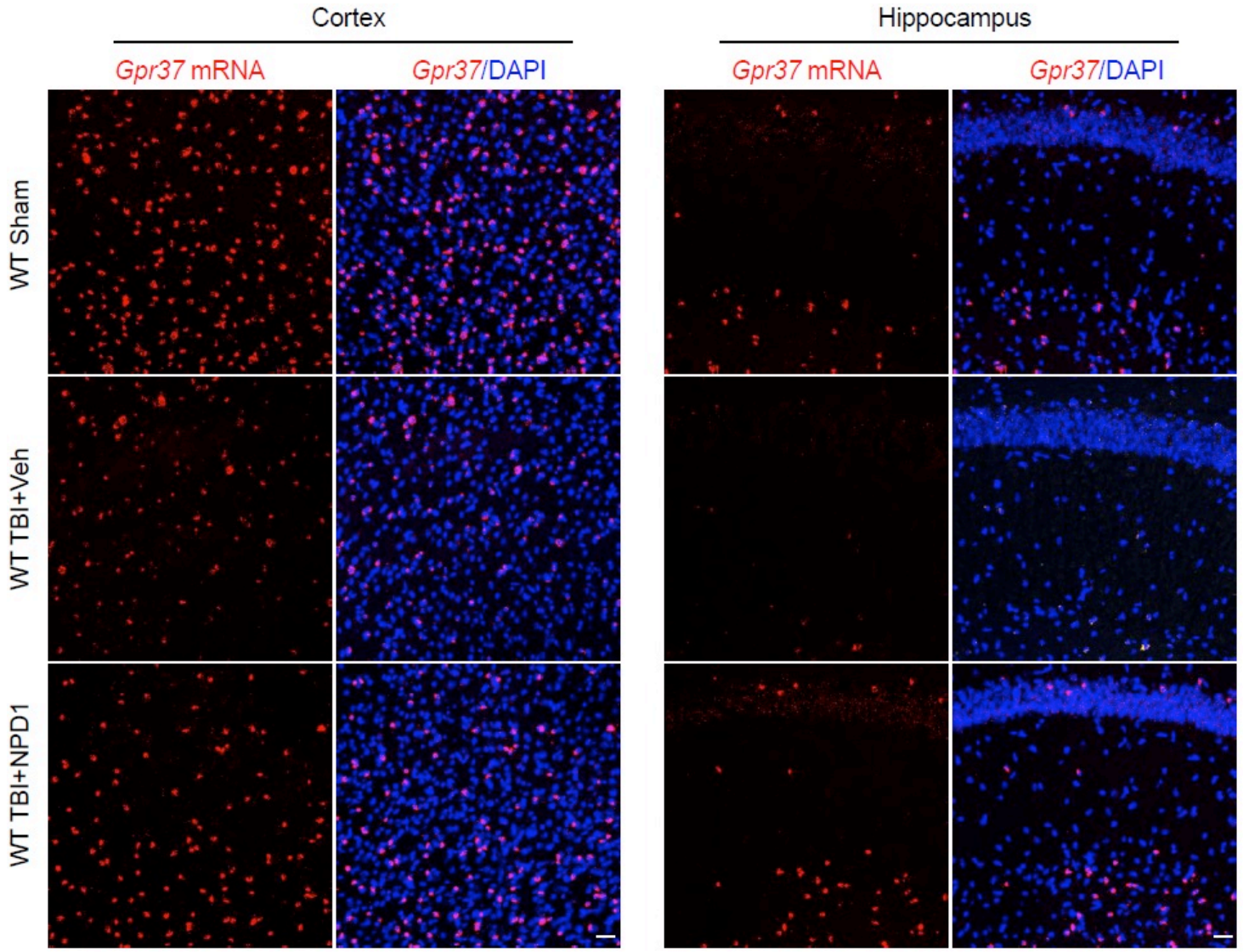
Unpublished data

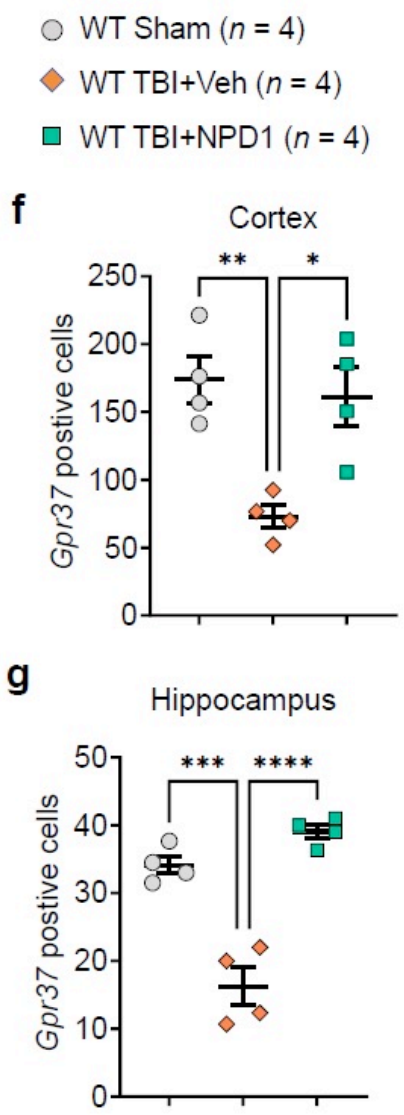
Demyelination in sensory cortex and hippocampus after mTBI



Unpublished data

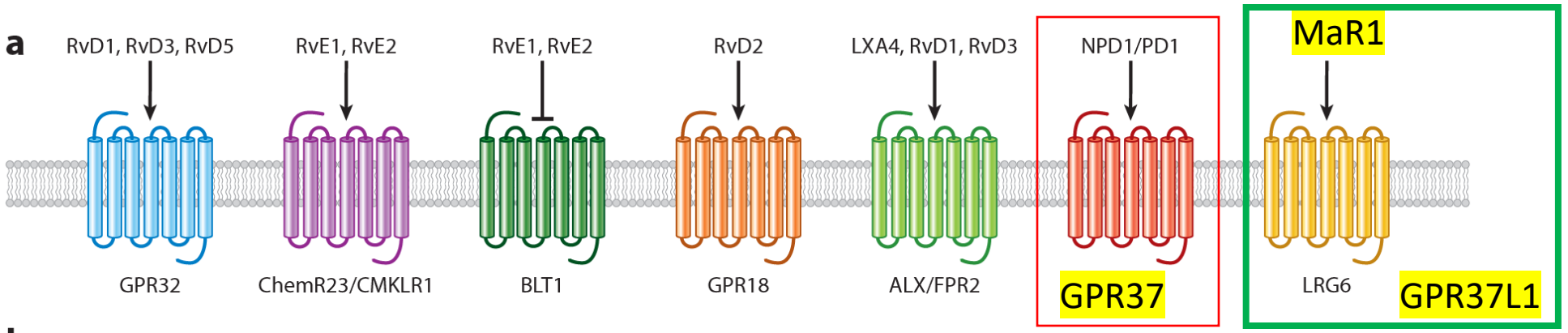
NPD1 restores TBI-induced down-regulation of GPR37

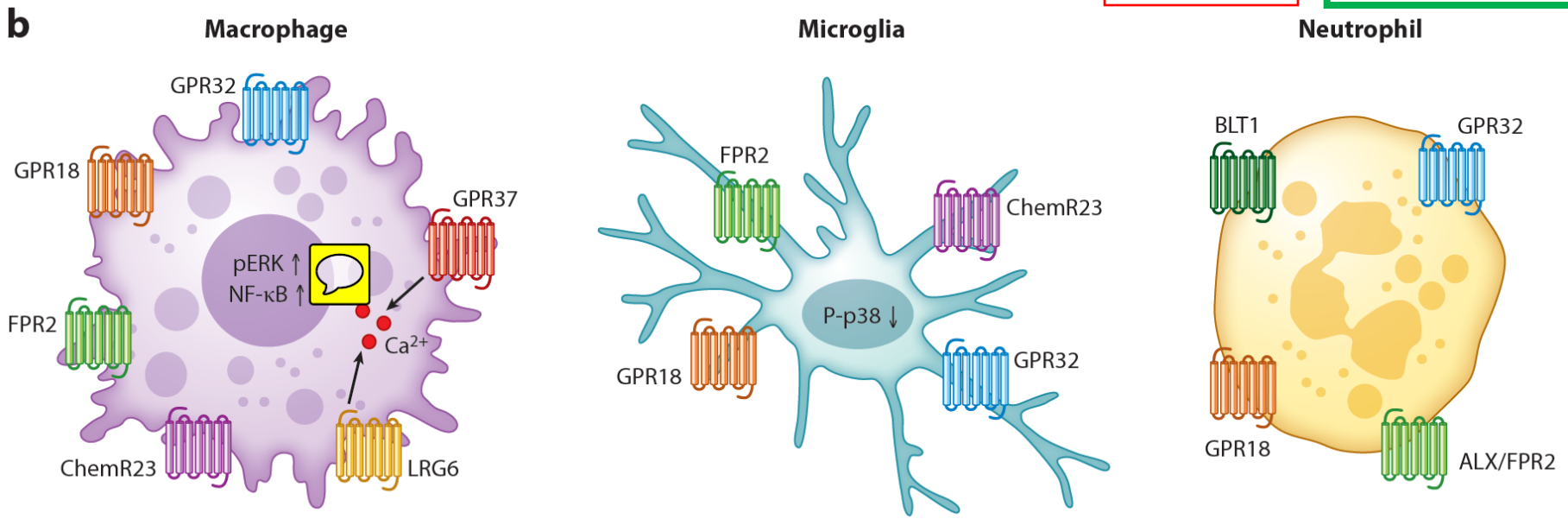




Unpublished data

SPM receptors and signaling





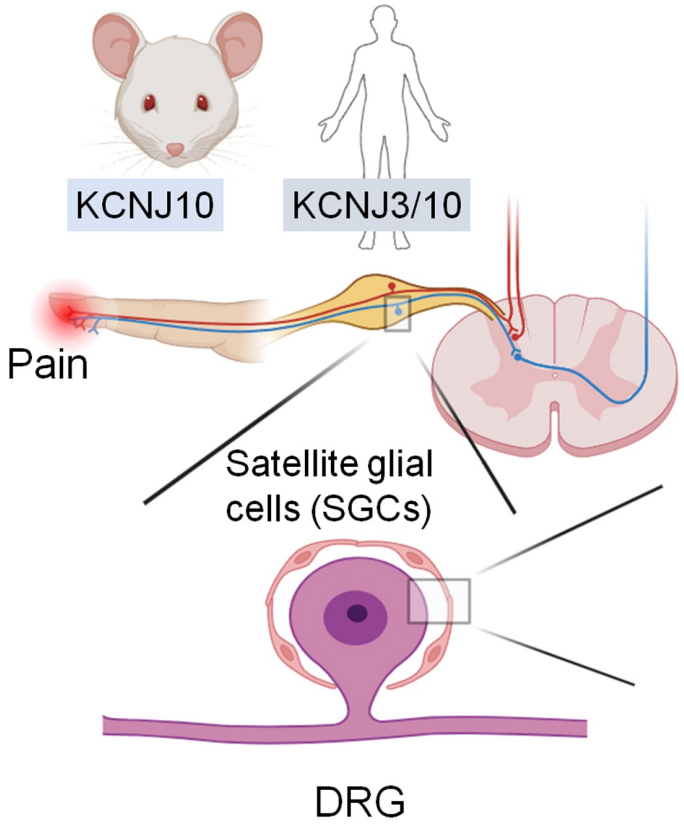
⬆Phagocytosis (RvE1, RvD1, NPD1, MaR1)
⬆Ca^{2+} (NPD1, MaR1)
⬆pERK/pAKT (RvE1, NPD1)
⬆IL-10, TGF-β (RvE1, NPD1)
⬇IL-1β, IL-6 (RvE1, NPD1)

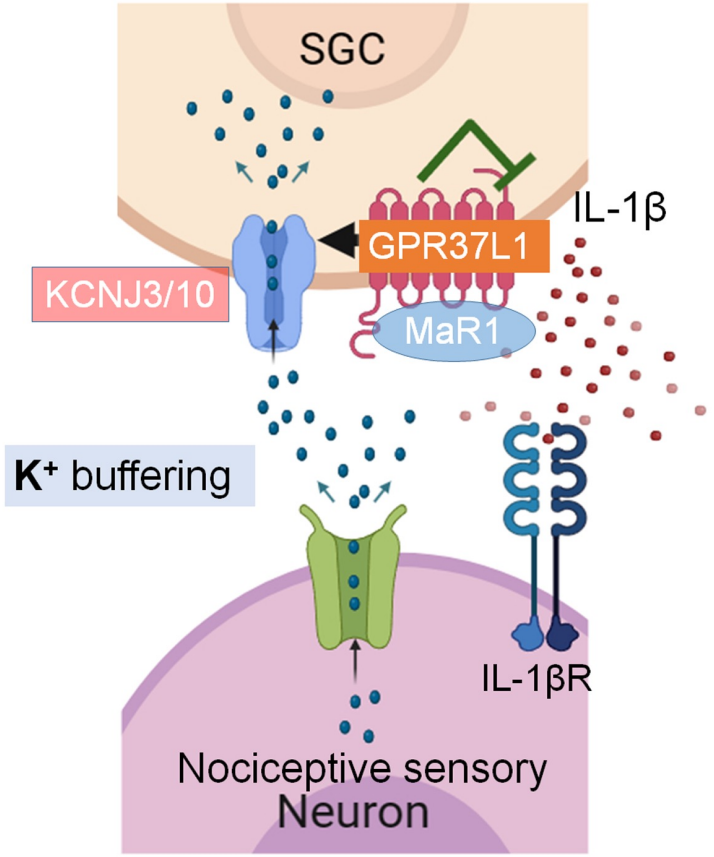
⬇TNF (RvE1, NPD1, LXA4)
⬇P-p38 (RvE1)

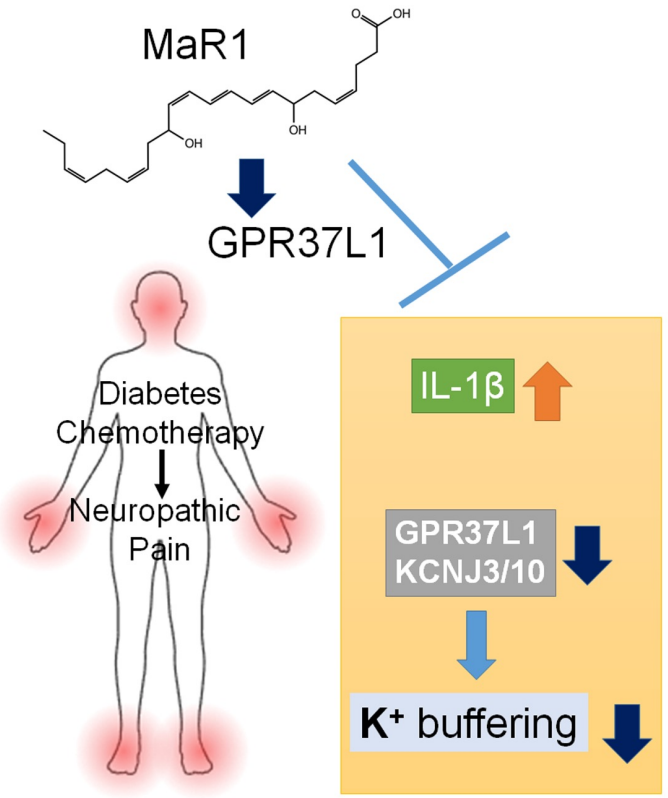
⬇LTB4 functions (RvE1, LXA4)
⬇NF-κB activation (RvE1, RvD1)
⬇Infiltration (RvD1/D2, RvE1)

Ji, Annu. Rev. Pharmacol. Toxicol. 2023

GPR37L1 signaling in SGCs in mouse and human pain





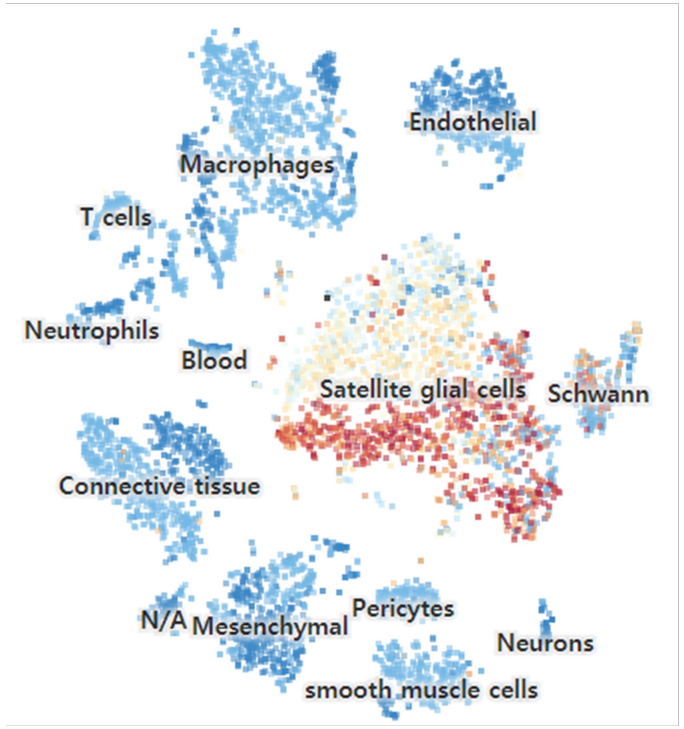


GPR37L1-E296 mutation

Bang et al., JCI, 2024

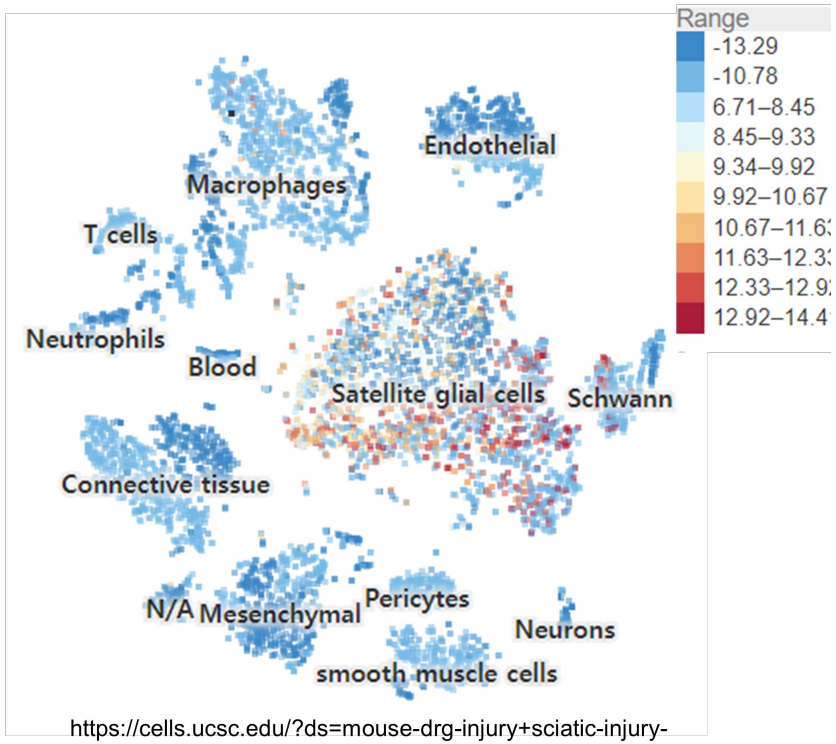
GPR37L1 identifies satellite glial cells in the DRG

Gpr37l1 single cell-seq in DRG



https://cells.ucsc.edu/?ds=mouse-drg-injury+sciatic-injury-comp&gene=GPR37L1

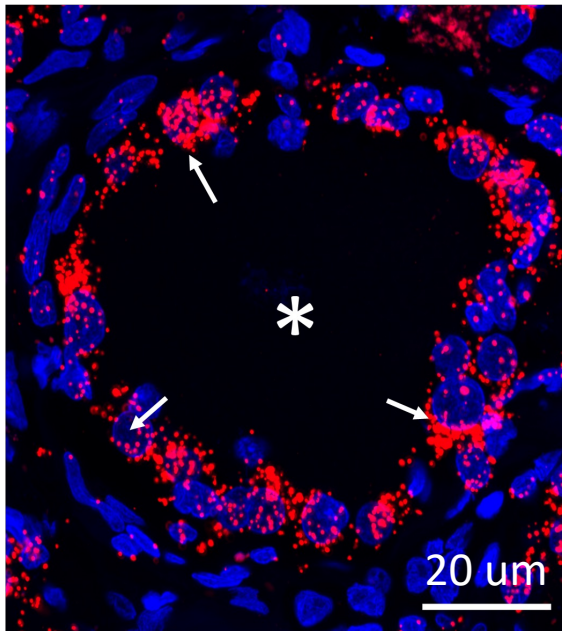
Kcnj10 single cell-seq in DRG



https://cells.ucsc.edu/?ds=mouse-drg-injury+sciatic-injury-comp&gene=KCNJ10

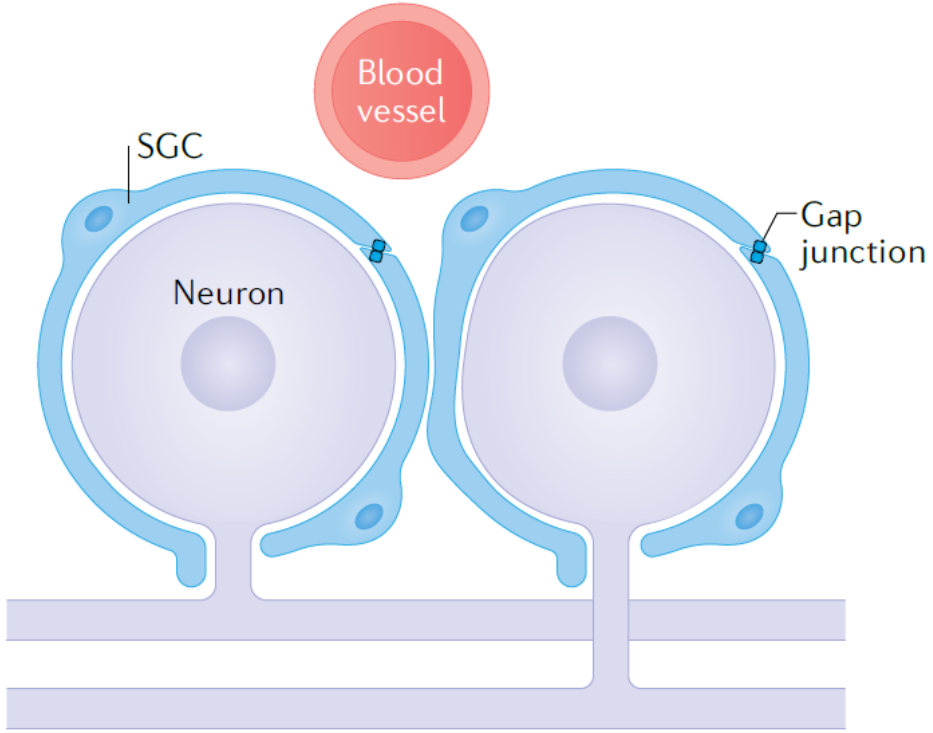
Human DRG-ISH

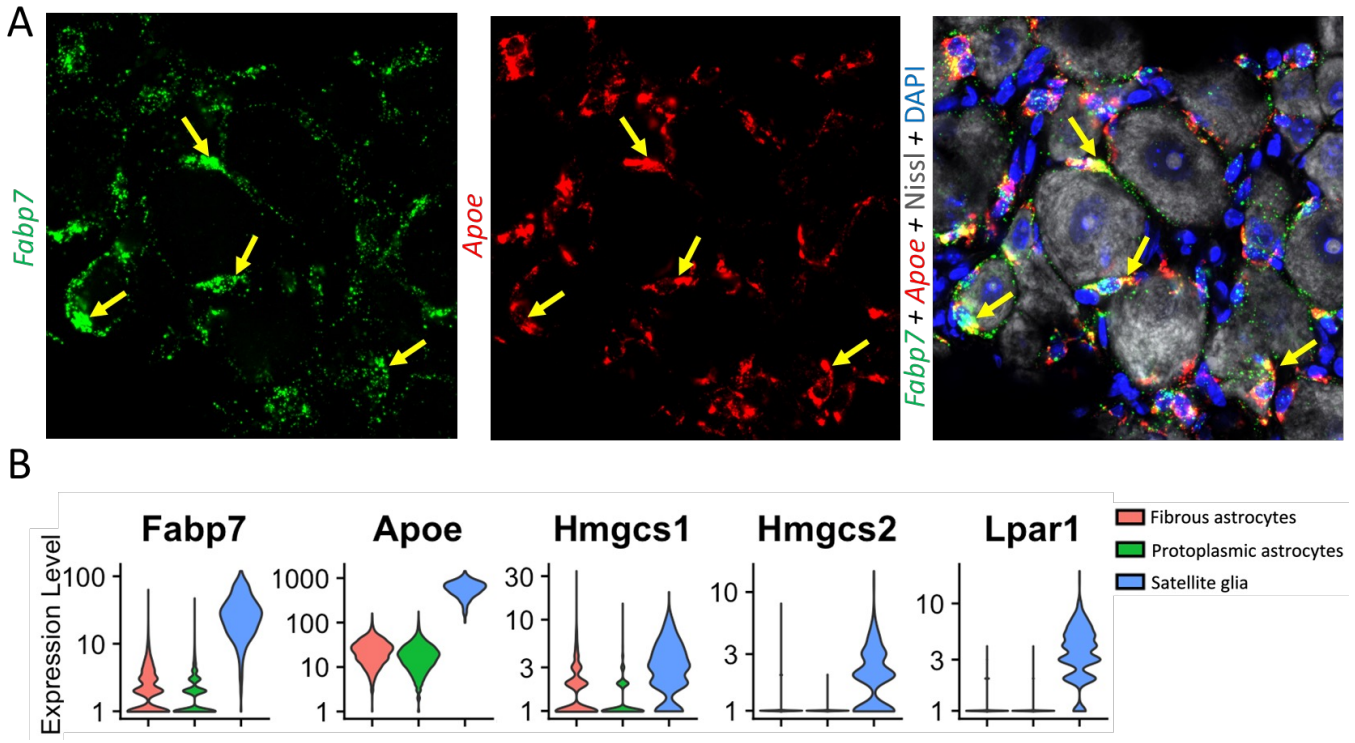
DAPI + *GPR37L1*



Bang et al., JCI, 2024

Satellite Glial Cells (SGCs) and lipid signaling



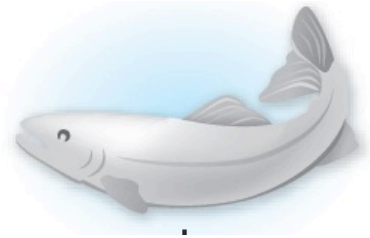


Hanani and Spray, Nat Rev Neurosci, 2020

McGinnis and Ji, *Cells*, 2023

SPMs and resolution of inflammation

SPMs: specialized pro-resolving mediators



Dietary essentially fat

Omega-3 polyunsaturated fatty acids

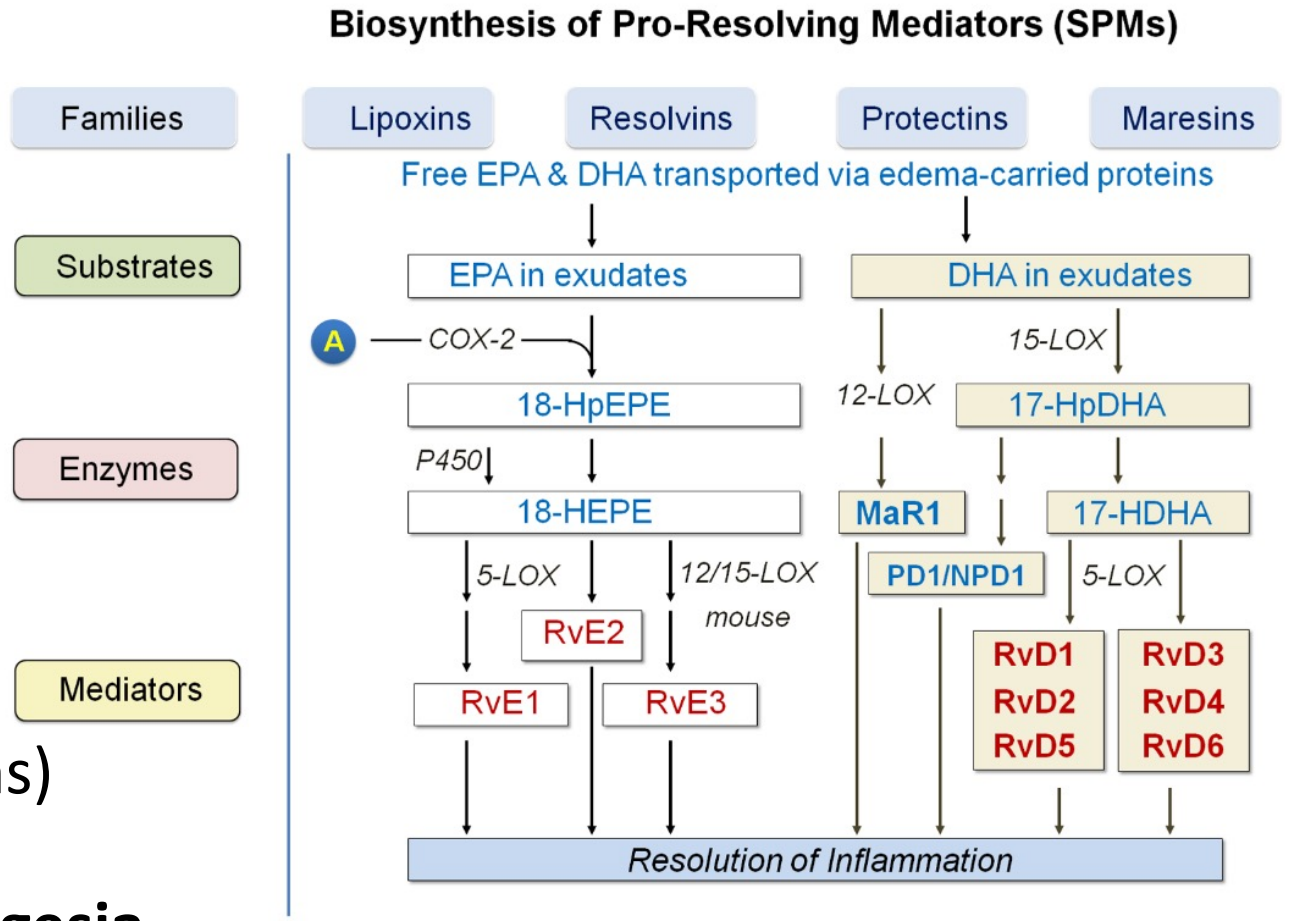
Docosahexaenoic acid (DHA)

Eicosapentaenoic acid (EPA)

SPMs (resolvins, protectins, and maresins)

Anti-inflammation, pro-resolution, analgesia

Charles Serhan



Chen et al., *Neuron, 2019*

Neuroimmune Modulation for Pain Resolution

Neuromodulation
Acupuncture / EA
Vagus nerve stimulation
Spinal cord stimulation
DRG stimulation

Dietary supplements
Fish oil (DHA, EPA)
↓
SPMs

Cell therapies
Bone marrow stem cells
Mesenchymal stromal cells
T cells
Macrophages

Immunotherapy
Cytokine antibodies
PD-L1/PD-1 modulators
STING/IFN modulators

Blood products
Autologous conditioned serum (ACS)
Platelet Rich Plasma (PRP)

Inflammation
Neuroinflammation

Microglia
Astrocytes
Satellite glial cells
Immune cells

Health ⇄ **Disease**

↓

Neuroimmune Modulation

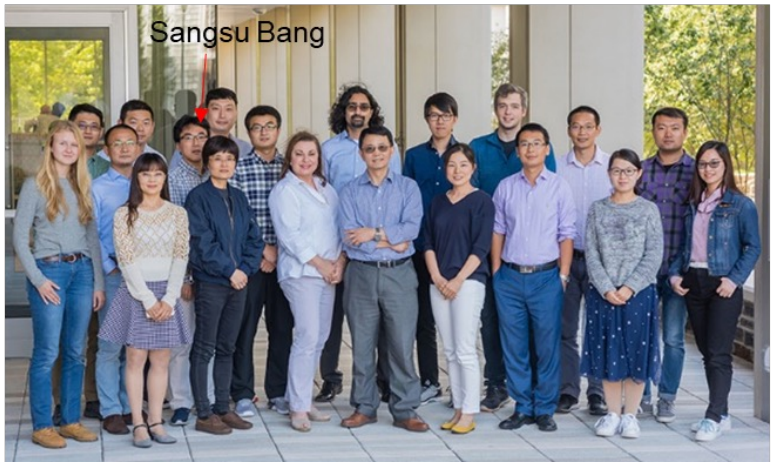
Multiple beneficial effects (pain relief, cognitive improvement)

Ji et al., Anesthesiology, 2018
Buchheit et al., JCI, 2020
Zhao et al., Pharmacol Ther. 2023

Center for Translational Pain Medicine (CTPM)

Acknowledgement

Sensory Plasticity and Pain Signaling Laboratory



NIH grants: DE17794, NS67686, NS87988, 1RF1NS131812-01A1

DoD grants: X81XWH 2110885, 2110756, 2210267, 2210646

Charles Serhan

Luda Diatchenko

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Overcoming Pain Together

anesthesiology.duke.edu/ctpm

Transforming the way we study, diagnose, and treat painful conditions.

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Duke University School of Medicine