Role of SPMs in Inflammation & Disease

Sharon McQuillan, MD

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Disclosures

- Chief Science Officer, Great Healthworks
- Adjunct Professor, Integrative Medicine, Nova Southeastern University
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- Medical Director of New You Medical

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CIRS- Chronic Inflammatory Response Syndrome

Person is exposed to biotoxin-producing situation (ex. WDB).

Biotoxins are not recognized properly by the immune system, are not removed, and remain in the body indefinitely.

Biotoxins pass from cell to cell, creating cell damage, including damage to cells in immune system, causing immune system dysfunction.

The cell damage and immune system dysfunction leads to system-wide inflammation.

Inflammation causes multiple symptoms across multiple body systems, frequently leading to misdiagnoses, leaving patient suffering.

Understanding Chronic Inflammatory Response Syndrome (CIRS). Natasha Thomas, MD.
https://www.survivingmold.com/docs/UNDERSTANDING_CIRS_EDITV2A.PDF

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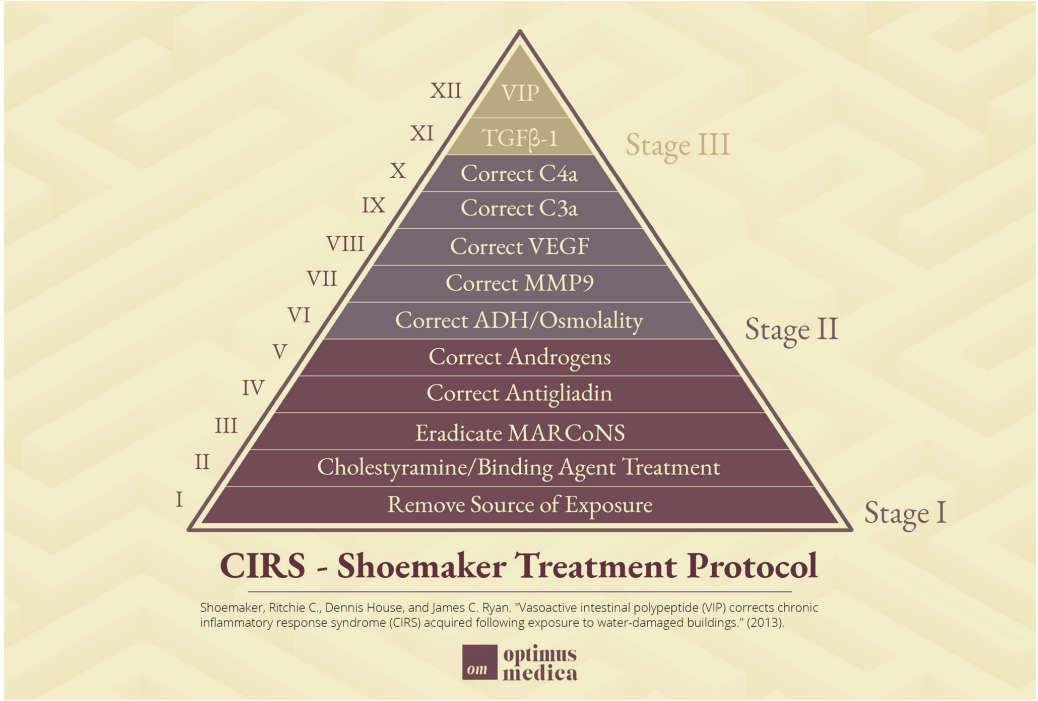
CIRS Treatment- Shoemaker Protocol

- Remove exposure
- Detoxify
- Address Inflammation
- Restore damaged systems- hormonal, immune, etc.



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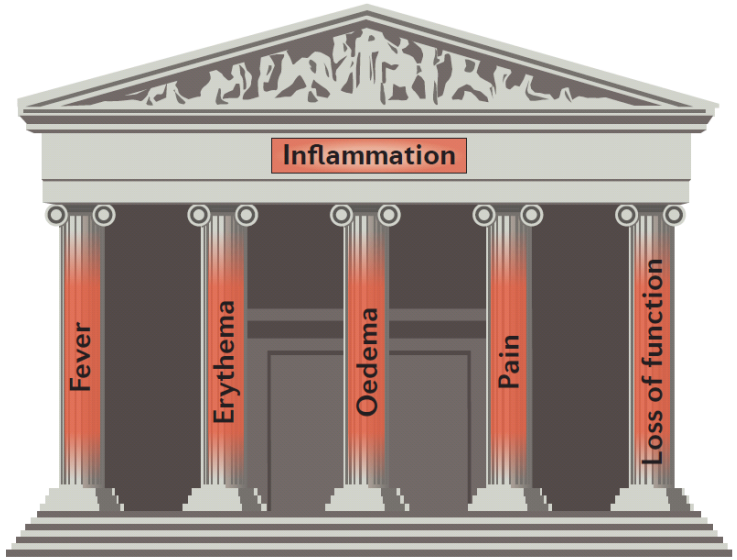
Inflammation

- Acute inflammation
  - Localized
  - Normal response to tissue injury/infection
  - Self-limiting
  - If uncontrolled, leads to acute, chronic, and systemic inflammatory disorders
- Five pillars of inflammation
  - Fever
  - Erythema
  - Edema
  - Pain
  - Loss of function



Basil MC, Levy BD. Specialized pro-resolving mediators: endogenous regulators of infection and inflammation. Nat Rev Immunol 2016;16(1):51-67. doi: 10.1038/nri.2015.4 [published Online First: 20151221]

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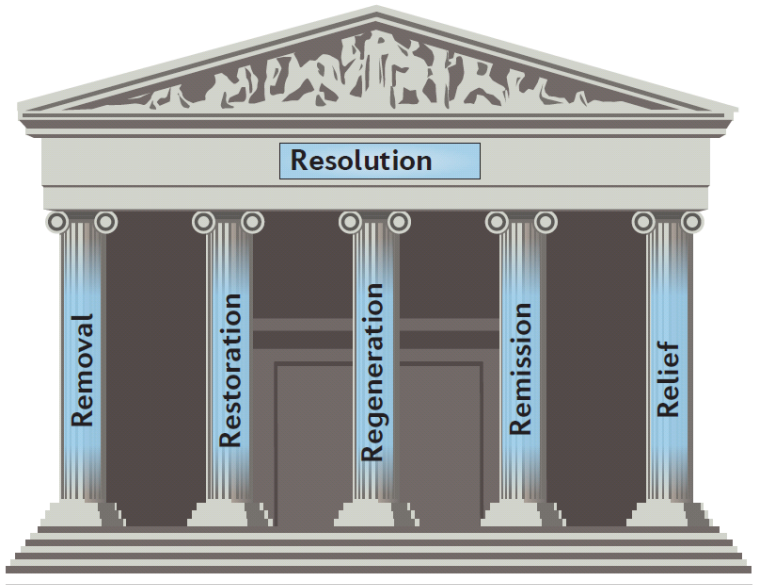
Inflammation Resolution

- Removal of microbes, dead cells, and debris
- Restoration of vascular integrity and perfusion
- Regeneration of tissue
- Remission of inflammatory process
- Relief of pain, restoration of function



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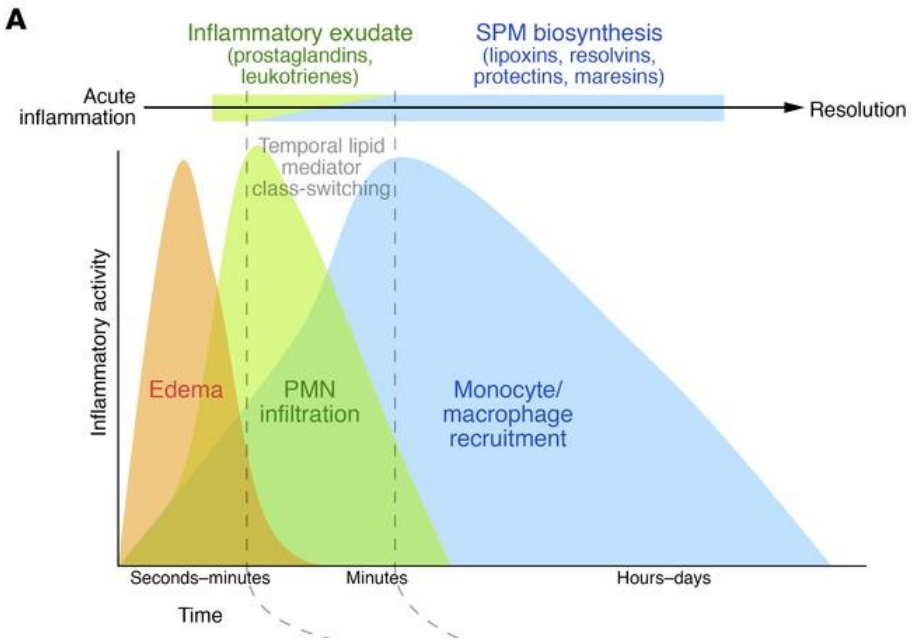
Inflammation Resolution

- First believed that the resolution of inflammation was a passive process
- Serhan et al. have uncovered that the resolution of inflammation is an **active process** regulated by biochemical mediators and receptor-signaling pathways driven by Specialized Pro-resolving Mediators (SPMs)



J Clin Invest. 2018;128(7):2657-2669. https://doi.org/10.1172/JCI97943

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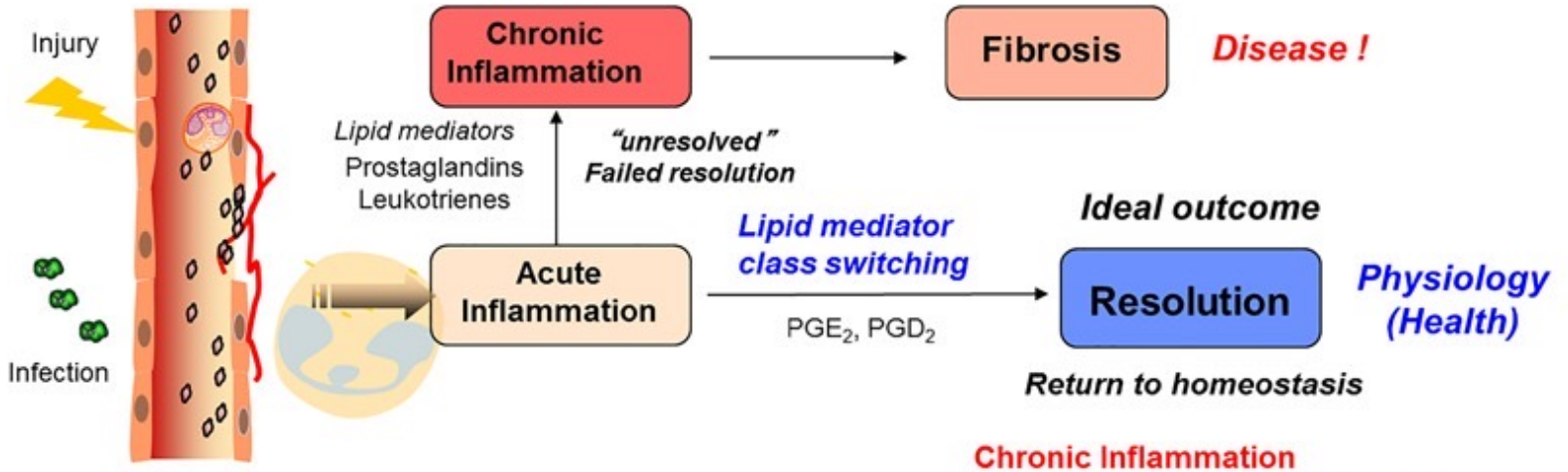
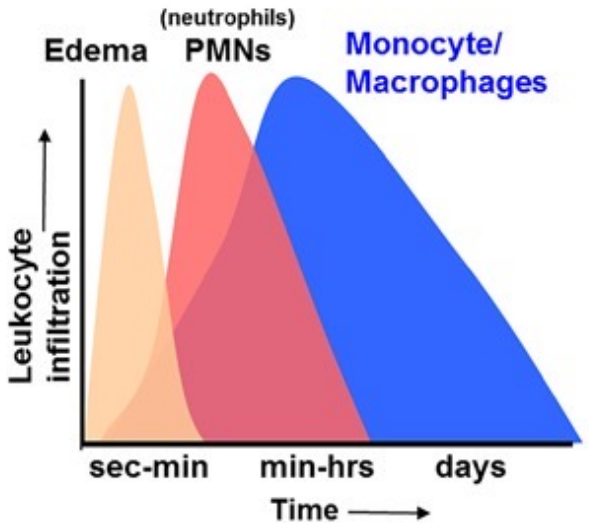
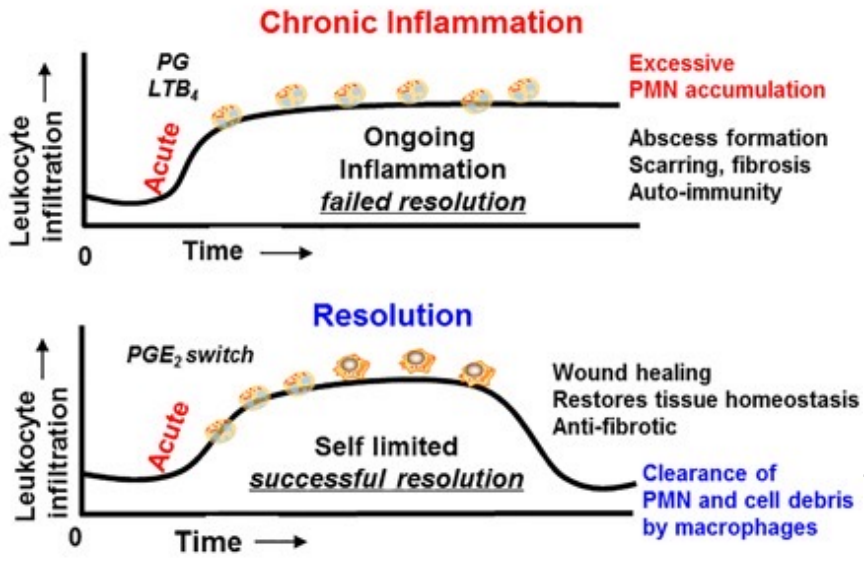
Essential Lipid Mediator Switch







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Specialized Pro-Resolving Mediators

- Derived from omega-3 fatty acids
  - EPA
  - DPA
  - DHA
- Play pivotal anti-inflammatory and anti-infective role in disease decline

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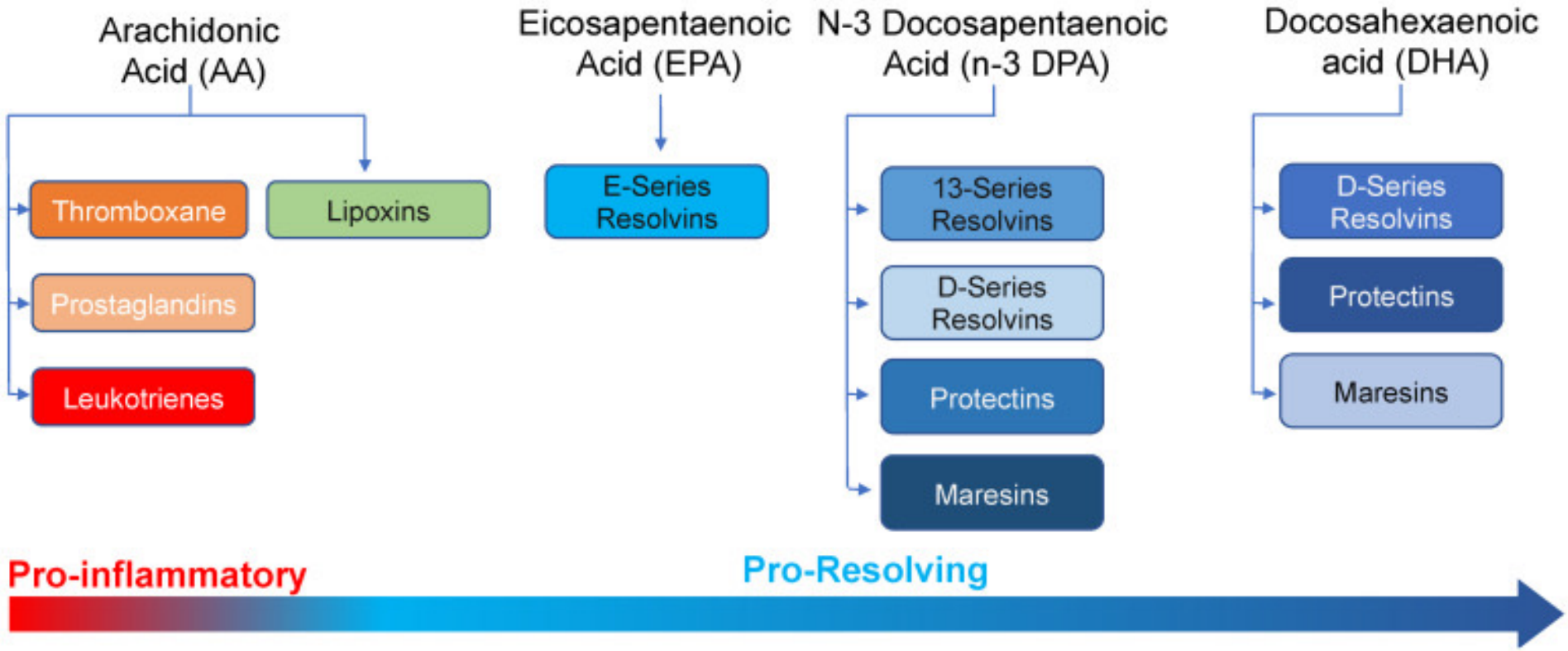
Specialized Pro-Resolving Mediators



Dalli J, Gomez EA, Jouvene CC. Utility of the Specialized Pro-Resolving Mediators as Diagnostic and Prognostic Biomarkers in Disease. Biomolecules. 2022 Feb 23;12(3):353. doi: 10.3390/biom12030353. PMID: 35327544; PMCID: PMC8945731.

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Lipoxins

- PGs, LTs, and thromboxanes are pro-inflammatory when in excess and are biosynthesized from AA
- AA also involved in biosynthesis of anti-inflammatory and pro-resolving mediators LXA4 and LXB4
- Leukotrienes, prostaglandins, and lipoxins act via individual GPCRs and play important role in initiation of inflammatory response by activating neutrophils, known as polymorphonuclear leukocytes (PMNs)
- PMNs serve as “first responders” to site of inflammation to neutralize and clear foreign pathogen
- This occurs within seconds to minutes, increasing over time
- Lipoxins are function as strong “stop” signals for PMNs

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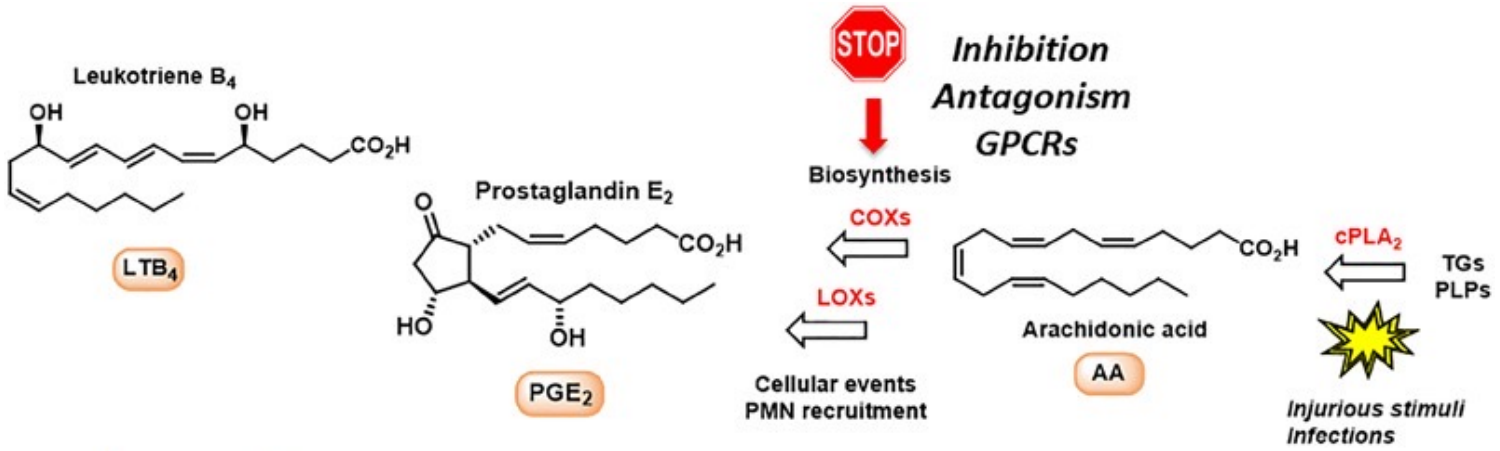
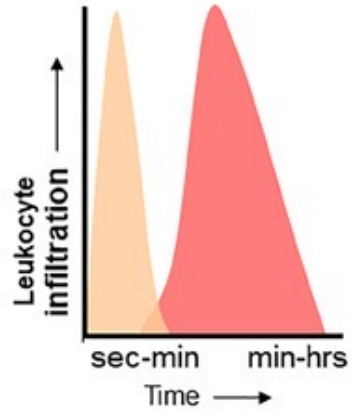
Inflammatory Response and AA Pathways





Clinical and Pharmacological Relevance for Modulating Oxygenated PUFA Mediator Biosynthesis:

Steroids
Prostaglandins and synthetic analogs
NSAIDs
COX-2 inhibitors
5-LOX inhibitors
Leukotriene-antagonists

Serious side effects
Inefficient towards complete resolution of inflammation
Immunosuppressive

Hansen, Trond Vidar et al. "The Protectin Family of Specialized Pro-resolving Mediators: Potent Immunoresolvents Enabling Innovative Approaches to Target Obesity and Diabetes." Frontiers in pharmacology vol. 9 1582. 17 Jan. 2019, doi:10.3389/fphar.2018.01582

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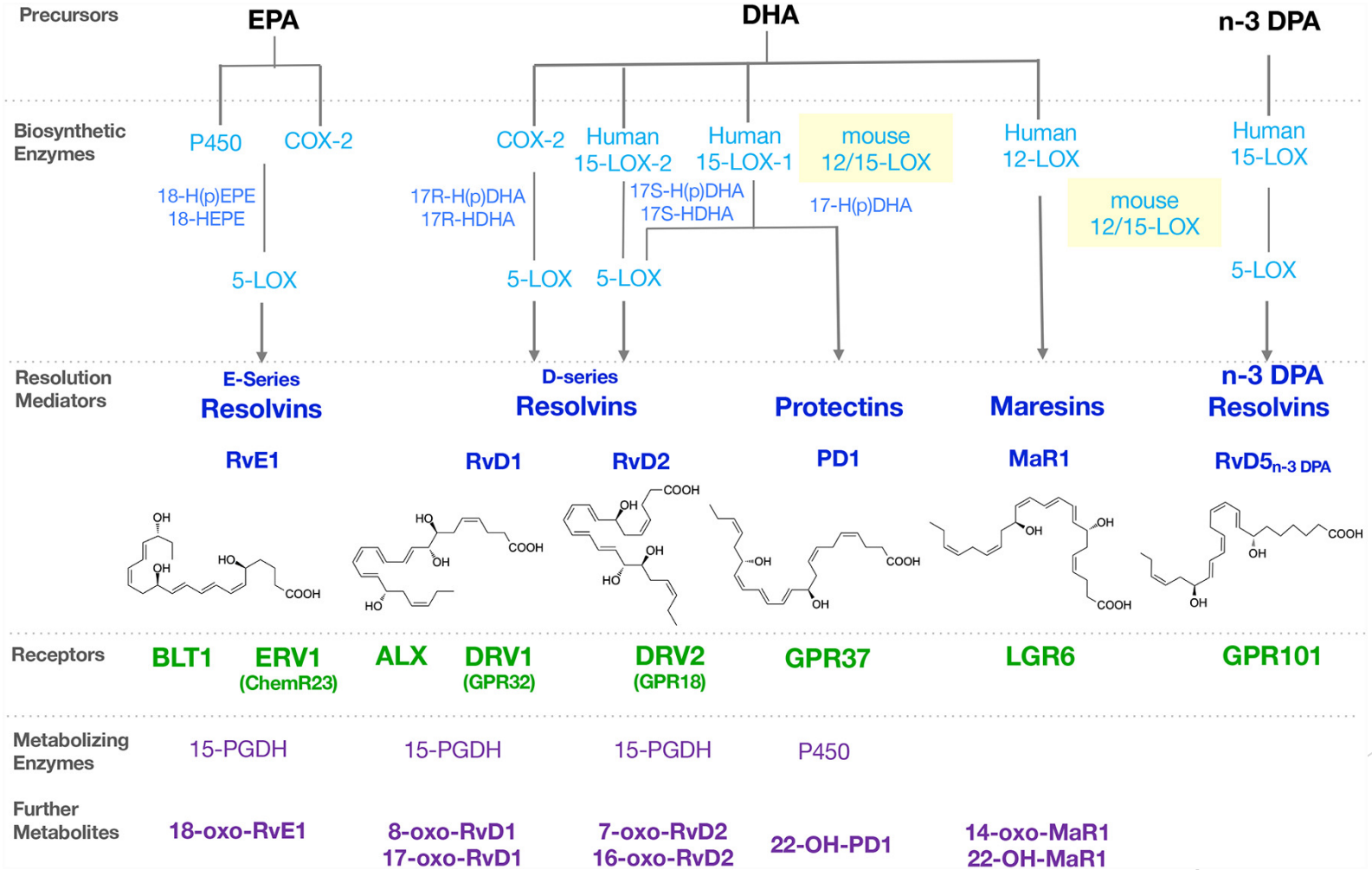
Resolution Metabolome



Chiang N, Serhan CN. Specialized pro-resolving mediator network: an update on production and actions. Essays Biochem. 2020;64(3):443-462. doi:10.1042/EBC20200018

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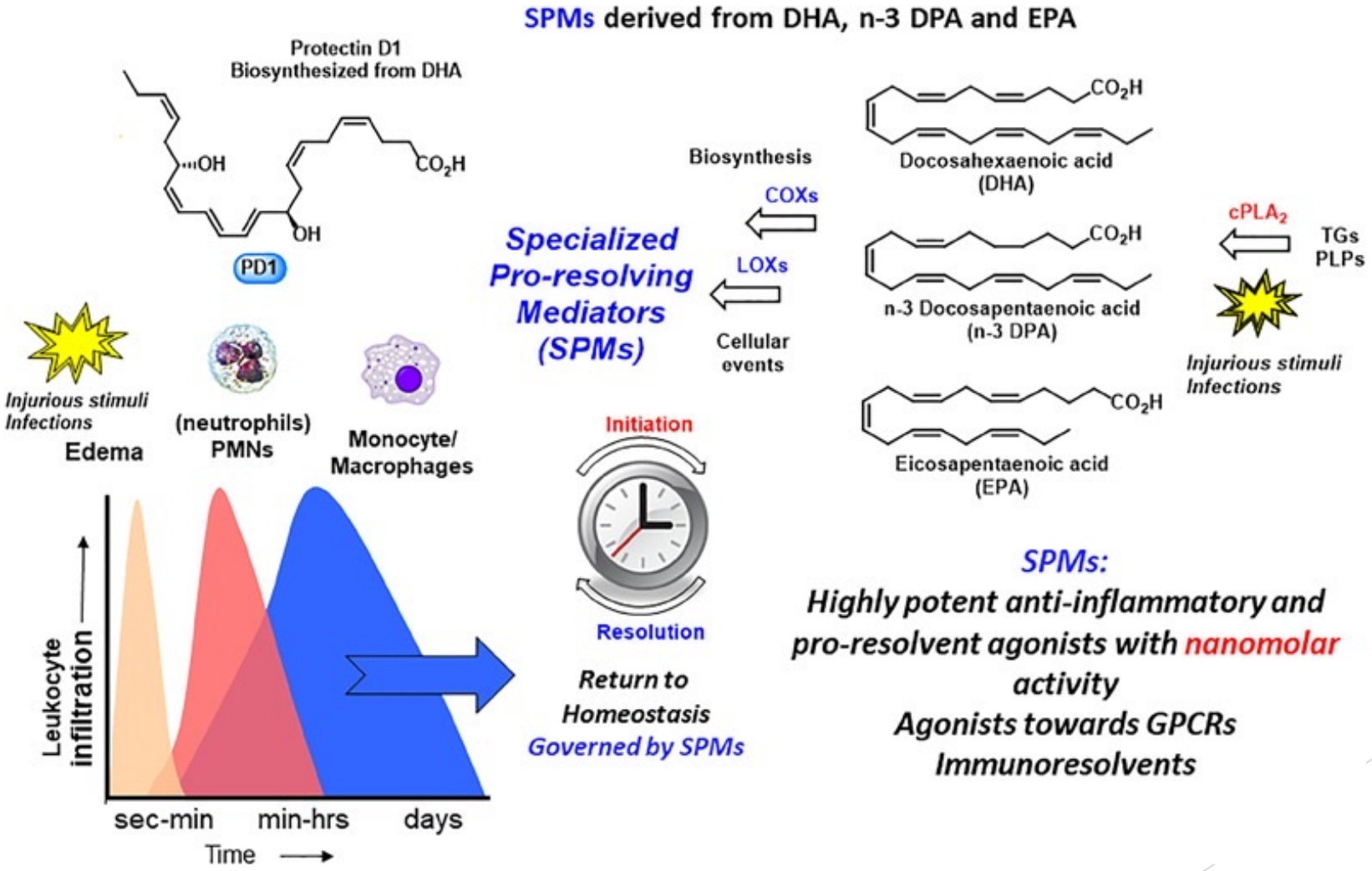
SPMs- Resolvins, Protectins, Maresins



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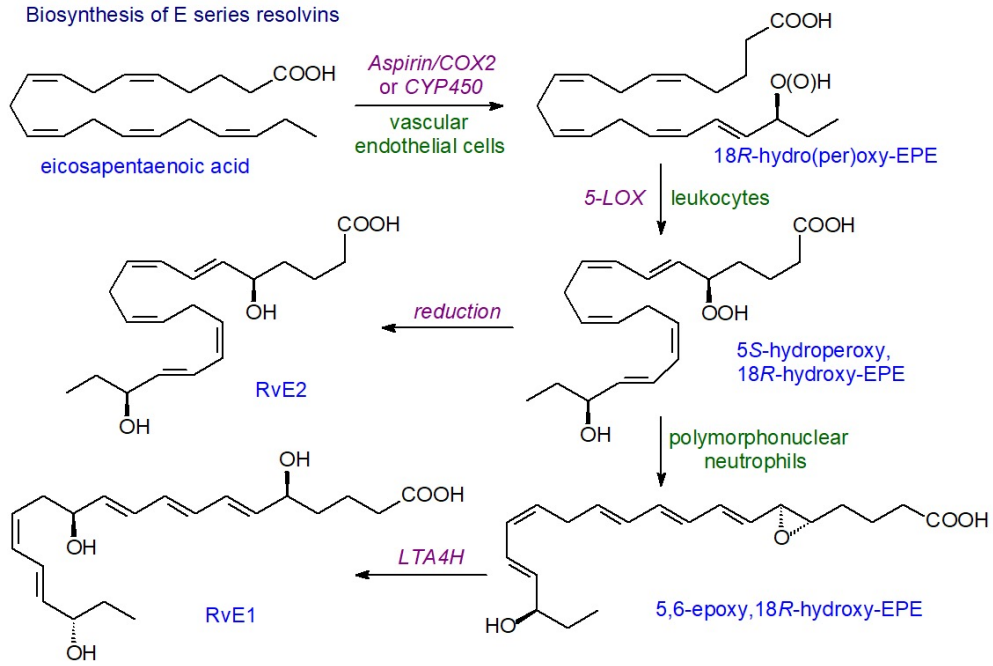
Resolvins Mechanism of Action

- Potent anti-inflammatory
- Suppress PMN chemotaxis
- Promote macrophage recruitment



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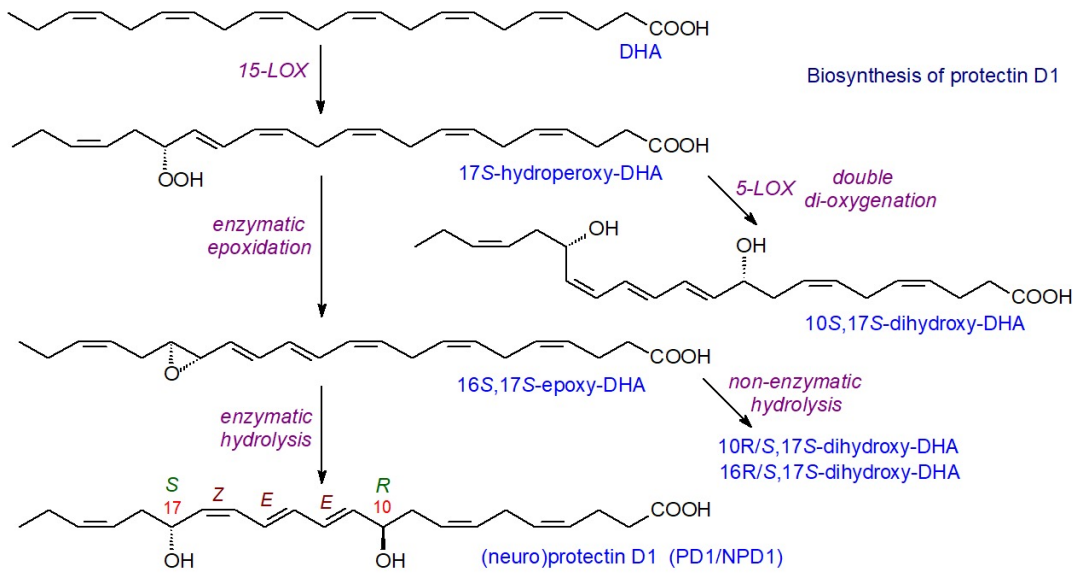
Protectins: Mechanism of Action

- Inhibit PMN chemotaxis/migration
- Enhance macrophage efferocytosis of apoptotic PMNs



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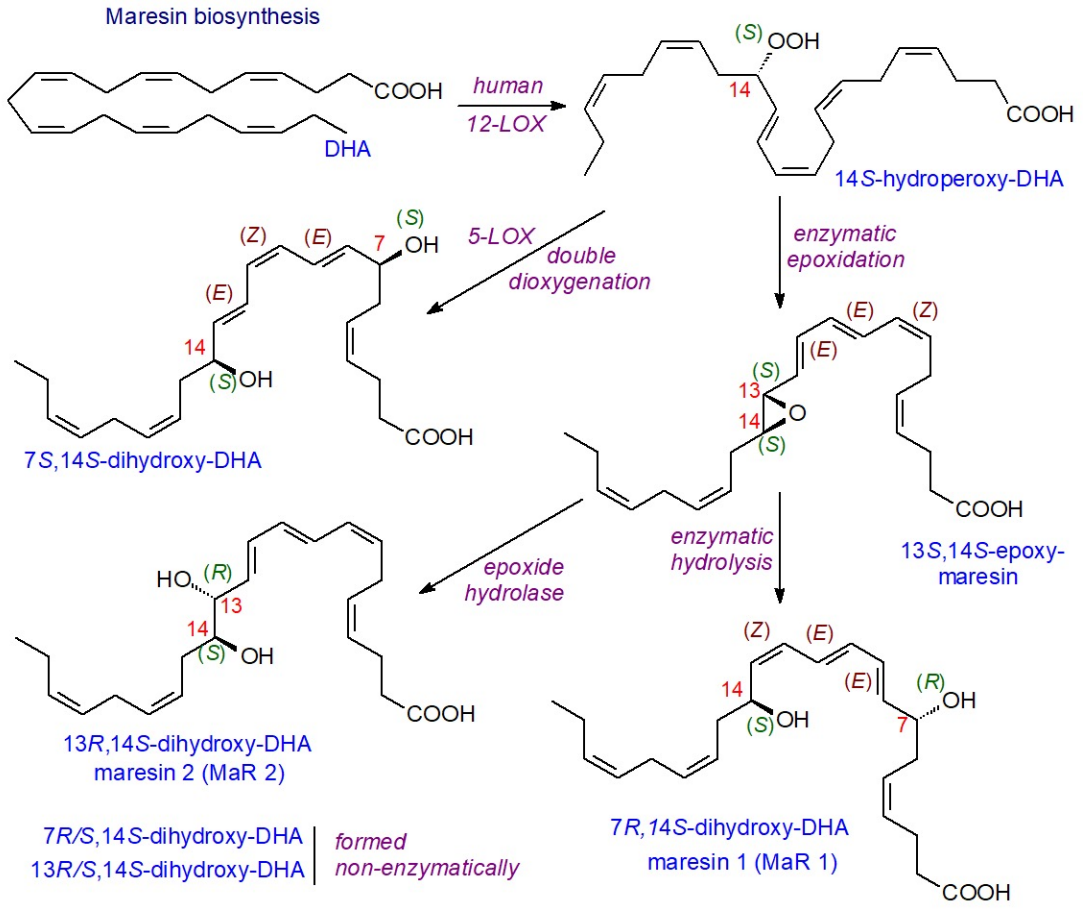
Maresins: Mechanism of Action

- Potent anti-inflammatory
- Tissue regenerative
- Anti-nociceptive actions



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Summary: Bioactions and Functions of SPMs

- Limit PMN tissue infiltration, cessation
- Reduce collateral tissue damage by phagocytes
- Shorten R_i resolution interval
- Enhance macrophage phagocytosis and efferocytosis
- Counter regulate proinflammatory chemical mediators (PAF, LTs, PGs)
- Increase anti-inflammatory mediators (IL-10 and others)
- Increase microbial killing and clearance by innate immune cells
- Enhance tissue regeneration
- Not immunosuppressive

Serhan CN. Treating inflammation and infection in the 21st century: new hints from decoding resolution mediators and mechanisms. FASEB J 2017;31(4):1273-88. doi: 10.1096/fj.201601222R [published Online First: 20170113]

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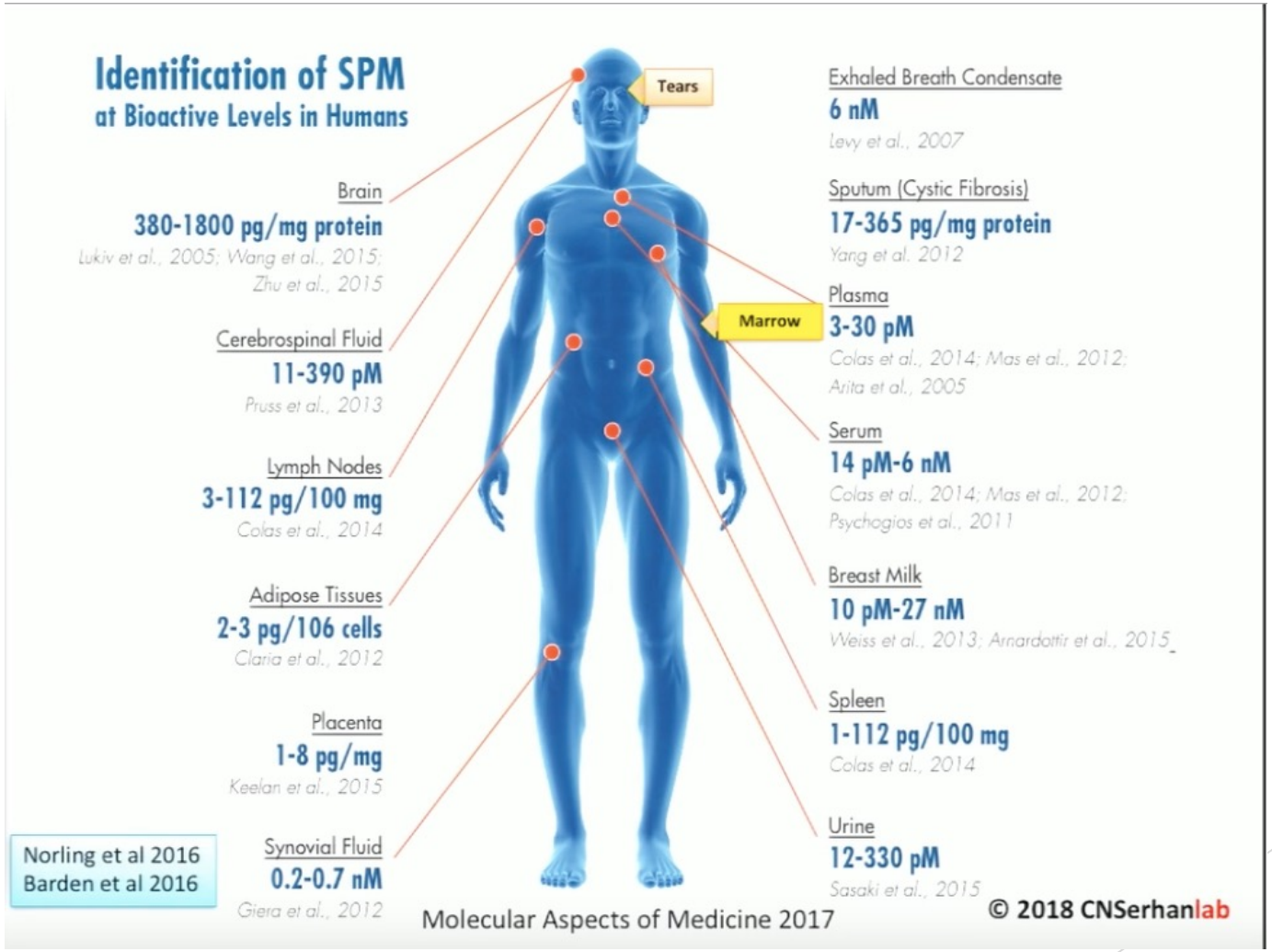
SPMs Levels in Body



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Causes of SPM Deficiency/Dysfunction

- Environmental toxins
- Standard American Diet
  - Lack of PUFA
  - Processed carbohydrates
- Illness
- Stress
- Age
- Poor sleep hygiene
- Genetics predisposition

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SPM Dysfunction in Medical Disease/Disorders

	Disease	SPM Identified	Tissue
Neuronal Inflammation	Ischemic Brain Injury	↓LXA_4	Plasma
	Alzheimer's Disease	↓LXA_1, RvD1,MaR1,5,15-diHETE ↓RvD5,PD1,Mar1	CSF, hippocampus Entorhinal cortex tissue
Cardiovascular Disease	Myocardial Infarction	↑PD1, 10S,17S-diHDHA, AT-PD1, AT-LXA_4, $PD2_{n-3DPA}$, 10S,17S-diHDPA, PD1 ↑LXA_4, $RvD5_{n-3DPA}$,RVE1	Plasma
	Peripheral Artery Disease	↑LXA_4, ↓10,17-diHDHA	Plasma
	Atherosclerosis	↓RvD1, ↑7-epi,Δ12-trans-MaR1	Human carotid atherosclerotic plaques
Infections	Infection, low-dose endotoxin	↑RvD1,RvE1	Plasma, serum
	Periodontal Disease	↑PD1, MaR1 ↓LXA_4	Saliva
	Rhinosinusitis	↓RvD1, RvD2 ↑LXA_4	Ethmoid sinus tissue
	Tuberculosis	↑RvD2,17R-PD1,PCTR3 ↓PDI_{n-3DPA},RvE3,15-oxo-LZA_4	Serum
	Sepsis	↑RvD5,PD1,17R-PD1, RvE1,RvE2,RvE3,5S,15S-diHETE ↓17R-RvD1	Plasma

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SPM Dysfunction in Medical Disease/Disorders

	Disease	SPM Identified	Tissue
Metabolic Disease	Obesity	↓RvD2,RvD4,LXA_4,RvE3, MaR1 ↑RvD1,RvD2,10S,17S-diHDHA, LXA_4, LXA_5 ↑RvD3,RvD4,PD1	Plasma Plasma Serum
	Diabetes	↓RvD1,RvE1 ↑RvD2,17R-PD1,PCTR3 ↓$PDI_{n\text{-}3DPA}$,RvE3,15-oxo-LXA_4	Plasma Serum Serum
Autoimmune Disease	Rheumatoid Arthritis	↓RvD1,17R-RvD1,RvD2,PD1,10S,17S-diHDHA,MaR1,RvE1,RvE2,RvE3,18R-RvE3 ↑RvD1,RvD2,RvD3,RvD4,10S,17S-diHDHA, 10S-17SdiHDPA,$MaR1_{n\text{-}3DPA}$,15R-LXA_4 ↑PD1,LXA_4,LXB_4	Plasma, synovial fluid Plasma Synovial fluid
	Osteoarthritis	↑PD1,LXA_4,LXB_4	Synovial fluid
	Hashimoto's Thyroiditis	↓RvD1	Serum
Omega-3 Supplementation	Healthy volunteers	RvD1,17R-RvD1,RvD2,RvE1,RvE2,RvE3,18R-RvE3	Plasma
	Peripheral Artery Disease	↑LXA_4,PDX(10S,17S-diHDHA)	Plasma
	Major Depressive Disorder & Inflammation	↑RvE2,RvE3,LXB_4	Plasma
	Chronic Inflammation	↑$RvD5_{n\text{-}3DPA}$,$MaR1_{n\text{-}3DPA}$	Plasma

Dalli J, Gomez EA, Jouvene CC. Utility of the Specialized Pro-Resolving Mediators as Diagnostic and Prognostic Biomarkers in Disease. Biomolecules. 2022 Feb 23;12(3):353. doi: 10.3390/biom12030353. PMID: 35327544; PMCID: PMC8945731.

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Clinical Effect of SPMs in Disease

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SPM Actions in Disease Models

Disease/Condition	SPMs that resolve inflammation and reduce disease severity
Infection	Bacterial: MCTRs, PCTRs, RCTRs
	$RvD5_{n\text{-}3\ DPA}$
	Viral: 17R-RvD1
Acute Lung Injury	MCTRs
ARDS	PCTR1
Skin and Burn Wound	RvD2
Colitis/IBD	RvE1
	$RvD5_{n\text{-}3\ DPA}$, $PD_{n\text{-}3\ DPA}$
Arthritis	RvD1
	RvTs
	$RvD5_{n\text{-}3\ DPA}$

Chiang N, Serhan CN. Specialized pro-resolving mediator network: an update on production and actions. Essays Biochem 2020. 64(3): 443-462

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SPM Actions in Disease Models

Disease/Condition	SPMs that resolve inflammation and reduce disease severity
Periodontitis	RvD2
Regeneration	Planaria head regeneration: MaR1, RvE1, MACTRs, PCTRs, RCTRs
	Bone: MaR1
	Muscle: RvD2
	Zebrafish fin regeneration: PD1
Alzheimer's Disease	RvE1
Neuroinflammation	Neurocognitive disorders: MaR1
	Epileptogenesis: $PD1_{n\text{-}3\ DPA}$
Dermatitis	RvE1
Multiple Sclerosis	RvD1, PD1
Cancer	RvE1, RvD1, RvD2
	17R-RvD1, 17R-RvD3

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SPM Actions in Disease Models

Disease/Condition	SPMs that resolve inflammation and reduce disease severity
Atherosclerosis	RvE1
	$RvD5_{n\text{-}3\ DPA}$
Aortic Aneurysm	RvD1
Depression	RvE3
Aging	RvD1
Parkinson's Disease	RvD1
Sickle Cell Disease	AT-RvD1
Ischemia-Reperfusion Kidney Injury	RVD1
Deep Vein Thrombosis	RvD4
Neuropathic/Inflammatory Pain	RvD5
	MaR1
Traumatic Brain Injury	NPD1
Stroke	NPD1, 17R-NPD1

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SPMs and Immunity

- Healthy subjects enrolled in double-blind placebo-controlled, crossover study to determine relationship between:
  - Supplementation and peripheral SPM concentrations
  - Changes in plasma SPM concentrations and peripheral blood platelet and leukocyte response
- Administered placebo or one of three doses of an enriched marine oil supplement and evaluated at baseline, 2, 4, 6, and 24 hours post administration
- Results
  - Time- and dose- dependent increase in plasma SPM concentrations
  - Dose-dependent increase in neutrophil and monocyte phagocytosis of bacteria
  - Reduction in adhesion molecule expression
  - Change in transcript levels of immune and metabolic genes 24 hours post supplementation
- Conclusion
  - Supplementation with marine oil leads to increase in peripheral blood SPM concentrations and reprograms peripheral blood cells, indicating role for SPMs in mediating immune-directed actions

Souza, PR et al. Enriched marine oil supplements increase peripheral blood specialized pro-resolving mediators concentrations and reprogram how immune responses. Circulation Res. 2020;126:75-90.

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SPMs and Pediatrics

- Study showed infants born to pregnant women who supplemented with Omgea-3 PUFAs during pregnancy developed fewer lower respiratory tract infections and were one-third less likely to develop asthma in childhood
- SPMs present in both placental tissue and human breast milk

Bisgaard H, et al. Fish il-derived fatty acids in pregnancy and wheeze and asthma in offspring. N Engl J Med 2016;375: 2530-39

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SPMs and Acute Respiratory Distress Syndrome (ARDS)

- Meta-analysis of 12 randomized trials evaluating omega-3 PUFA supplementation compared to placebo in patients with ARDS
- Oxygenation significantly improved in supplement group
- Trend towards reduced intensive care unit length of stay and days on mechanical ventilation

Langlois PL, et al. Omega-3 polyunsaturated fatty acids in critically ill patients with acute respiratory distress syndrome: a systematic review and meta-analysis. Nutrition 2019; 61: 84-92

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SPMs and COVID-19

- SPM levels in BAL fluid of 33 patients requiring ventilation for severe COVID-19 found increased levels of LXA_4 and D-series resolvins compared to healthy controls
- Patients with COVID-19 had simultaneously elevated BAL inflammatory mediators (thromboxane B_2, prostaglandins, LTs) demonstrating competing roles, suggesting a lipid mediator storm
- Plasma SPM levels in patients with COVID-19 (PCTR3, MCTR3) were higher in hospitalized patients with mild symptoms compared to those requiring oxygen
- Serum from hospitalized patients with COVID-19 not requiring ICU admission had elevated levels of SPMs (RvE3) compared to those in ICU

Cagnina RE, et al. Specialized pro-resolving mediators in respiratory diseases. Curr Opin Clin Nutr Metab Care 2022;25: 67-74.

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Evidence of Omega-3 PUFA/SPM Supplementation and Pain Relief Outcomes

Disease	n	Treatment	Duration	Outcomes
Joint Discomfort	45	370 mg fish oil EPA/DHA (10/8), 230 mg lemon verbena	9 weeks	Improvement of joint status, physical function, stiffness, pain relief
	49	27mg/kg EPA, 18mg/kg DHA(low dose) or 54mg/kg EPA, 36mg/kg DHA(high dose)	24 weeks	Improvement of pain, grip strength, # of swollen joints mainly in high-dose group
	90	2.6 g/day omega-3 fatty acid	12 months	Improvement in global evaluation, physician pain assessment, reduction of anti-rheumatic medication
Rheumatoid Arthritis	28	6 g/day (fish oil)	3 months	Improvement in # of swollen joints, joint pain index, Ritchie articular index
Rheumatic Diseases	15	2.4 g/day omega-3 fatty acid	4 weeks	Plasma SPM elevated compared to healthy control; RvE2 negatively associated with pain score
Gout	4	2.4 g/day omega-3 fatty acid	4 weeks	Plasma SPM elevated compared to healthy control; RvE2 negatively associated with pain score
Psoriatic arthritis	6	2.4 g/day omega-3 fatty acid	4 weeks	Plasma SPM elevated compared to healthy control; RvE2 negatively associated with pain score
Rheumatic Diseases	58	10 g cod oil (2.2g n-3FA)/day	9 months	Reduction of NSAID intake without any worsening of disease activity
Sickle Cell Syndrome	13	Menhaden fish oil (.25g/kg/day)	12 months	Frequency of pain episodes decreased by about 50%
Chronic headaches	67	Dietary intervention (↓n-6 LA, ↑ n-3 EPA, DHA)	12 weeks	Reduction in pain frequency, pain intensity, and psychological distress
Diabetic neuropathy	40	1000 mg DHA, 200 mg DHA daily	3 months	Reduction of neuropathic pain symptoms
Migraines	67	400 mg/day Na valproate with or without combination EPA 180 mg, DHA 120 mg	12 weeks	Reduction of migraine headache (combination)

Fattori V, et al. Specialized pro-resolving mediators: a new class of non-immunosuppressive and non-opioid analgesic drugs. Pharmacol Res 2020; 151: 104549.

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SPMs and Chronic Pain

- Prospective, non-randomized, open-label trial of 40 subjects with moderate pain intensity for 3 months administered SPM-enriched marine lipid orally for 4 weeks
- Outcome measures (Baseline, week 2, week 4)
  - Patient Reported Outcome Measurement Information System (PROMIS-43)
  - American Chronic Pain Association (ACPA) QOL scale
  - Exploratory outcomes: safety, tolerability, blood biomarkers of inflammation (hs-CRP, ESR), pain intensity, depression and anxiety
- Results
  - PROMIS-43 changes significant from baseline
  - Borderline changes in ACPA QOL scale
  - Significant changes in measures of pain intensity, pain interference, depression, anxiety
  - No statistically significant changes in hs-CRP or ESR

Callan N, Hanes D, Bradley R. Early evidence of efficacy for orally administered SPM-enriched marine lipid fraction on quality of life and pain in a sample of adults with chronic pain. J Transl Med 2020;18:401. https:/doi.org/10.1186/s12967-020-02569s

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SPMs and Neuroinflammation

- Preclinical studies from Alzheimer's and Parkinson's disease models suggest SPM and SPM receptor dysregulation
  - Inadequate substrate
  - SPM/pro-inflammatory mediator imbalance
  - SPM synthesis disruption

Ponce J, Ulu A, Hanson C, Cameron-Smith E, Bertoni J, Wuebker J, Fisher A, Siu KC, Marmelat V, Adamec J, Bhatti D. Role of Specialized Pro-resolving Mediators in Reducing Neuroinflammation in Neurodegenerative Disorders. Front Aging Neurosci. 2022 Feb 17;14:780811. doi: 10.3389/fnagi.2022.780811.

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SPMs and Alzheimer's Disease

- SPMs may provide neuroprotection in AD
  - Altering expression of pro-inflammatory genes
  - Modulating macrophage production
  - Serve as biomarker for AD status
  - Promote resolution of neuroinflammation

Ponce J, Ulu A, Hanson C, Cameron-Smith E, Bertoni J, Wuebker J, Fisher A, Siu KC, Marmelat V, Adamec J, Bhatti D. Role of Specialized Pro-resolving Mediators in Reducing Neuroinflammation in Neurodegenerative Disorders. Front Aging Neurosci. 2022 Feb 17;14:780811. doi: 10.3389/fnagi.2022.780811.

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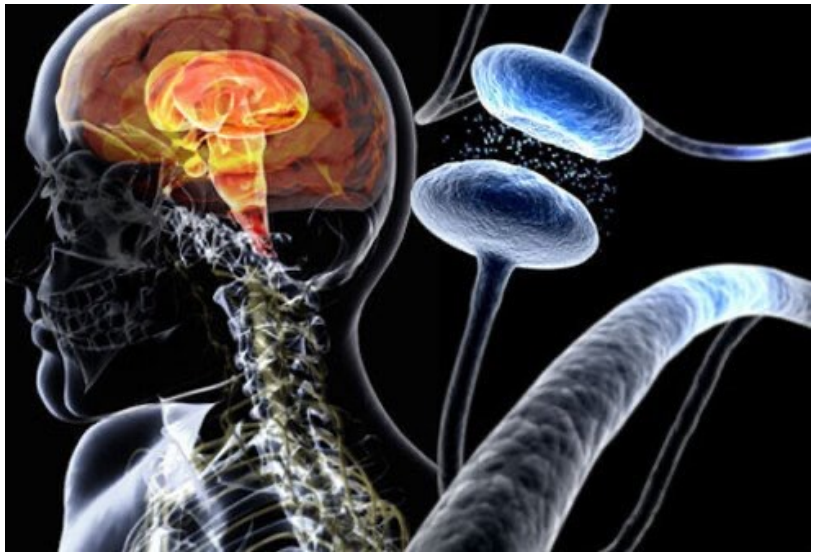
SPMs and Parkinson's Disease

- SPMs can cross blood-brain barrier
- Inhibit microglial activation
- Decrease induced markers of inflammation, due to ability to downregulate NFκB signaling pathways



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Impact of SPMs on Neuroinflammation in Disease Models

AUTHOR	MODEL	SPMs	EFFECT ON NEUROINFLAMMATION
Zhu et al. (2016)	STS-induced apoptosis in neuroblastoma cells	LXA_4, MaR1, RvD1, PDX	Improvement
	Aß42 phagocystosis in human micrglia	LXA_4, RvD1, PDX MaR1	Improvement
	Aß42 stressed/activated microglia	MaR1	Improvement
Zhao et al. (2012)	Aß42-treated human neuronal-glial culture	NDP1	Improvement
Yin et al. (2019)	Aß42-treated C57BL/6 mouse hippocampus	MaR1	Improvement
Lee et al. (2020)	Murine AD	Aspirin-triggered SPM	Improvement
Kovisto et al. (2014)	Microglia activation of APP/PS1 mice	SPM substrate (fish-oil)	Improvement
Flala et al. (2015)	Aß42-exposed PBMCs	SPM substate (1g DHA, 1g EPA) RvD1	Improvement
Mizwicki et al. (2013)	**AD patient PBMCs**	**RvD1 + Vitamin D**	**Improvement**
Hopperton et al. (2018)	Aß40-exposed mice	SPM substrate (fish-oil)	Improvement
Xu et al. (2013)	LPS-induced murine microglial cells	RvD1	Improvement
Xu et al. (2017)	MPP + PC12	RvD1	Improvement
Tian et al. (2015)	LPS-induced SD rats	RvD2	Improvement
Krashia et al. (2019)	Syn rats	RvD1	Improvement

Ponce J, Ulu A, Hanson C, Cameron-Smith D, Bertoni J, Wuebker J, Fisher A, Shu KC, Marmelat V, Adamec J, Bhatti D. Role of Specialized Pro-resolving Mediators in Reducing Neuroinflammation in Neurodegenerative Disorders. Front Aging Neurosci. 2022 Feb 17;14:780811. doi: 10.3389/fnagi.2022.780811.

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Choosing an SPM Supplement

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SPM Supplementation

- Most people do not produce enough SPMs on their own to confer resolution of inflammation
- Conversion of omega-3 fatty acids to SPMs is complex, slow, and inefficient
- Contributing factors include
  - Medical conditions
  - Genetic predisposition
  - Age
  - Diet
  - Sedentary lifestyle
- Supplementation necessary for resolution of inflammation

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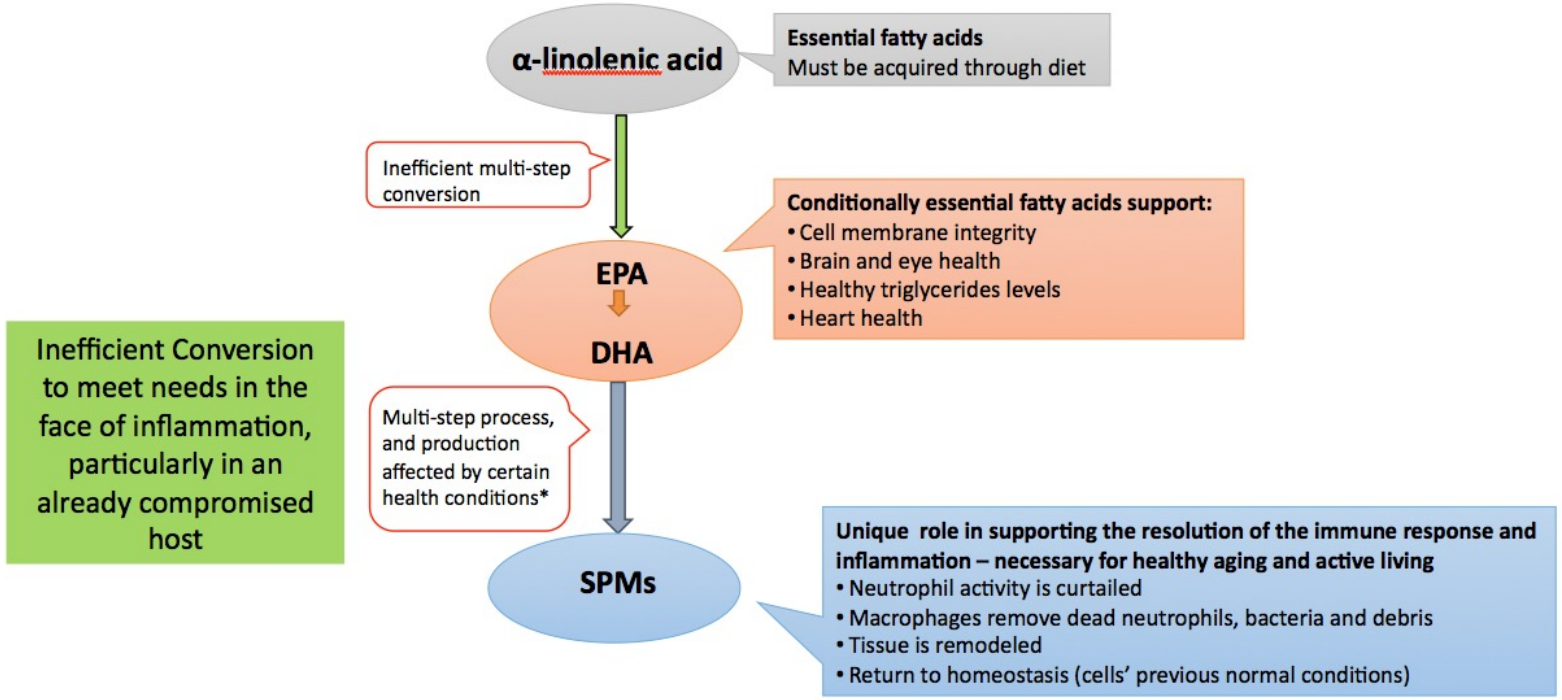
SPM Biosynthesis: Potential Roadblocks

Specialized Pro-Resolving Mediators (SPM)



Serhan CN. *Nature*. 2014;510:92-101

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SPM Supplement Considerations

- Source
- Fatty acid form
- EPA/DHA/SPM metabolite content
- Studies substantiating safety and efficacy

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Novel Marine Oil –High SPM Content

- *Perna canaliculus* (PCSO-524)
- Derived from green-lipped mussels of New Zealand
- Sustainably farmed in the pristine waters of New Zealand's Marlborough Sound.
- Evolved to have extraordinary antioxidant content due to ozone deficiency
- Blue Ocean Institute, ranked New Zealand Green-lipped mussels as one of the top two 'eco-friendly seafoods' in the world.*

*http://www.purenzgreenshell.com/aquaculture/quality-assurance/sustainability.cfm

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Marine Oil Extraction Processes

- Cold press
- Distillation
- Super critical fluid extraction

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Marine Oil Extraction Process

- Cold press and distillation processes result in bound forms of essential fatty acids
  - Triglyceride
  - Ethyl esters
- Supercritical fluid extraction results in free fatty acids

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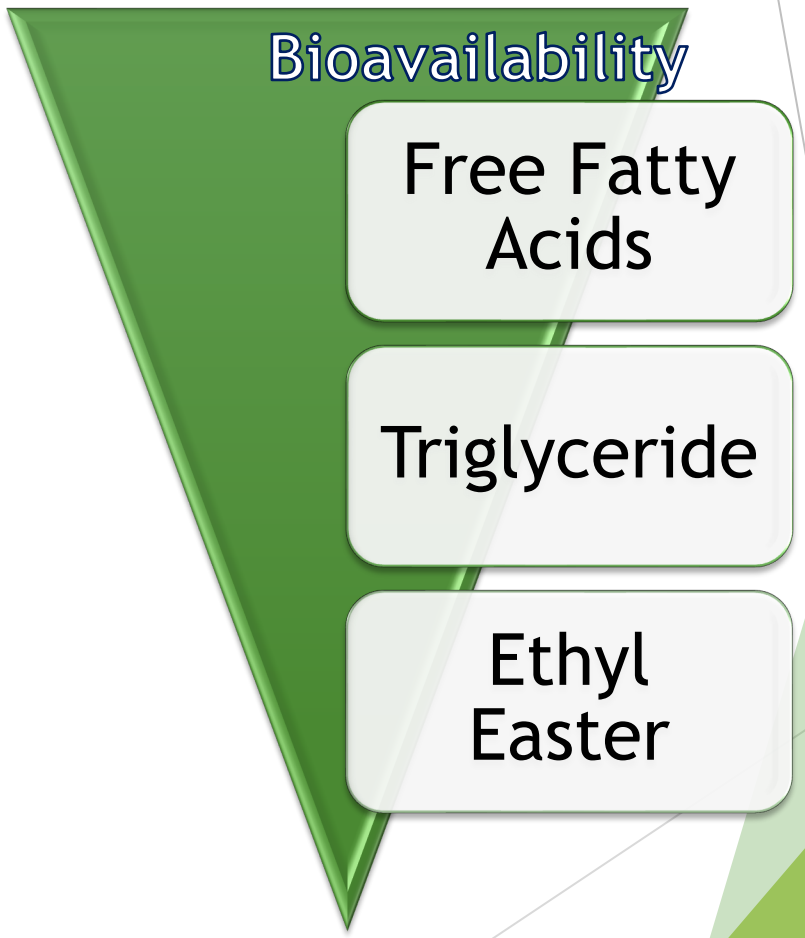
Extraction Processes

- Free Fatty Acids - easily absorbed and have been shown to have superior bioavailability*
- Triglyceride form- have a triglyceride “backbone” to the grouping of Fatty Acids
- Ethyl Easter- The Fatty acids are grouped together. The body must add the triglyceride backbone for absorption



HUMAN ABSORBTION OF FISHOIL FATIY ACIDS AS TRIACYLGLYCERLS, FREE ACIDS, OR ETHYLESTERS
Tarry D. Lawson andBronwynG. Hughes

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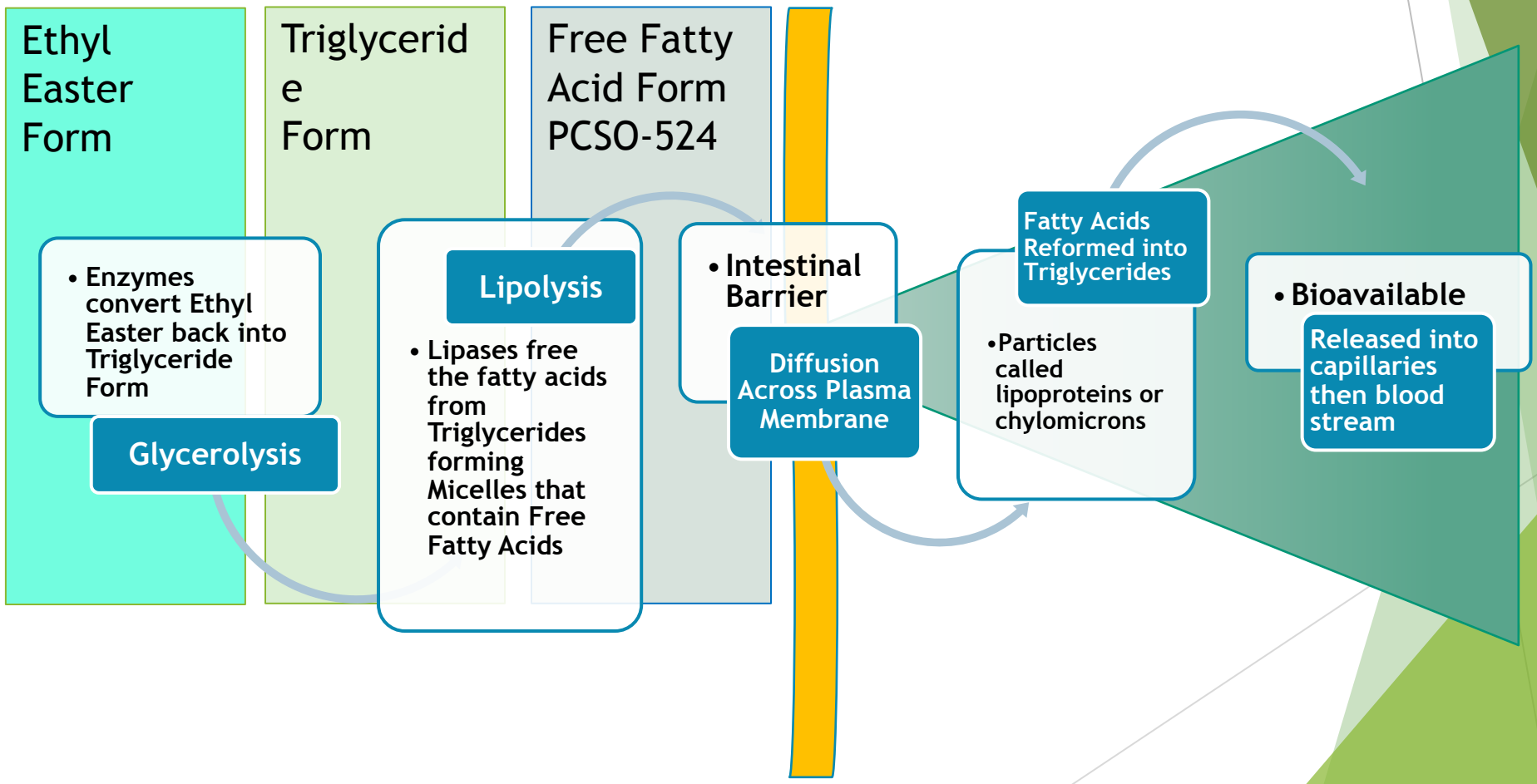
Fatty Acid Absorption



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Potency

Bioavailability

The PCSO-524 oil has been shown to 22 times more free fatty acid form DHA and EPA than standard fish oil.

*Convance –Certificate of Analysis 594817-0 10-jul-2012, 594835-0,594836-0

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Smaller but More Potent

Omaprem is 20 times more effective at reducing inflammation than standard fish oil

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PCSO-524

- PCSO524
  - 10 marine sterols
  - Over 90 fatty acids
  - Powerful pro-resolving lipid mediators
  - Phospholipids
  - Triglycerols

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Fatty Acids Composition

- PCSO-524 contains over 90 fatty acids (including the popular Omega-3's DHA and EPA)
- The array of fatty acids offers many unique properties not found in any other marine source

EPA
Palmitic
DHA
Palmitoleic
Stearic
Vaccenic
Linoleic
C18:3n4
Oleic
ALA
Arachidonic
Docosapenaenoic
Heptadecanoic
Eicosatetraenoic
Arachidic

Elaidic
Linoelaidic
γ-Linoleic Gadoleic
Behenic
Tricosanoic
Lignoceric
Nervonic
Butyric
Caprylic
Capric
Undecanoic
Lauric acid
Myristoleic
Eicosadienoic

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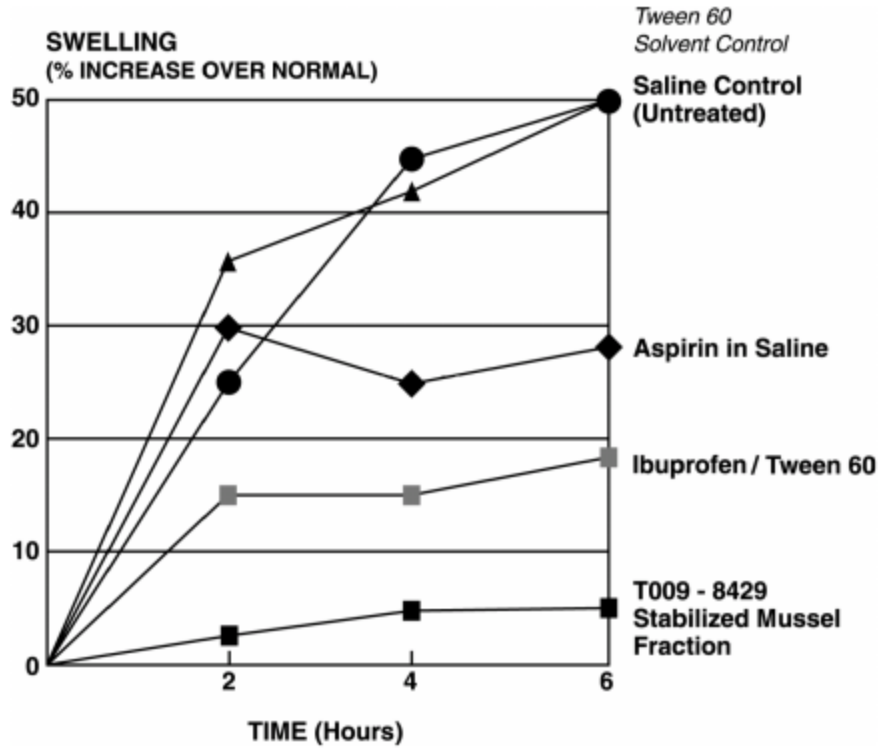
Anti-Inflammatory Effects of PCSO-524



ARTHRITIC INFLAMMATION IN RATS

TREATMENT	DOSAGE (MG/KG)	% REDUCTION IN INFLAMMATION
A. Dietary Marine Lipids (Lyprinol)	5	91%
B. Indomethacin	5	83%
C. Indomethacin	3	68%
D. Indomethacin	1	26%
E. No Treatment	0	0%

THE EFFECT OF OILS GIVEN PROPHYLACTICALLY TO PREVENT SWELLING ASSOCIATED WITH ADJUVANT-INDUCED POLY-ARTHRITIS

TYPE OF OIL	DOSE (MG/KG)	PERCENT EFFECTIVENESS
Flax Oil	2000	2%
Evening Primrose Oil	2000	25%
Norwegian Salmon Oil	2000	32%
EPA Fish Oil	2000	50%
Lyprinol	20	79%

Halpern GM. Anti-inflammatory effects of a stabilized lipid extract of Perna canaliculus (Lyprinolp). Allerg Immunol. 2000;32(7):272-278.

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Mechanism of Action

- Compared to standard fish oil, the studies demonstrate more effective anti-inflammatory activity in models of allergic airway disease, IBD, edema
- The effects are due to the following:
  - Synergistic activity of over 90 identified free fatty acids found in green-lipped mussels forming SPM metabolites
  - Anti-inflammatory polyphenols (oleuropein, hyroxytyrosol) and oleic acid, thought to reduce risk factors for heart disease, lower cancer mortality, reduce inflammation and pain
  - Furan fatty acids also exhibit more potent anti-inflammatory activity in arthritis

Mickelborough TD, et al. Marine lipid fraction PCSO-524 of the New Zealan green lipped mussel attenuates hyperpnea-induced bronchoconstriction in asthma. Resp Med 2013;107:1152-63

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Clinical Safety and Efficacy

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Arthritis

- 50 patients older than 50 years
- Patients treated with PCSO-524™ showed a statistically significant improvement of both their pain symptoms related to osteoarthritis and improved quality of their daily lives ($p = 0.05$)
- **Conclusion:** Reduction of pain was statistically evident at four weeks among the subjects who took capsules that contained PCSO-524™.

Szechinski J et al. Measurement of pain relief resulting from the administration of Perna canaliculus lipid complex PCSO-524™ as compared to fish oil for treating patients who suffer from osteoarthritis of hip and/or knee joints. Reumatologia 2011; 49: 244-252.

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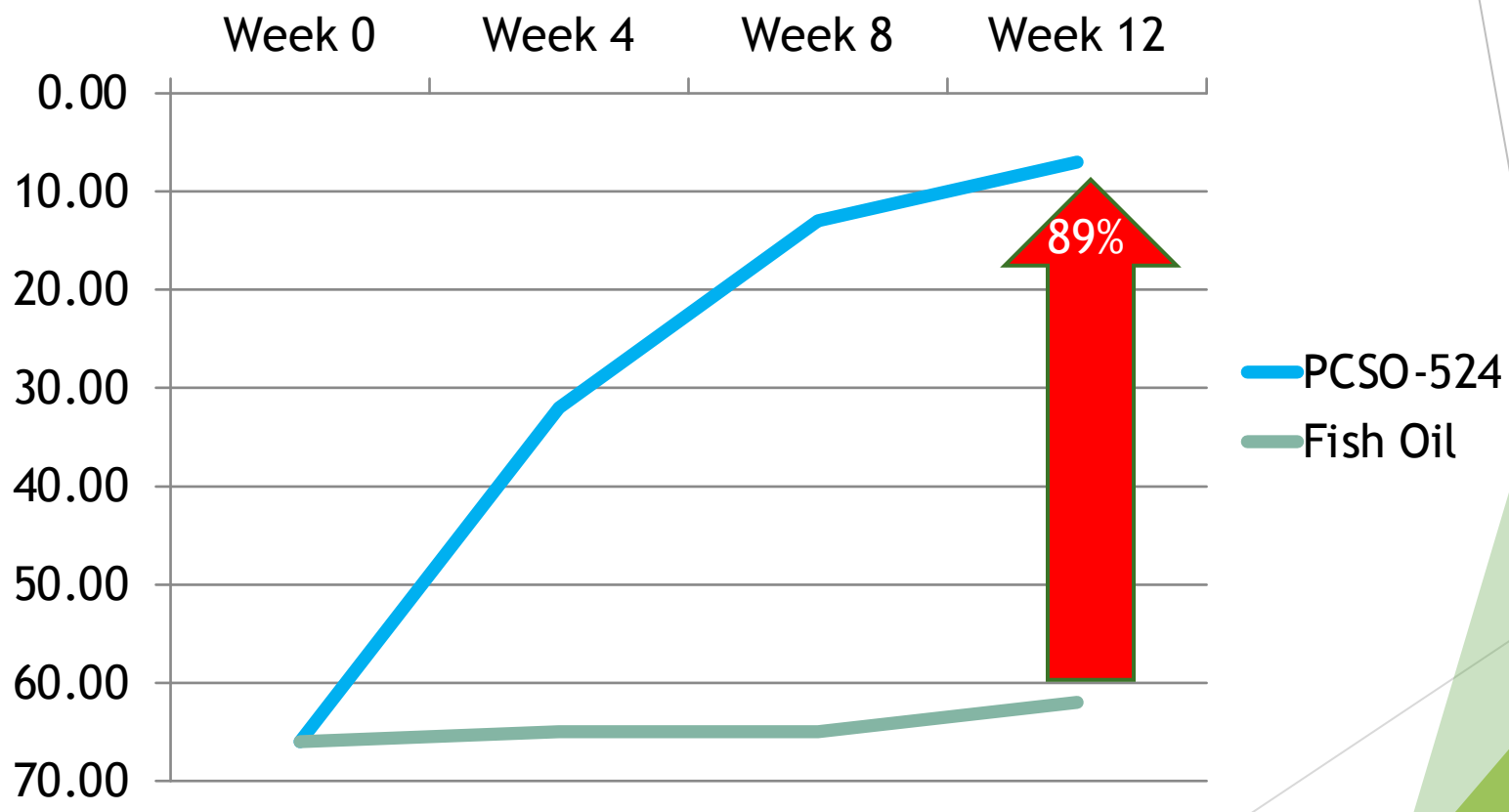
Visual Analog Scale (Arthritis)



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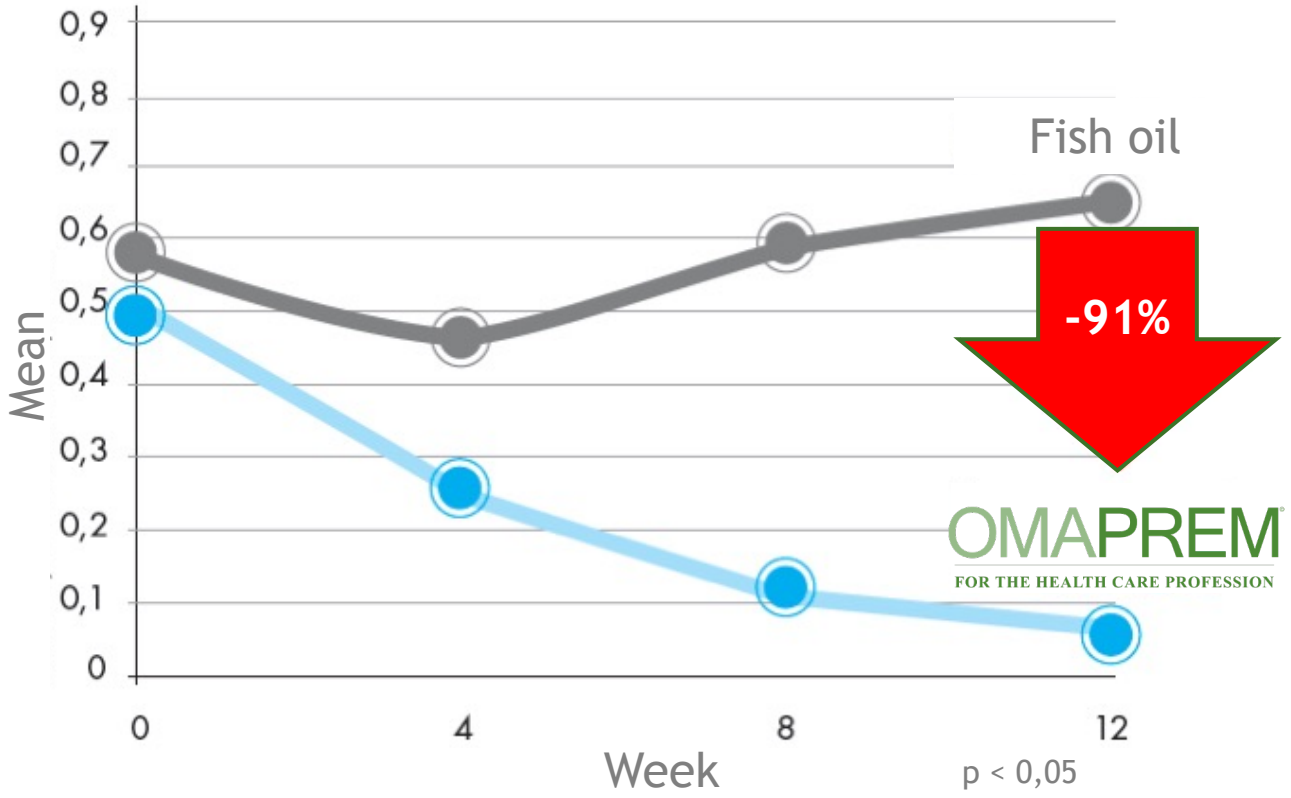
Quality of Life – Health Assessment Questionnaire



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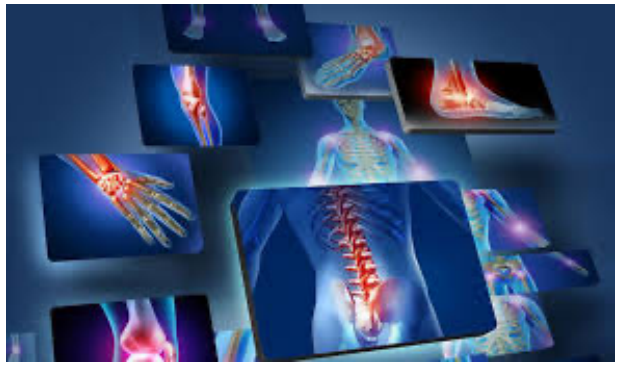
Rheumatoid Arthritis

- 12-week drug monitoring study evaluated the effects of PCSO-524™ on 50 adult men and women suffering from inflammatory rheumatoid arthritis
- 21 of the 34 subjects (64%) reduced or terminated current drug therapy
- 13 patients did not require further therapy
- 38 % of all subjects were regarded as being free from disorders
- Number of subjects suffering from severe pain was significantly decreased from 60% (at baseline) to 25 % (at 3 months)
- A significant positive effect was observed for all investigated parameters



Gruenwald J et al. Efficacy and tolerability of mussel-Lyprinol omega-3-complex on inflammatory rheumatoid disorders. PhytoPharm Research.

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Asthma

- Forty-six patients with atopic asthma received two capsules of lipid extract (PCSO-524™) or placebo BID. for 8 weeks
- Significant decrease in daytime wheeze concentration of exhaled H_2O_2
- Increase in morning PEF in the lipid extract group compared to the placebo group
- No reported significant side effects

Emelyanov A, et al. Treatment of asthma with lipid extract of New Zealand green-lipped mussel: a randomized clinical trial. Eur Respir J 2002: 20: 596-600.

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Asthma

- Placebo controlled double-blind randomized crossover trial to evaluate the effect of PCSO-524 on airway inflammation and bronchoconstrictor response to EVH (eucapnic voluntary hyperpnea) in 20 asthmatics for 3 weeks
- Results
  - PCSO-524 significantly reduced maximum fall in post-EVH FEV_1
  - EBC pH, asthma symptom scores significantly improved
  - Significant reduction in rescue medication use

Mickelborough TD, et al. Marine lipid fraction PCSO-524 of the New Zealand green lipped mussel attenuates hyperpnea-induced bronchoconstriction in asthma. Resp Med 2013; 107: 1152-63.

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Athletic Performance DOMS

- Randomized, placebo-controlled study to evaluate the effects of PSCO-524 on markers of muscle damage and inflammation following exercise in untrained subjects
- 32 untrained men received either 1200 mg/PCSO-524 or placebo for 26 days prior to downhill running
- Results: Compared to placebo, supplementation with green lipped mussel oil attenuated muscle damage and inflammation following muscle damaging exercise as demonstration via
  - Biomarkers of muscle damage (,myoglobin, CK)
  - Biomarkers of inflammation (TNF-α)
  - Functional markers of muscle damage (DOMS, pressure-pain threshold, ROM)

Mickelborough TD, et al. The effects of PCSO-524 a patented marine oil lip and omega-3 PUFA blend derived from the New Zealand green lipped mussel on indirect markers of muscle damage and inflammation after muscle damaging exercise in untrained men: a randomized, placebo controlled trial. J Int Soc Sports Nutr 2015; 12:10.

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Closing Thoughts

- SPMs are critical to the resolution of inflammation
- SPMs are deficient in individuals suffering from chronic or uncontrolled inflammatory condition
- SPM supplementation should be considered in the treatment of CIRS
- SPM supplementation is the future of inflammation resolution
- SPM supplement choice greatly influences the process
  - Fatty acid form
  - Source
  - SPM and/or metabolite content
  - Safety
  - Efficacy