The Lipid Revolution: Understanding the Role of Bioactive Lipids in Health and Disease

Sommer Lecture
May 1, 2025

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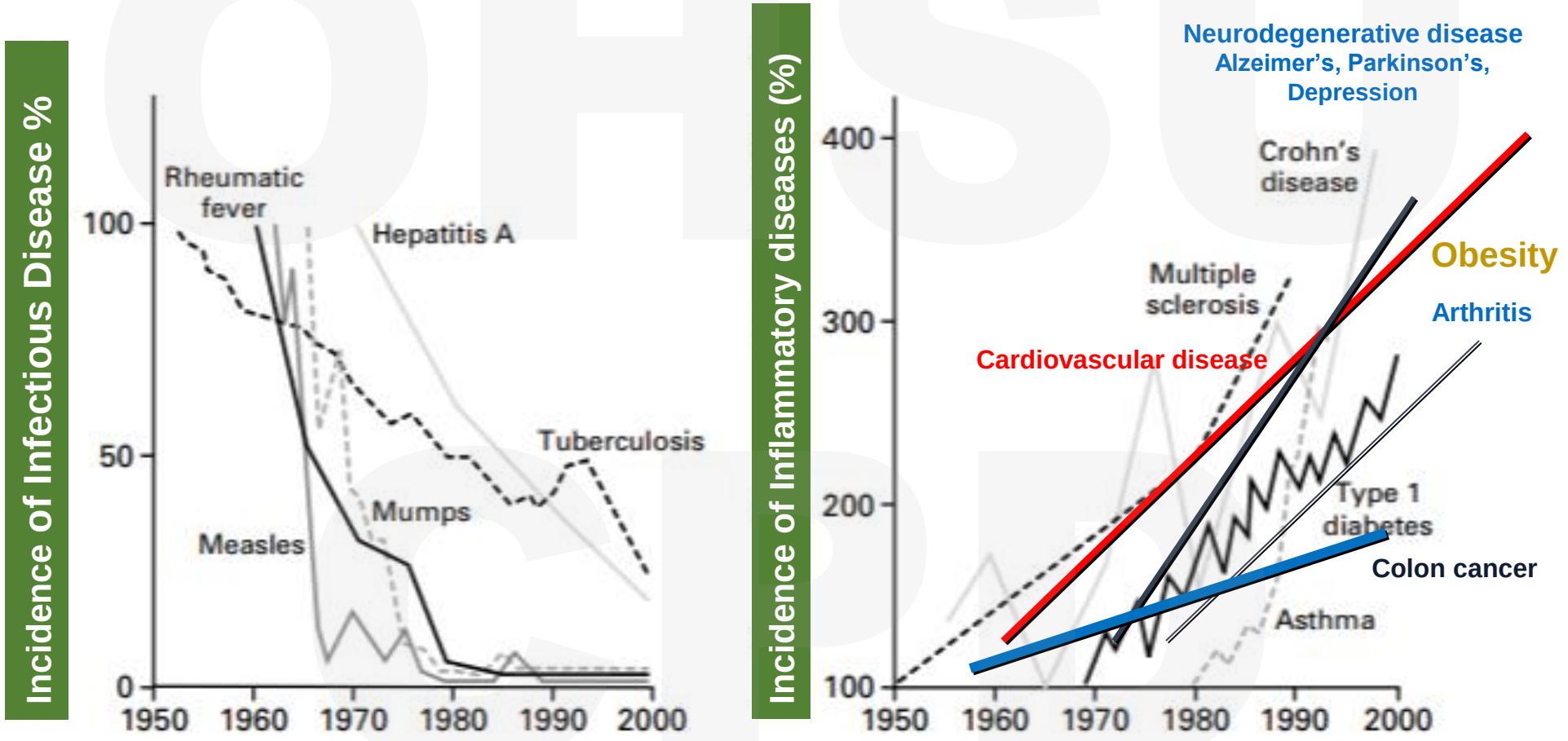
Oregon Health and Science University

Portland Oregon

Inflammatory Diseases have Replaced Infectious Diseases



Bach JF et al NEJM 2002 Bach JF et al Nature Rev Immunology 2017 Serhan CN et al JCI 2018

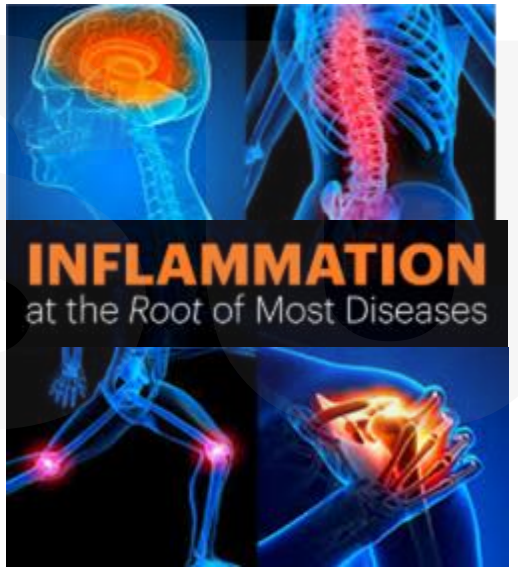
Diseases where Inflammation is now thought to be a major etiology of the disease !

- Diabetes
- Obesity
- Metabolic syndrome
- Heart disease
  - atherosclerosis
- Neuropsychiatric
  - Depression
  - Anorexia nervosa
  - Alzheimer's
  - Parkinson's
- Hepatic diseases
  - Non-alcoholic fatty liver
  - cirrhosis
- Infectious disease
  - General, TB, Malaria
- Asthma
- Allergy
- Inflammatory Bowel Disease
- Autoimmune diseases
- Peptic ulcer disease
- HIV / AIDS
- Cancer
  - Carcinogenic diets
  - Metabolic effects (cachexia)
  - Metastasis
- Critical Care / Surgery
  - Trauma
  - Pancreatitis
  - Sepsis
  - ARDS / ALI
  - COVID
- Aging (inflammaging)
- etc etc etc

Attempts at altering inflammation in hospitalized patients

- Corticosteroids
  - Sepsis
  - ARDS
  - Community acquired pneumonia
- Interleukin-6 and IL-1 receptor antagonists
  - Tocilizumab and sarilumab
    - Occasionally used for COVID-19 and cytokine release syndrome, widely mixed results
    - REMAP-CAP trial showed decrease mortality and organ failure "if" started early, within 24 hours of admission
  - Primarily data is in RA
- Janus Kinase (JAK) inhibitors
  - Several trials have shown improved mortality outcomes
    - Cochrane Database of Systematic Reviews found JAK inhibitors decrease mortality at 28 and 60 days
  - In combination with glucocorticoids tx for "hyperinflammation" appears to be best results
  - IDSA and NIH have recommended baricitinib for hospitalized patients with COVID-19
- β blockers (Propranolol) – non-specific β adrenergic antagonist
  - Primarily in burns
- IVIG
  - Modulation of macrophage activity, inhibits GM-CSF-STAT5 activation, promotes IL-10, blocks Fc receptors on immune cells
  - Induces autophagy in blood mononuclear cells
- Complement inhibition
  - Primarily targeting C3 – some data in COVID 19
- NSAIDs (Naproxen (Aleve), Ibuprofen (advil, motrin) celecoxib (Celebrex), indomethacin (Indocin, tivorbex) etc_
  - NOT recommended in ICU patients- side effects and inhibition of SPM formation
- ASA – which inhibits proinflammatory eicosanoid formation AND stimulates synthesis of SPMs
- Nutritional strategies

Is the Western Diet the Driving Force for these Inflammatory Diseases ?



Nutrients / compounds with immune and metabolic activity

- Vitamin C
- Vitamin E
- Zinc
- Selenium
- Probiotics
- Prebiotics
- Omega-3 FA (EPA/DHA)
- Carnitine
- Curry paste
- Resveratrol
- Nucleotides

- Glutamine
- Arginine
- Taurine
- Cysteine
- Willow Bark
- Leucine
- Threonine
- Glutathione
- Creatine
- Caffeine
- Glucosamine

Echinacea
Garlic
Boswellia
Tumeric
Saffron
Shark cartilage
Ginger
Licorice
Chamomile
Capsaicin
SCFAs

The early concepts regarding fish oils came from these classic studies

The American Journal of Clinical Nutrition
Volume 28, Issue 9, September 1975, Pages 958-966

Fatty acid composition of the plasma lipids in Greenland Eskimos

Dyerberg J, Bang HO, Hjørne N

1975

Inuit children in Greenland

The Lancet
Volume 297, Issue 7710, 5 June 1971, Pages 1143-1146

ORIGINAL ARTICLES

PLASMA LIPID AND LIPOPROTEIN PATTERN IN GREENLANDIC WEST-COAST ESKIMOS

H.O. Bang, J. Dyerberg, Aase Brøndum Nielsen

1971

Acta Medica Scandinavica

The Composition of Food Consumed by Greenland Eskimos

H. O. Bang, J. Dyerberg, N. Hjørne

First published: January/December 1976 | https://doi.org/10.1111/j.0954-6820.1976.tb08198.x | Citations: 720

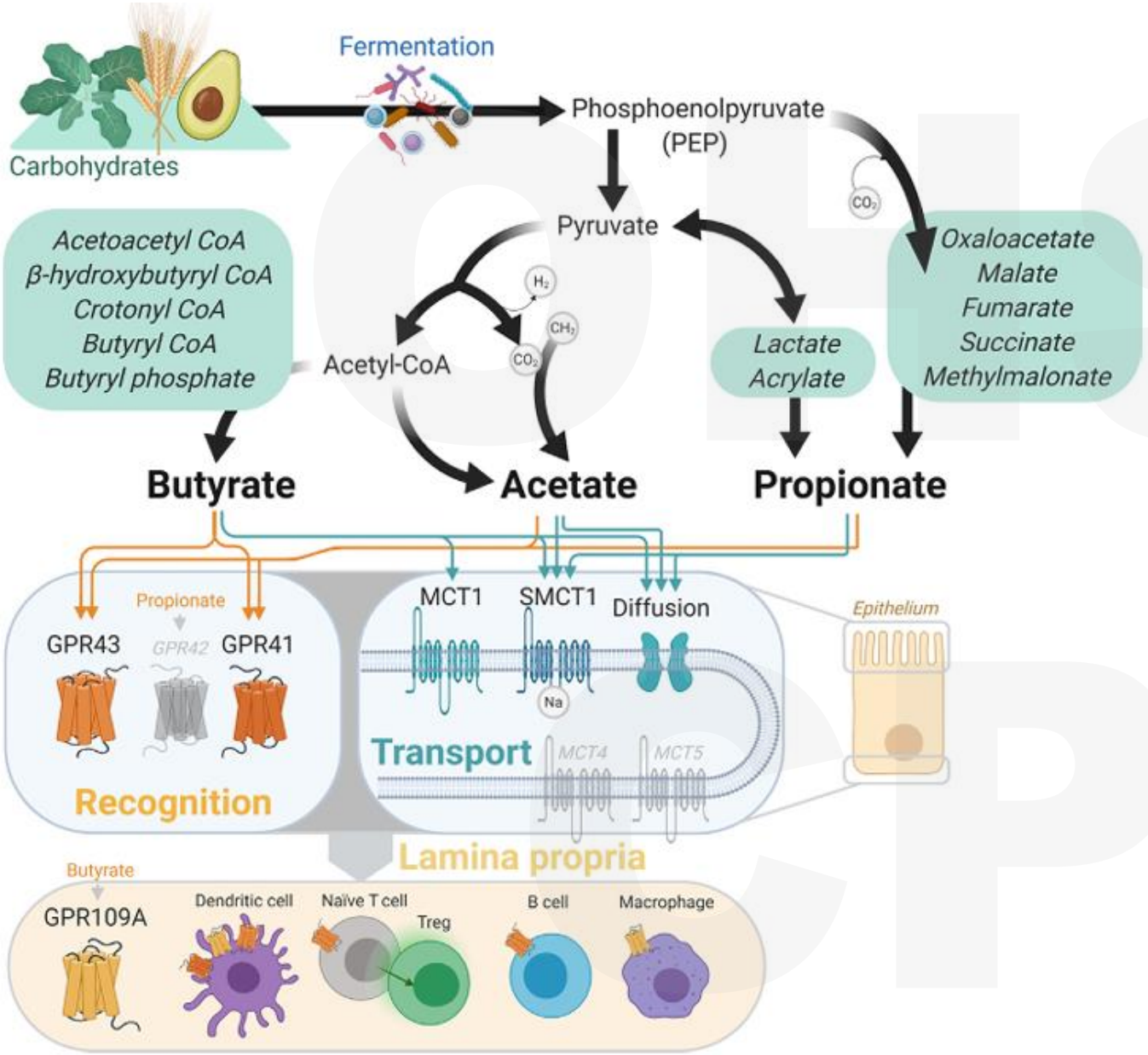
1976

Lipid Choices in Clinical Medicine 2025:

Can lipid choice alter the metabolic responses in clinical setting ?

- **Lipid Substrate**
  - **SCFA (2 to 6 carbons)**
    - **acetate, butyrate, proprionate most common**
    - **Increase metabolic utilization**
    - **Metabolic products of microbiome fermentation**
  - **MCT (6 to 12 carbons)**
    - **Dual absorption via portal and lymphatics**
      - **Decrease lipogenesis**
    - **no acyl-carnitine carrier required for β oxidation**
      - **Rapid clearance via oxidation**
      - **Utilization of MCT > LCT in times of metabolic stress**
      - **Thermogenic and ketogenic**
  - **LCT (14 to 20 carbons)**
    - **Omega 3**
      - **SPM's**
    - **Omega 6**
      - **EFA easily met**
    - **Omega 9**

SCFA effects on metabolism and immunoregulation



Regulation of gene expression for ICAM-1 and E-Selectin on endothelial cells

Activates G-protein-coupled receptors GPR41, GPR43

Reduces mucosal inflammation

Regulates trans-epithelial fluid transport

Strengthens epithelial defense barrier

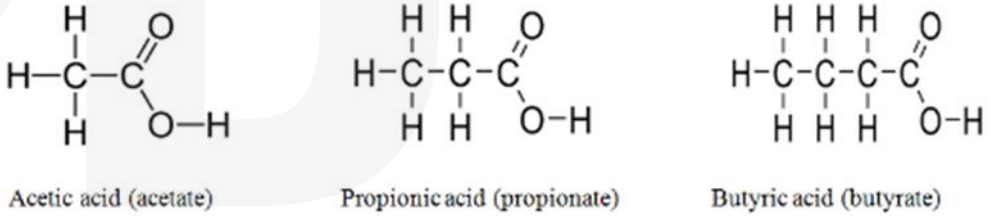
Lowers cholesterol

Decreases insulin resistance

Improves recovery in I/R injury

Regulator HDAC (anti-mitogenic activity)

Known transporters described in colonic mucosa



van der Hee B et al Trends Micro 2021

Martindale R et al Curr Opin Nutrition Met Care 2025

Relative Inflammation Scale

Less inflammatory

Proinflammatory

Anti-inflammatory

Safflower oil

Soybean oil

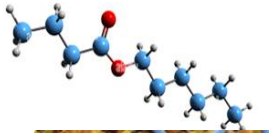
Medium chain triglyceride oil

Olive oil

Fish oil

Downstream metabolites

SCFA (Butyrate)

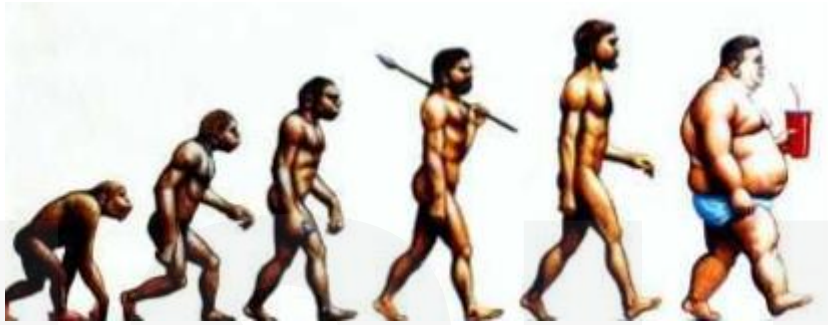


SPM's
Inflammation Resolution

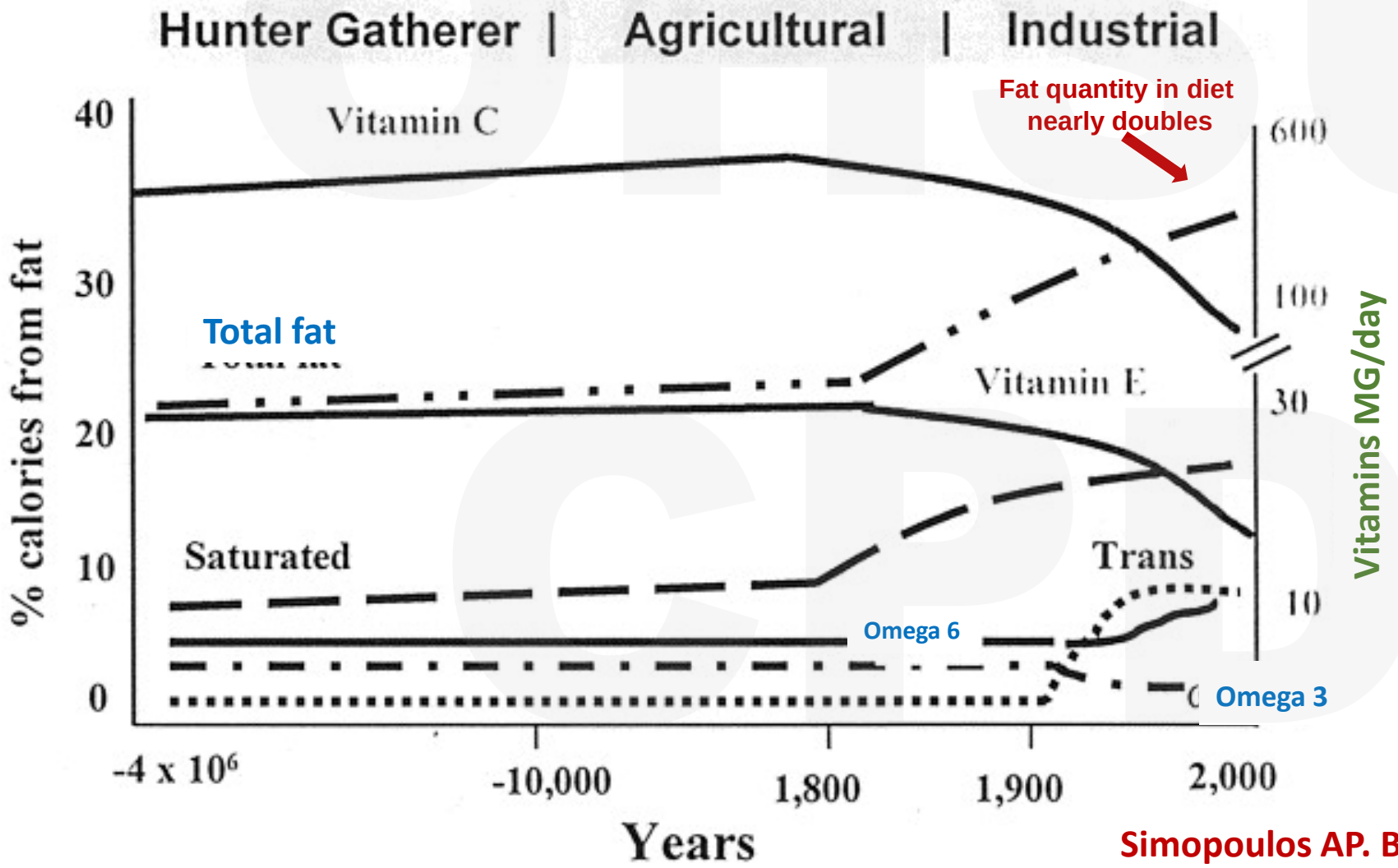
Calder PC et al JPEN 2020
Martindale RG et al JPEN 2020
Vanek VW et al Nutr Clin Pract 2012

What can be done with Nutrition ?

Enteral Nutrition
Bioactive lipids
Pre, Pro, and Postbiotics



Omega 6: Omega 3 ratios in various populations	
Population	ω6/ω3
Paleolithic	**0.79**
Greece <1960	**1.5**
Current Japan	**4**
Current India, rural	**6**
Current India, urban	**15**
Current US	**17**
Current UK, N Europe	**45**

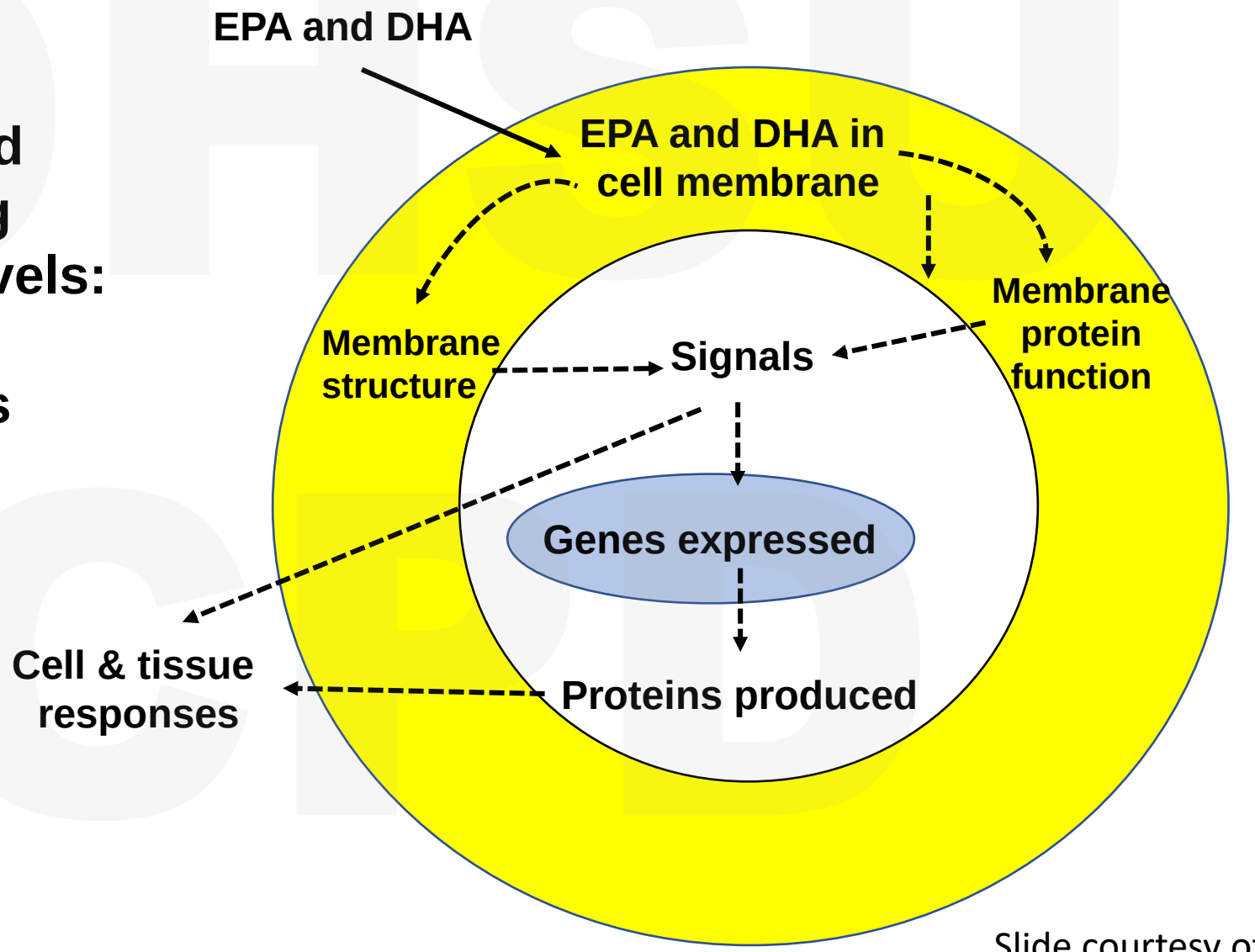


These changes in type of lipid and quantity dramatically change cellular physiology

Simopoulos AP. Biomed Pharmacotherapy 2002

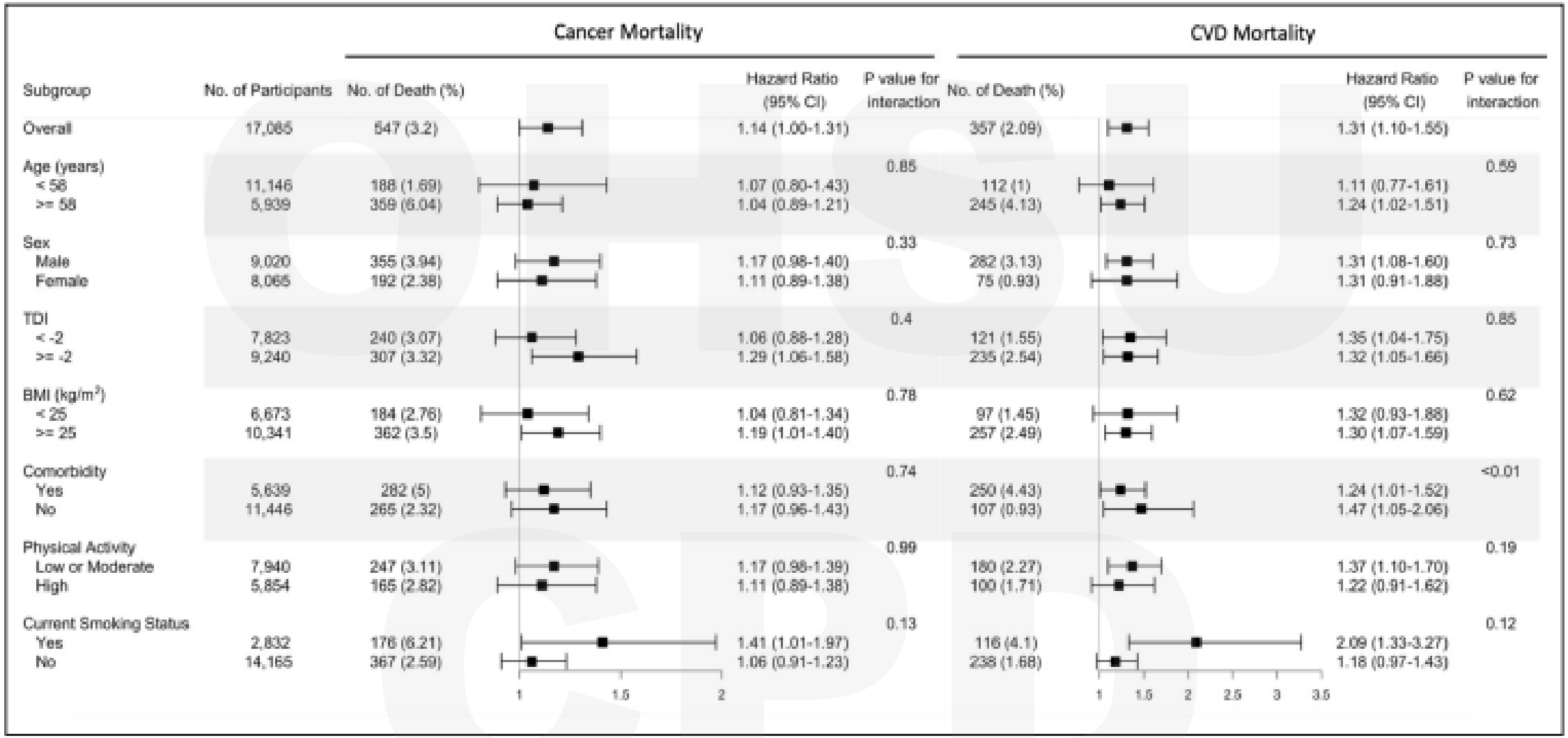
Why is this ratio of Omega 6 to Omega 3 so important to consider?

- **Altered expression and activation of signalling proteins at multiple levels:**
  - **Cell membrane**
  - **Cytosolic receptors**
  - **Nucleus**



Slide courtesy of Phil Calder

Omega 6 to Omega 3 Ratio and All Cause Mortality



Subgroup	No. of Participants	Cancer Mortality: No. of Death (%)	Cancer Mortality: Hazard Ratio (95% CI)	Cancer Mortality: P value for interaction	CVD Mortality: No. of Death (%)	CVD Mortality: Hazard Ratio (95% CI)	CVD Mortality: P value for interaction
Overall	17,085	547 (3.2)	1.14 (1.00-1.31)		357 (2.09)	1.31 (1.10-1.55)	
Age (years)				0.85			0.59
< 58	11,146	188 (1.69)	1.07 (0.80-1.43)		112 (1)	1.11 (0.77-1.61)	
>= 58	5,939	359 (6.04)	1.04 (0.89-1.21)		245 (4.13)	1.24 (1.02-1.51)	
Sex				0.33			0.73
Male	9,020	355 (3.94)	1.17 (0.98-1.40)		282 (3.13)	1.31 (1.08-1.60)	
Female	8,065	192 (2.38)	1.11 (0.89-1.38)		75 (0.93)	1.31 (0.91-1.88)	
TDI				0.4			0.85
< -2	7,823	240 (3.07)	1.06 (0.88-1.28)		121 (1.55)	1.35 (1.04-1.75)	
>= -2	9,240	307 (3.32)	1.29 (1.06-1.58)		235 (2.54)	1.32 (1.05-1.66)	
BMI (kg/m^2)				0.78			0.62
< 25	6,673	184 (2.76)	1.04 (0.81-1.34)		97 (1.45)	1.32 (0.93-1.88)	
>= 25	10,341	362 (3.5)	1.19 (1.01-1.40)		257 (2.49)	1.30 (1.07-1.59)	
Comorbidity				0.74			<0.01
Yes	5,639	282 (5)	1.12 (0.93-1.35)		250 (4.43)	1.24 (1.01-1.52)	
No	11,446	265 (2.32)	1.17 (0.96-1.43)		107 (0.93)	1.47 (1.05-2.06)	
Physical Activity				0.99			0.19
Low or Moderate	7,940	247 (3.11)	1.17 (0.98-1.39)		180 (2.27)	1.37 (1.10-1.70)	
High	5,854	165 (2.82)	1.11 (0.89-1.38)		100 (1.71)	1.22 (0.91-1.62)	
Current Smoking Status				0.13			0.12
Yes	2,832	176 (6.21)	1.41 (1.01-1.97)		116 (4.1)	2.09 (1.33-3.27)	
No	14,165	367 (2.59)	1.06 (0.91-1.23)		238 (1.68)	1.18 (0.97-1.43)	

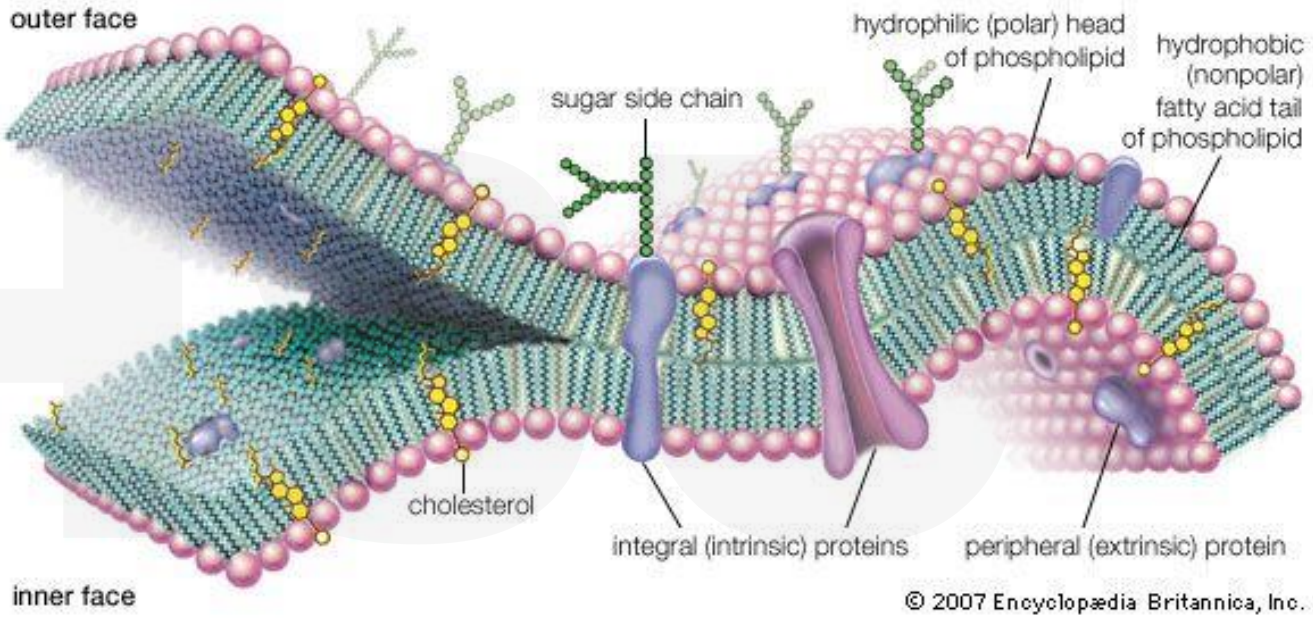
UK Biobank Study

502,384 subjects with 85,425 subjects with complete data on PUFA followed for 4 years (2006 to 2010)

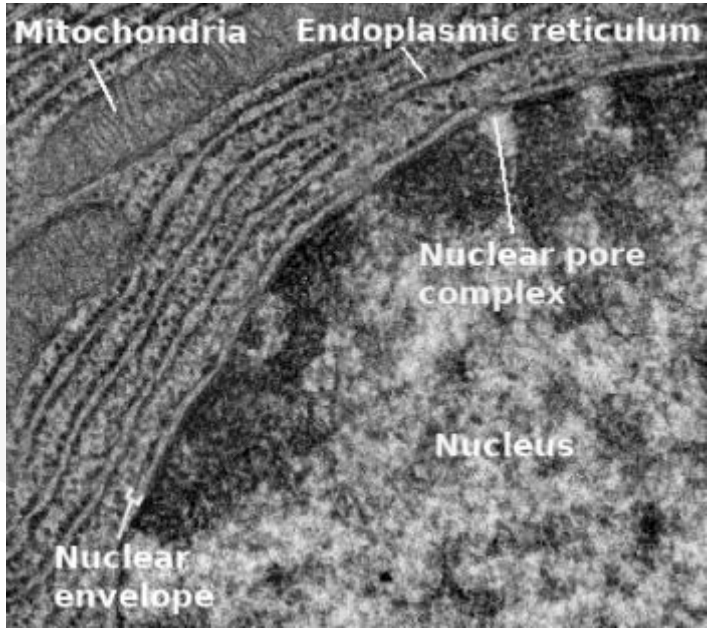
14% decrease Cancer mortality and 31% cardiac mortality --- 26% decrease in all cause mortality

Zhang Y et al eLife 2023

Mechanisms: a closer look



1) **Cell membranes**
   - lipid rafts
   - Membrane fluidity
2) **Nucleus**
3) **Mitochondria**
4) **Autophagy / mitophagy**



Is modulation of inflammation a laudable goal in numerous human maladies ?

Original Investigation | Nutrition, Obesity, and Exercise

Association of Baseline Inflammation With Effectiveness of Nutritional Support Among Patients With Disease-Related Malnutrition

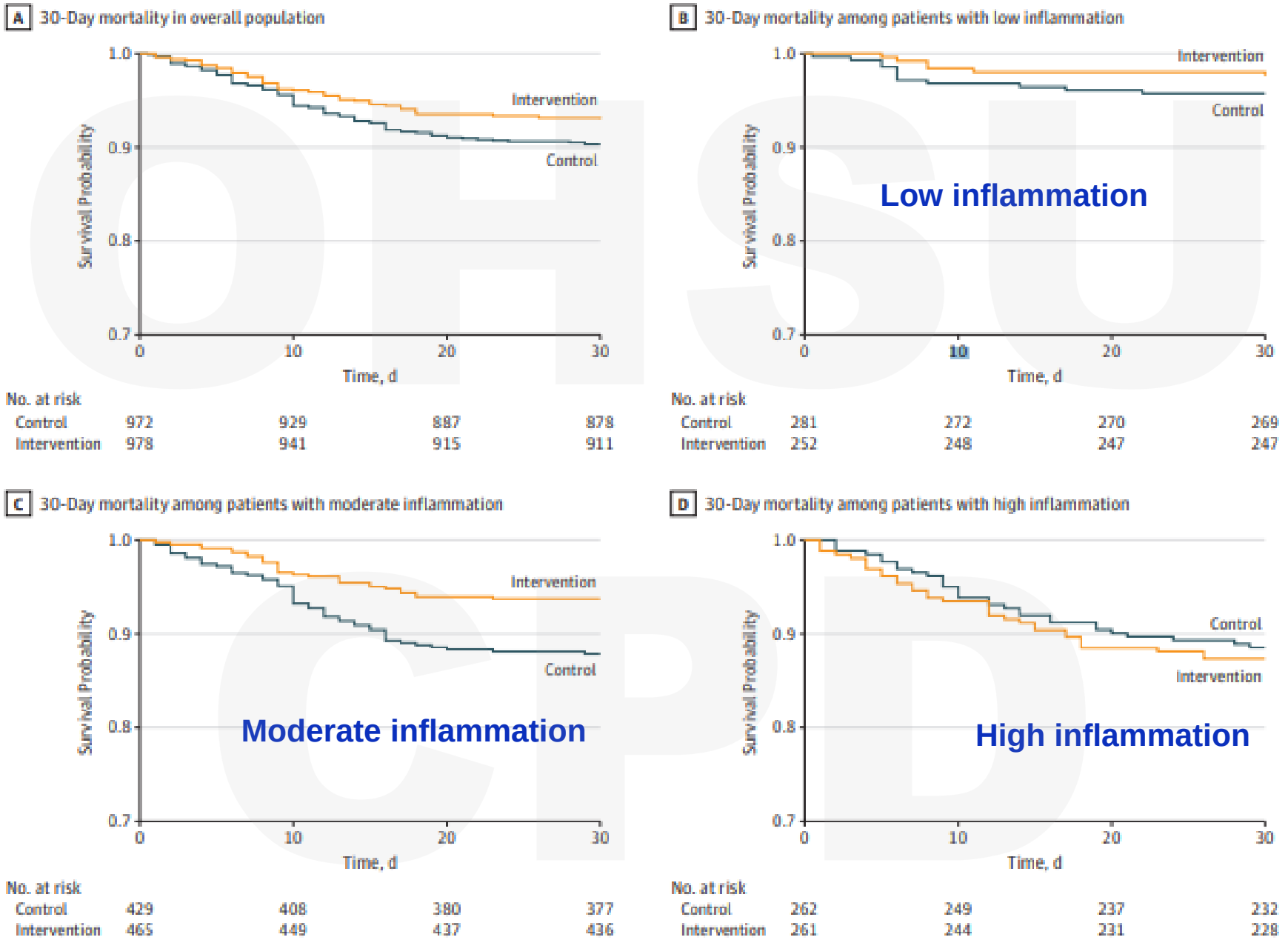
A Secondary Analysis of a Randomized Clinical Trial

JAMA 2020

Meret Merker, MD; Martina Felder, BMSc; Louise Gueissaz, BMSc; Rebekka Bolliger, MD; Pascal Tribolet, MSc; Nina Kägi-Braun, MD; Filomena Gomes, PhD; Claus Hoess, MD; Vojtech Pavlicek, MD; Stefan Bilz, MD; Sarah Sigrist, MD; Michael Brändle, MD; Christoph Henzen, MD; Robert Thomann, MD; Jonas Rutishauser, MD; Drahomir Aujesky, MD; Nicolas Rodondi, MD, MAS; Jaques Donzé, MSc; Zeno Stanga, MD; Beat Mueller, MD; Philipp Schuetz, MD, MPH

- **RCT 8 Swiss Hospitals N=1950**
- **Personalized nutrition vs SOC hospital food**
  - protocol-guided individualized nutritional support to reach protein and energy goals (intervention group) or standard hospital food (control group).
- **End points**
  - **30 day mortality (primary)**
  - **Level of inflammation based on CRP (3 levels, low-moderate-high)**
- **Results**
  - **Personalized nutrition decreases mortality across entire study groups**
  - **Highest level of inflammation reported no benefit or effect of nutritional support**

Figure 2. Kaplan-Meier Estimate for Time to Death Within 30 Days According to Inflammatory Status

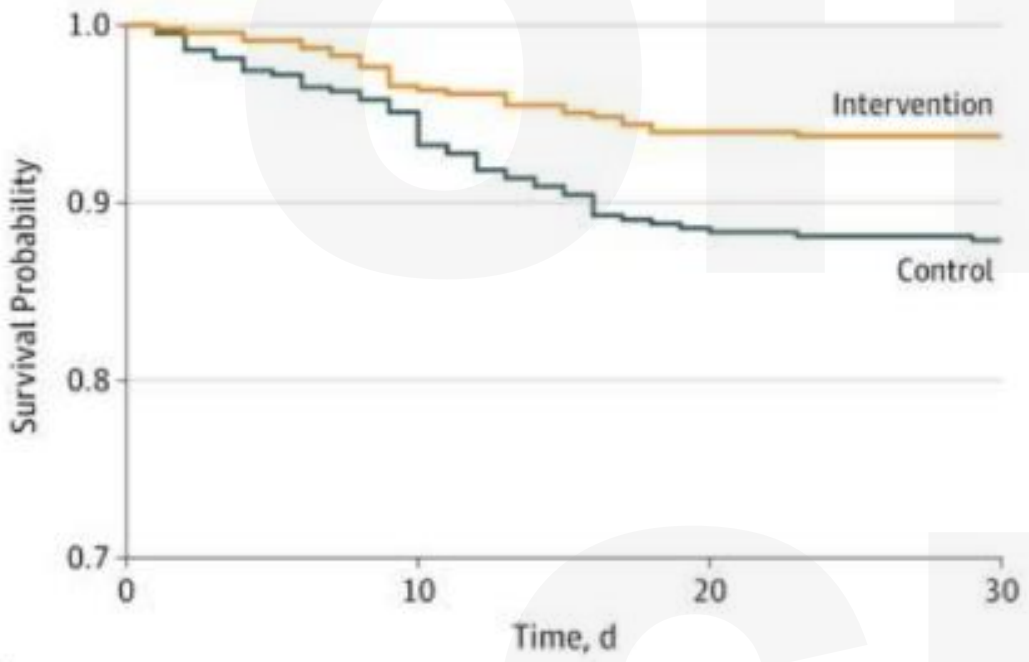


OREGON HEALTH & SCIENCE UNIVERSITY

Merker M et al JAMA 2020

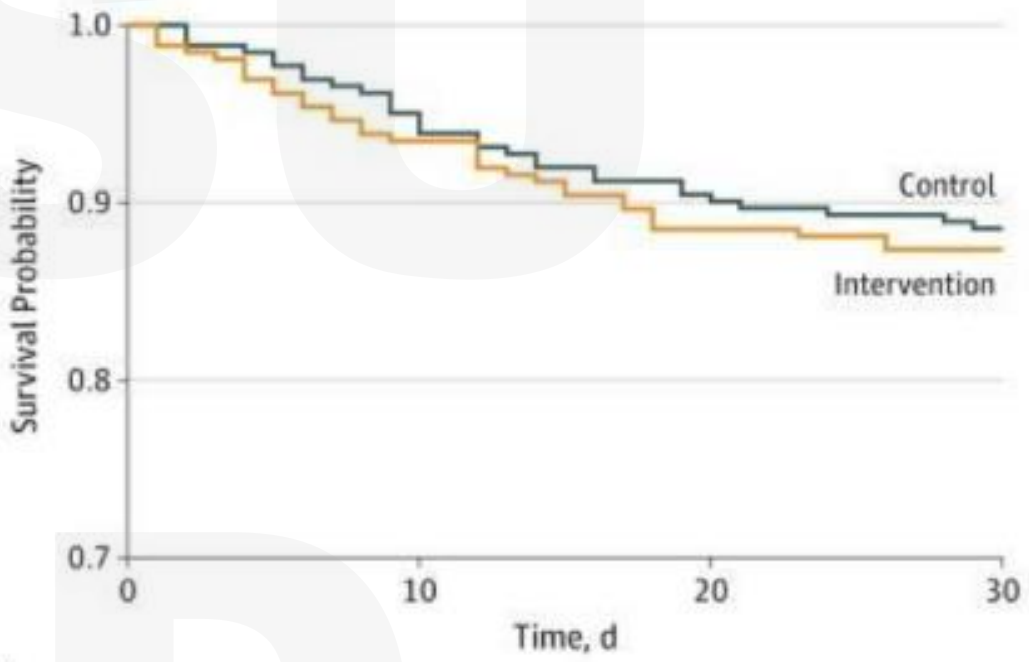
What happened here?
wrong nutrient ? wrong timing ? wrong patient ?

30 day mortality in patients with moderate inflammation



No. at risk				
Control	429	408	380	377
Intervention	465	449	437	436

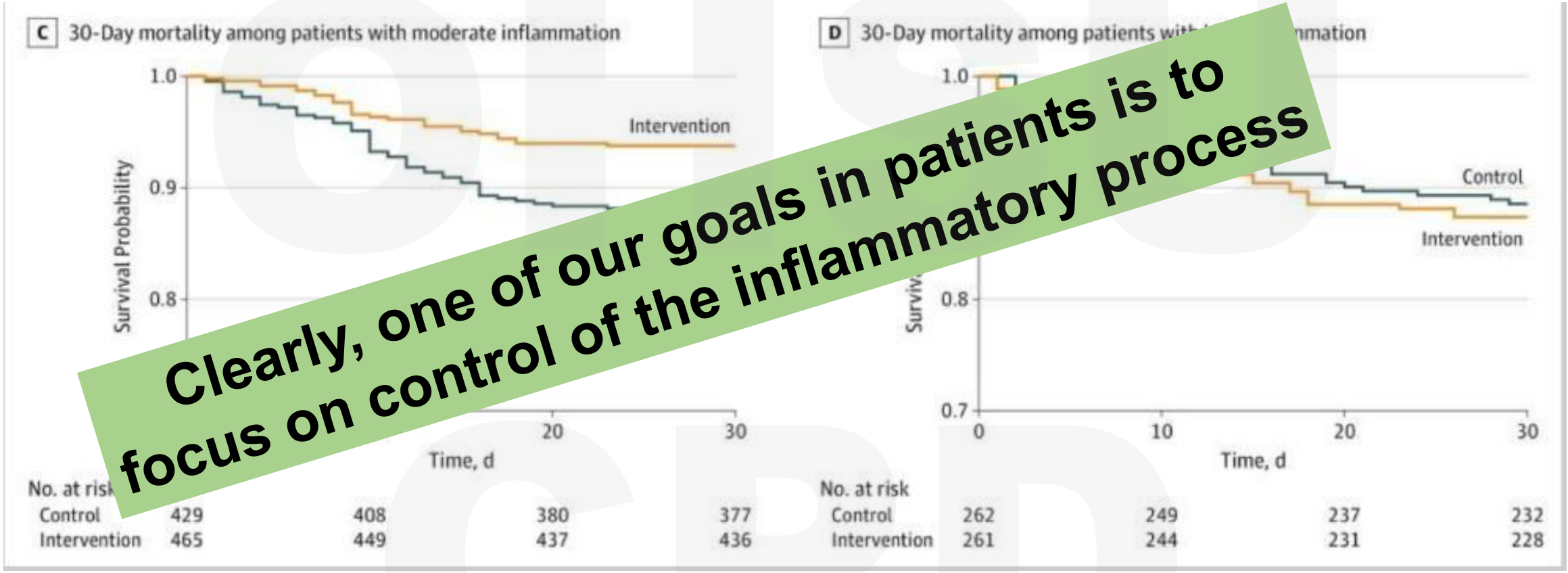
30 day mortality in patients with Highest level of inflammation



No. at risk				
Control	262	249	237	232
Intervention	261	244	231	228

Merker M, et al. "Association of Baseline Inflammation with effectiveness of Nutritional Support…"
JAMA Network Open. 2020; 3(3):e200663.

What happened here?
wrong nutrient ? wrong timing ? wrong patient ?



Clearly, one of our goals in patients is to focus on control of the inflammatory process

Merker M, et al. "Association of Baseline Inflammation with effectiveness of Nutritional Support…" JAMA Network Open. 2020; 3(3):e200663.

Inflammation as a Predictor of Response to Nutrition

15 Ventilated ICU Pts

vs

10 Healthy controls

Labeled AAs: Phe, Tyr, Leu (IV and enteral)

Arterial and muscle samples were measured.

- Myofibrillar protein synthesis did not differ
- Amino acid availability did not differ
- **Incorporation of amino acids into muscle was 60% less in inflamed ICU patients**

Lee-anne Chapple

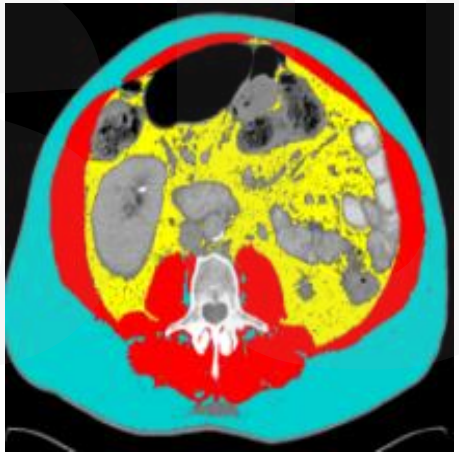
Chapple L. American J Resp and Critical Care Med 2022

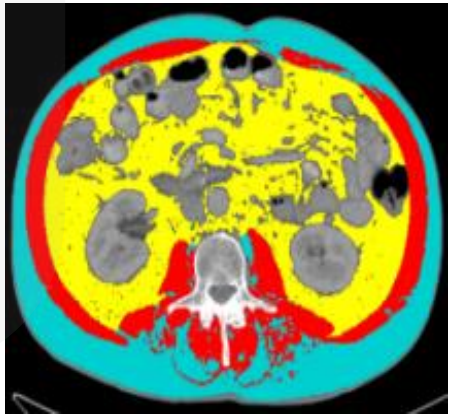
Maintaining Lean Body Tissue is Critical to Outcome !!

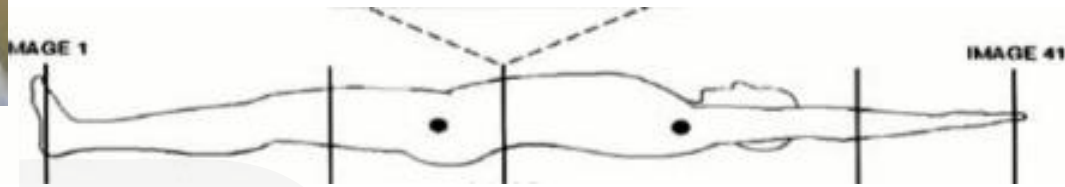
Can Dietary Changes Make a Difference ?

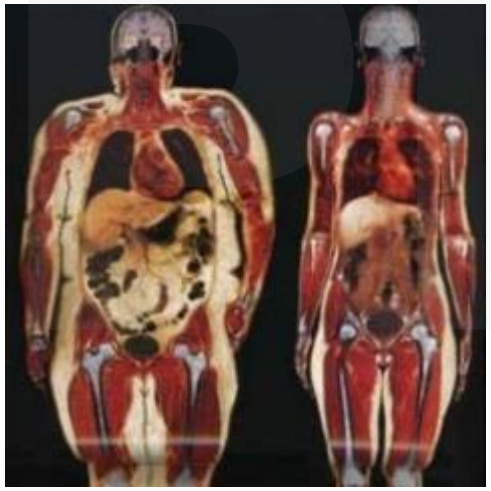
Diseases now proven to have correlated body composition to outcome:

- Colorectal Cancer
- Pancreatic Cancer
- Esophageal Cancer
- Lymphoma
- Elderly trauma in ICU
- Hepatoma
- Lung Cancer
- AWR and Ventral Hernia
- Liver Transplant
- 30 d mortality in sepsis
- Patients requiring ECMO
- COVID
- etc?





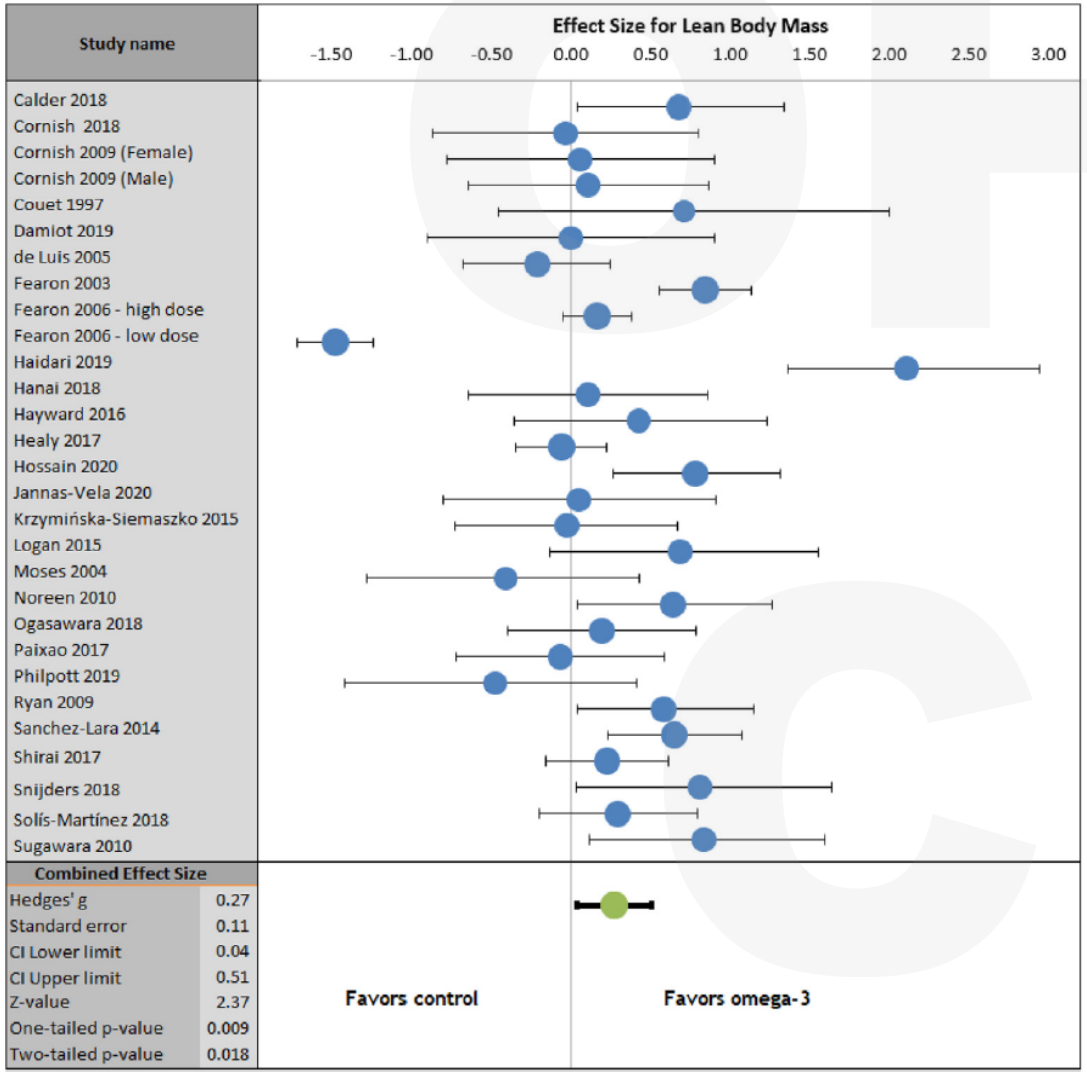




1. Peng P et al J GI Surgery 2012
2. Kirk PS et al J Surg Res 2015
3. Okumura S et al Surgery 2015
4. Mundi M et al Nutr Clin Practice 2019
5. Xiao J et al JAMA Surg 2020
6. Schlossse KA et al Am Surg 2019
7. Moisey LL et al CC 2013
8. Prado CM et al Ann Med 2018
9. Ji Y et al Jour Crit Care 2018
10. Bear D et al CCM 2021
11. van Rooijen MMJ WJS 2019
12. Jogiat UM et al Ann Surg 2023

What can be done to reduce the inflammation ?

RCTs show omega-3s promote lean mass and muscle mass

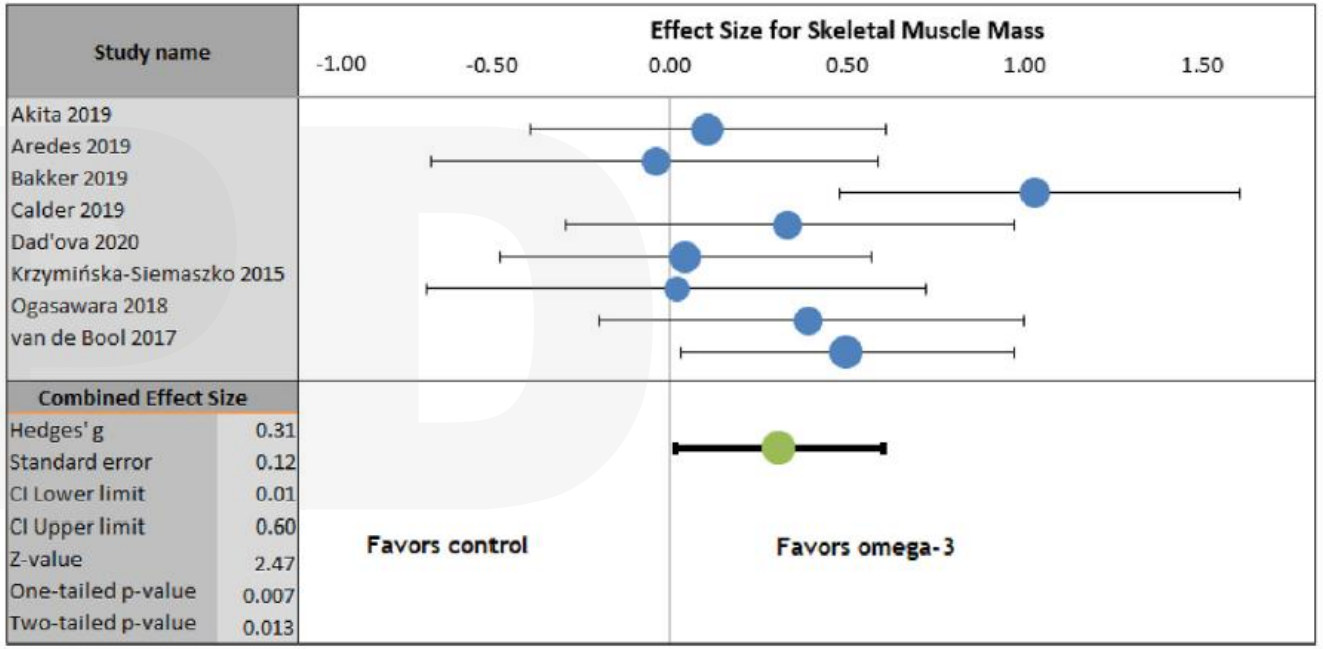


Meta-analysis

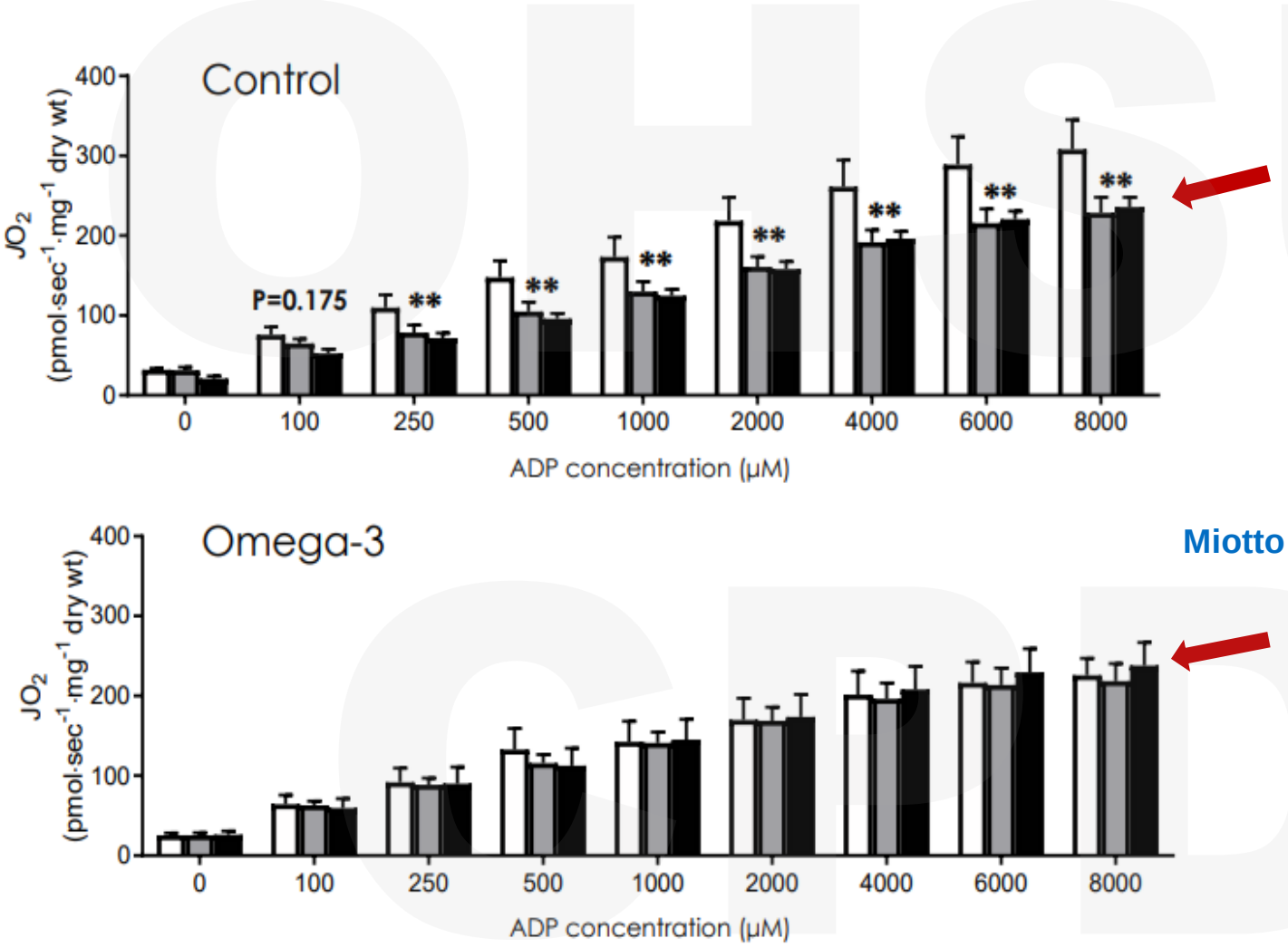
The effect of long chain omega-3 polyunsaturated fatty acids on muscle mass and function in sarcopenia: A scoping systematic review and meta-analysis

Julia K. Bird [a], Barbara Troesch [b, *], Ines Warnke [c], Philip C. Calder [d, e]

Bird JK et al Clin Nutrition 2021



Omega-3 fatty acids protect against declines in mitochondrial respiration



Miotto PM et al FASEB J 2019

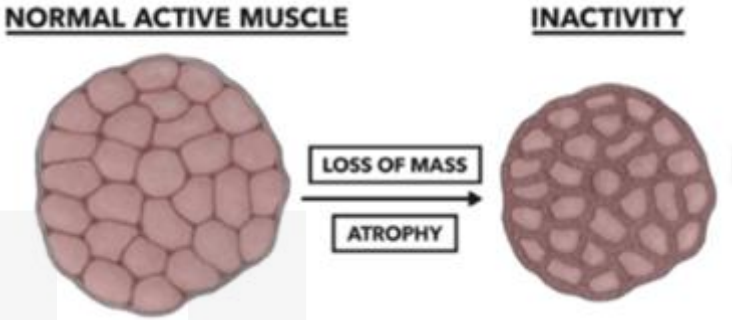
Note: no decrease in mitochondrial respiration in Omega 3 FA group

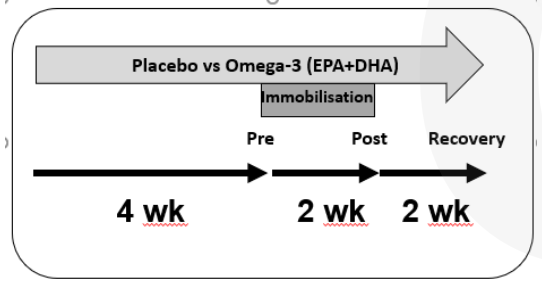
★ **4 wk 5 gm FO supplement pre immobilization and 2 weeks during immobilization**

Omega-3 fatty acid supplementation attenuates skeletal muscle disuse atrophy during two weeks of unilateral leg immobilization in healthy young women

Chris McGlory,*,[1] Stefan H. M. Gorissen,* Michael Kamal,* Ravninder Bahniwal,* Amy J. Hector,* Steven K. Baker,† Adrian Chabowski,‡ and Stuart M. Phillips*

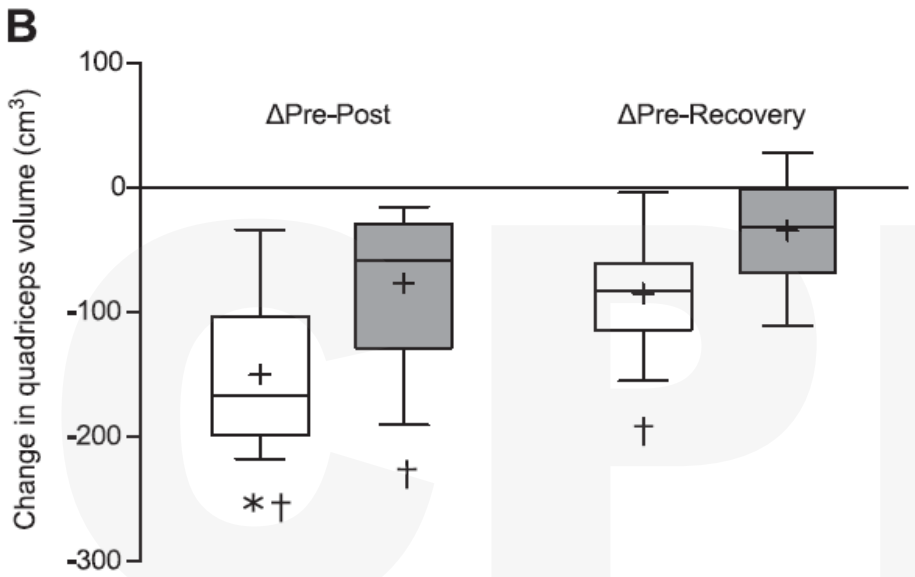
*Department of Kinesiology and †Division of Physical Medicine and Rehabilitation, Department of Medicine, McMaster University, Ham Ontario, Canada; and ‡Department of Physiology, Medical University of Bialystok, Bialystok, Poland



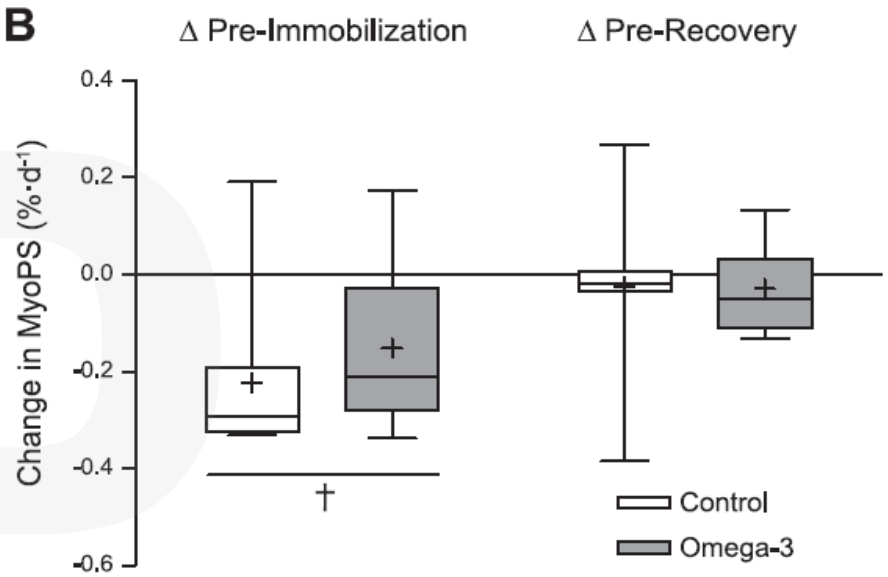


- 2.97 gm EPA + 2.03 gm DHA per day
- 8 weeks

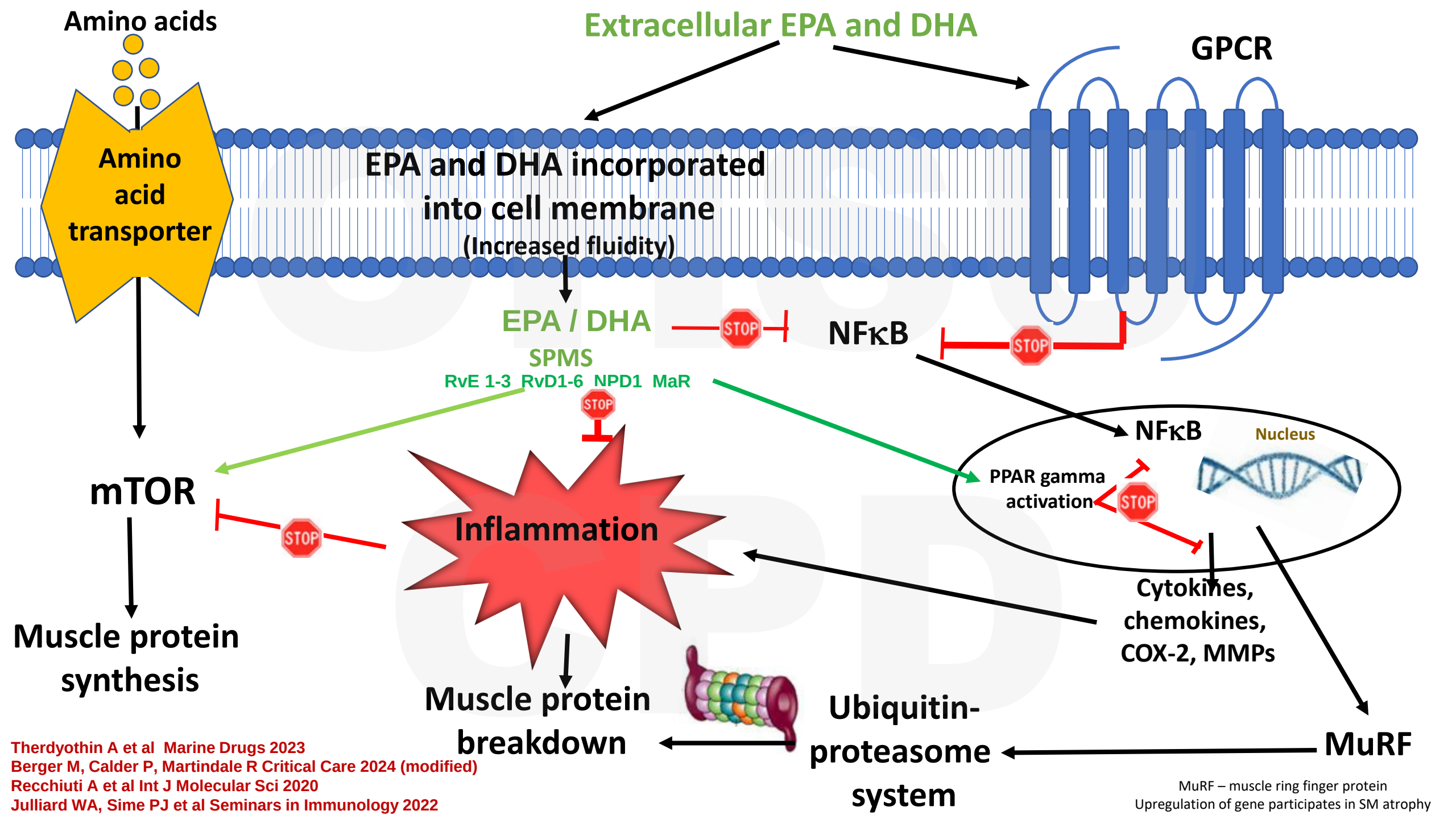
Omega-3 group lost less muscle (quadriceps) during immobilisation



Omega-3 group improved muscle protein synthesis during immobilisation was higher with omega-3s



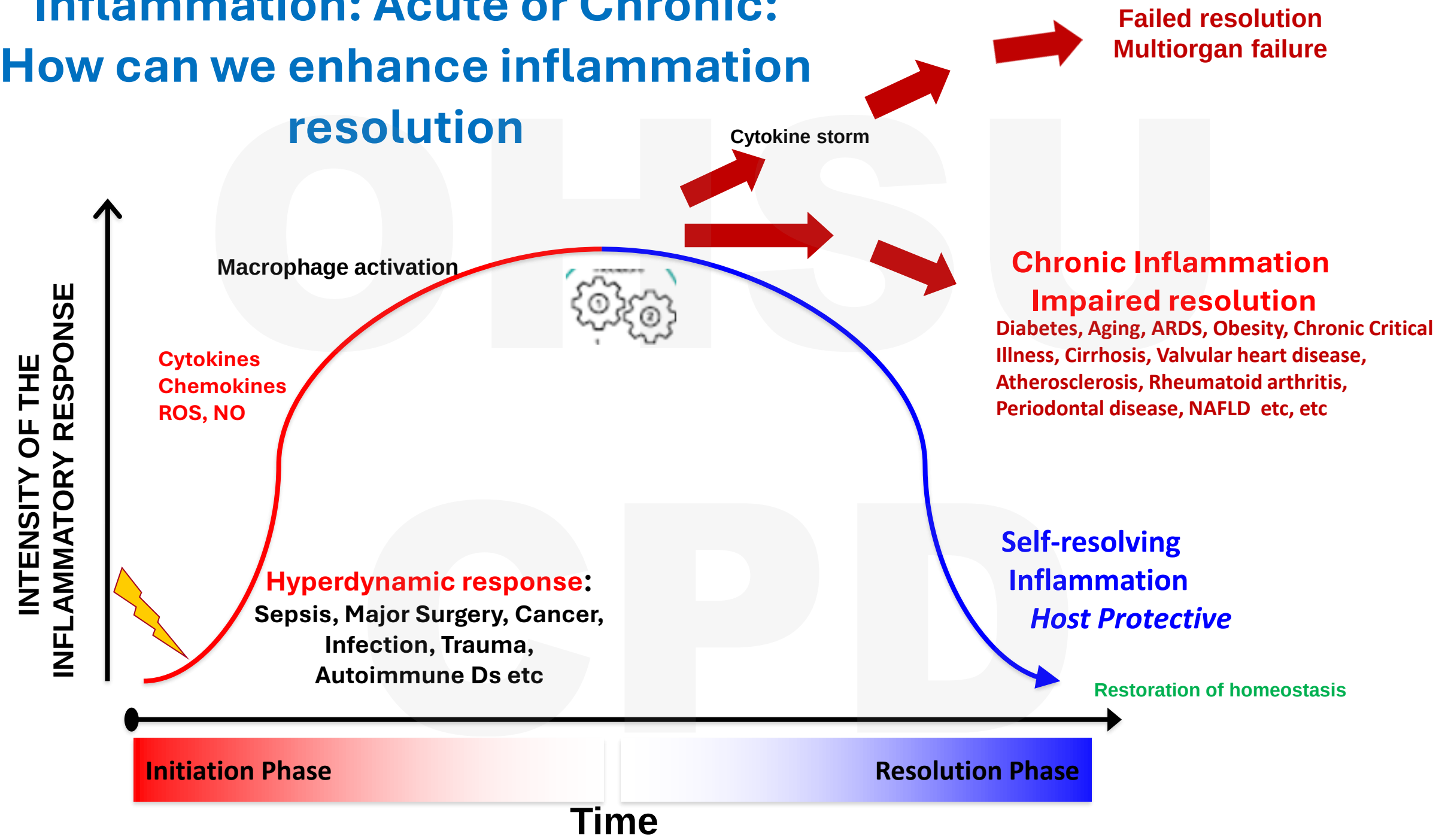
McGlory C et al. (2019) FASEB J 33, 4586-4597



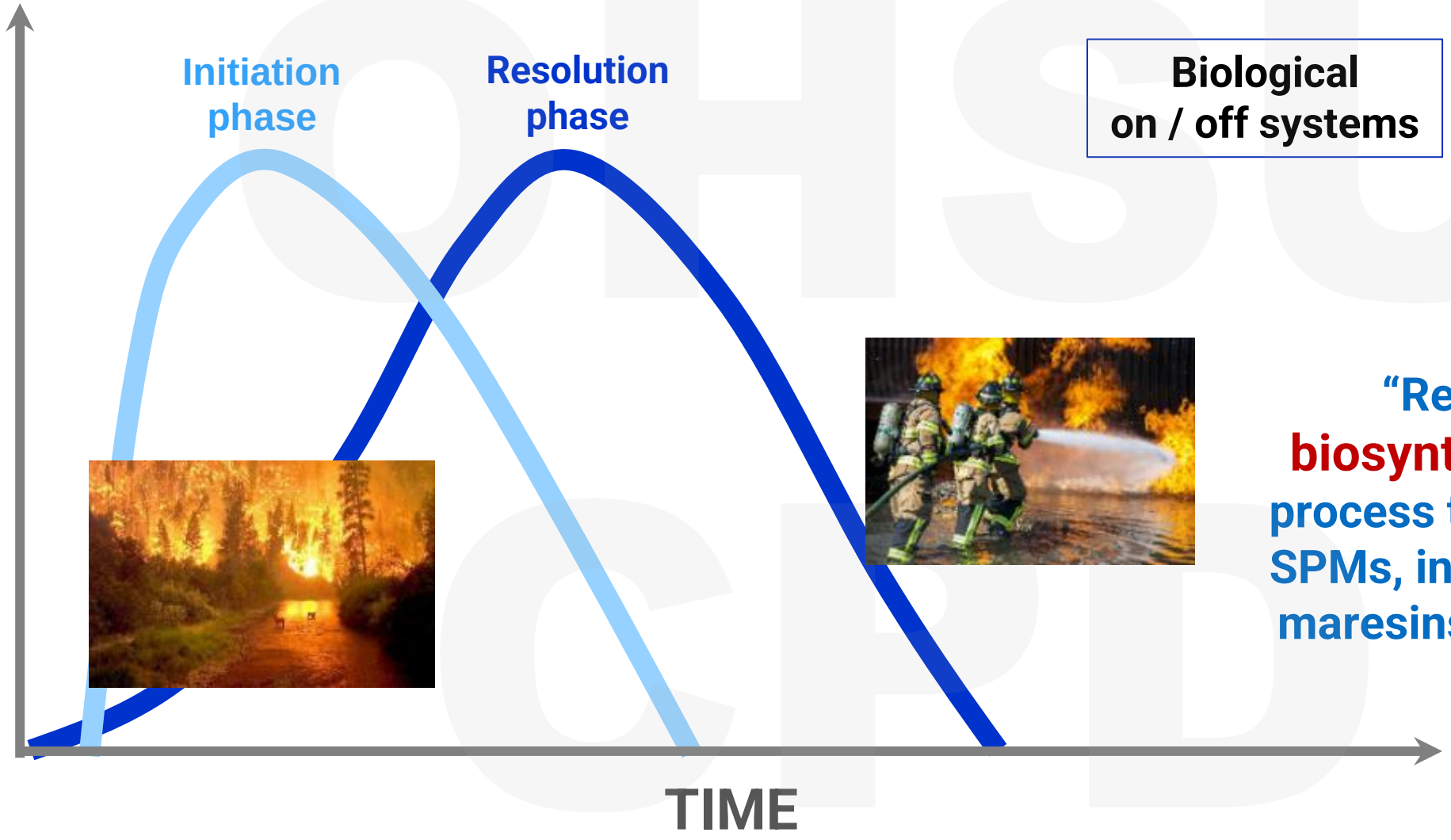
Therdyothin A et al Marine Drugs 2023
Berger M, Calder P, Martindale R Critical Care 2024 (modified)
Recchiuti A et al Int J Molecular Sci 2020
Julliard WA, Sime PJ et al Seminars in Immunology 2022

MuRF – muscle ring finger protein
Upregulation of gene participates in SM atrophy

Inflammation: Acute or Chronic: How can we enhance inflammation resolution



Inflammation has two phases:
Initiation and resolution



Biological on / off systems

Charlie Serhan

"Resolution is a biosynthetically active process that is initiated by SPMs, including resolvins, maresins, and protectins"

SPM = specialized pro-resolving mediator

A change in focus on inflammation: Inflammation's Stop Signals

Players in the endgame

An assortment of molecules shut down inflammation and promote tissue healing by targeting different cells.

Lipoxins
Lipids whose jobs include stimulating macrophages and preventing neutrophils from slipping between endothelial cells to enter damaged tissue.

Resolvins
Family of lipids that block neutrophils' exit from the bloodstream and prod macrophages to eat cellular debris.

Maresins
Made by macrophages, lipids that spur tissue repair and act on nerves to ease pain.

Protectins
Lipids that curtail release of inflammation-promoting molecules and are protective in the nervous system.

Annexin A1
A protein released by dying neutrophils, its functions include preventing other neutrophils from entering the injured site.

Hydrogen sulfide
Message-carrying gas that reduces pain and stimulates neutrophils to commit suicide.

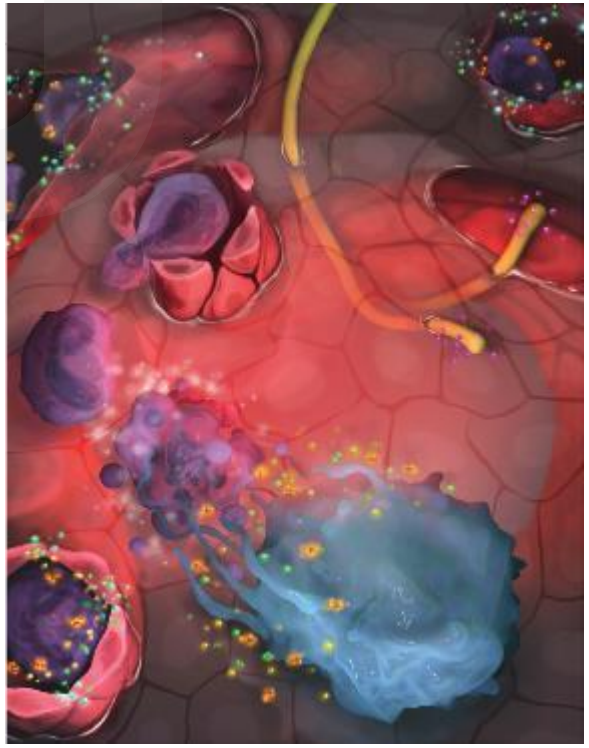
Macrophages
After clearing an infection, these immune cells consume proinflammatory cellular remains.

Neutrophils
First responders to wounds and infections, they release inflammatory cytokines.

Endothelial cells
These cells form the walls of blood vessels and make H_2S.

Nerves
Inflammatory molecules trigger nerve cells, creating pain and itchiness.

ILLUSTRATIONS: V. ALTOUNIAN/*SCIENCE*



Science 2015 – Charlie Serhan

Tissue injury:
Surgery, Cancer, Infection, Trauma, Autoimmune Diseases

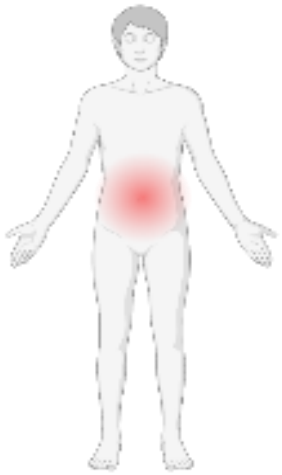
Acute inflammation

Resolvins, Protectins Maresins (SPMs)

SPM's

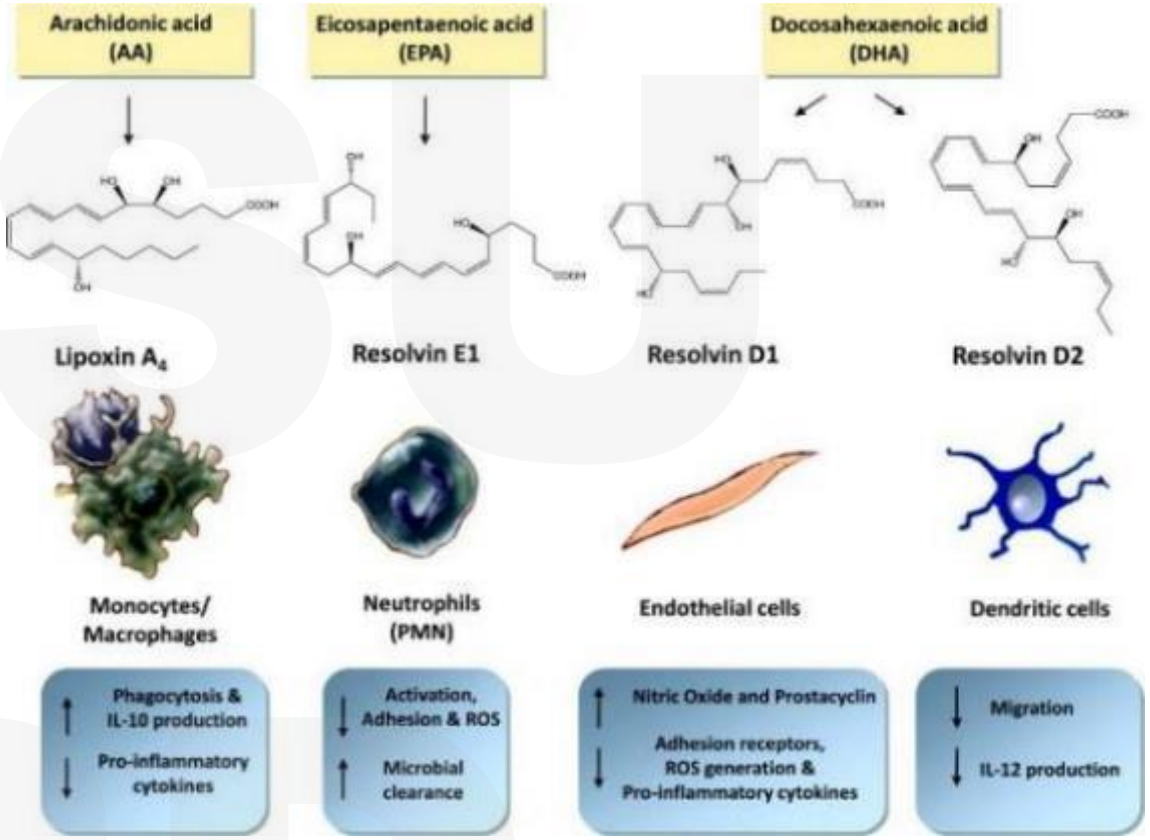
Chronic inflammation

Inflammation Resolution



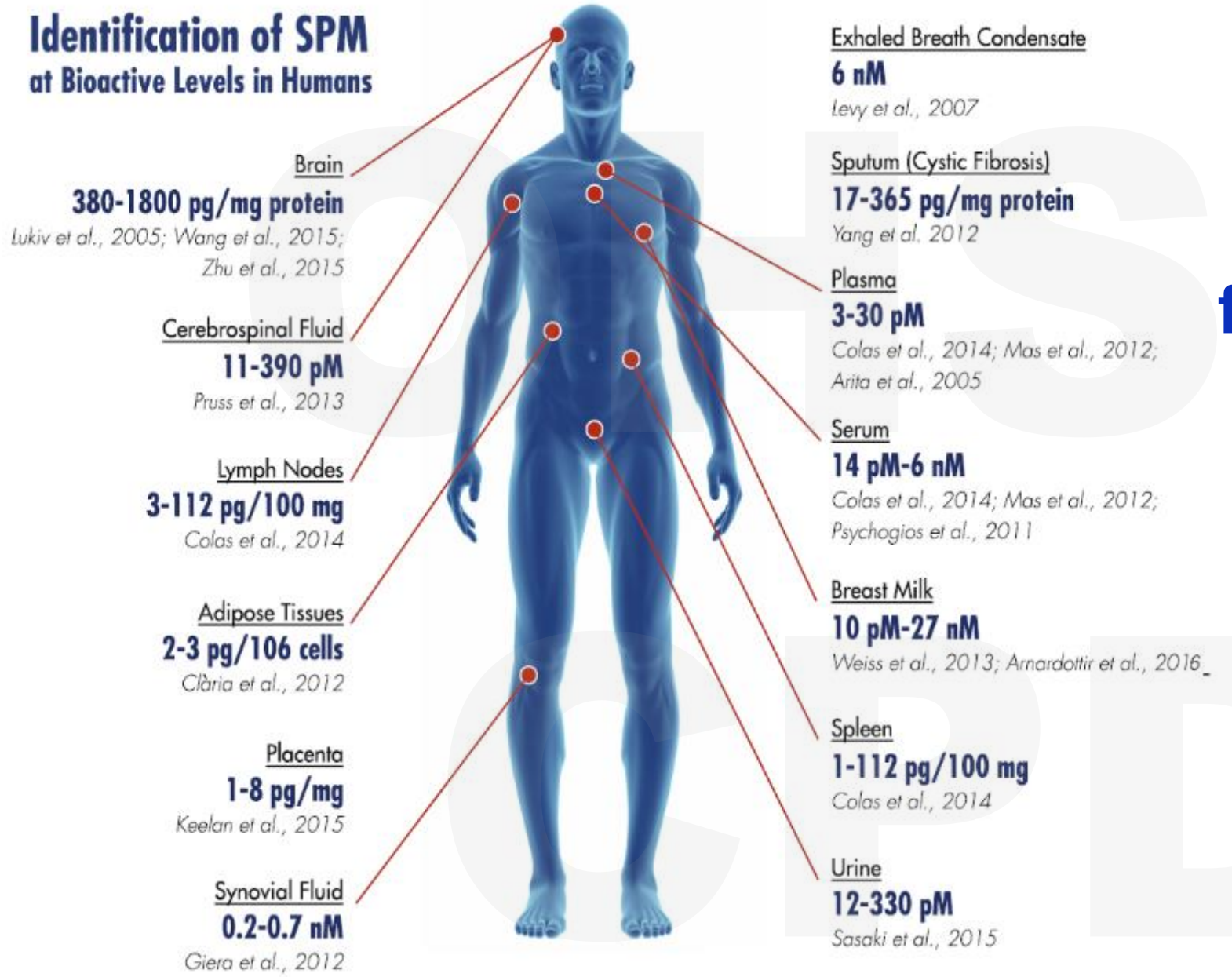
Tissue damage Persistent infection Autoimmune disease

Tissue repair, Healing



Serhan CN, Levy BD. J Clinical Investigations 2018
Chiang N et al Essays in Biochem 2020

SPM = specialized pro-resolving mediator; IL-10 = interleukin 10; ROS = reactive oxygen species; PMN = polymorphonuclear



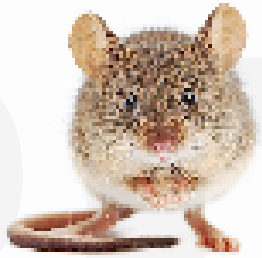
SPMs are *not* in diet, they are produced in-vivo from FO substrates primarily DHA and EPA

Serhan CN Molecular Aspects of Medicine 2017
Chiang N et al Essays in Biochemistry 2020
Serhan CN et al Seminars in Immunology 2022

SPM = specialized pro-resolving mediator; EPA = eicosapentaeoic acid, DHA = docosahexaenoic acid

Specialized pro-resolving mediator (SPM) synthesis is evolutionarily conserved

- **SPMs function at nanogram (10^{-9}) to picogram (10^{-12}) levels**



Chiang N et al Essays in Biochemistry 2020
Serhan CN et al Biochim Biophys Acta 2015

SPM = specialized pro-resolving mediator

Fish Oils (EPA and DHA) and SPMs in Patient Care 2025

Where to begin ?

CV Disease

Cancer

Intensive Care

General Surgery

Trauma

Burns /
Wound healing

Traumatic Brain Injury,
Neurosurgery,
Mood disorders,
Neurodegenerative diseases,
Postop cognitive function

Pain

Bacterial and viral
Infections/ sepsis

Orthopedic Surgery

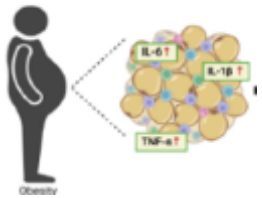
Tissue regeneration

Oral Surgery

IBD

Rheumatoid

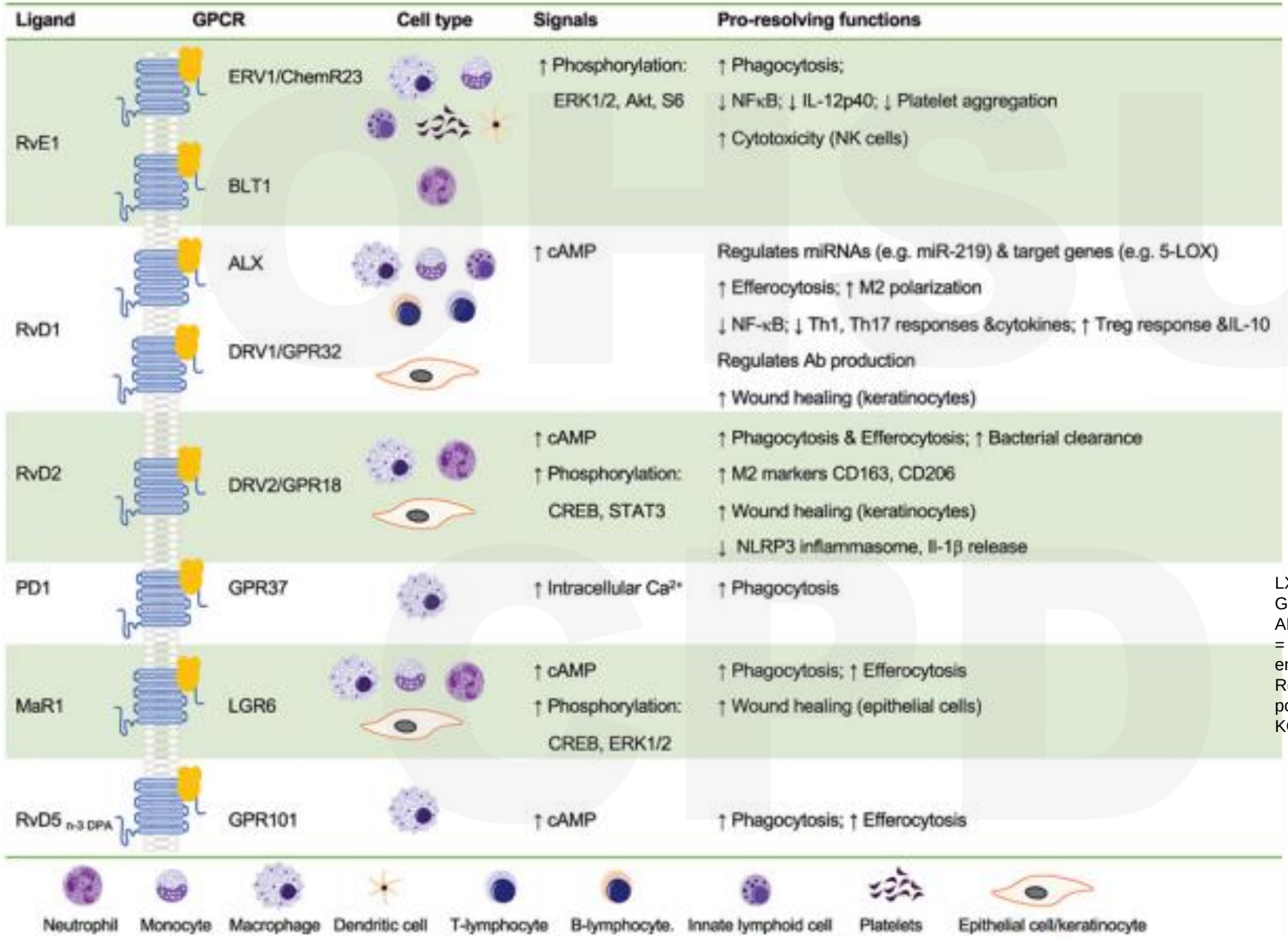
Asthma



Obesity

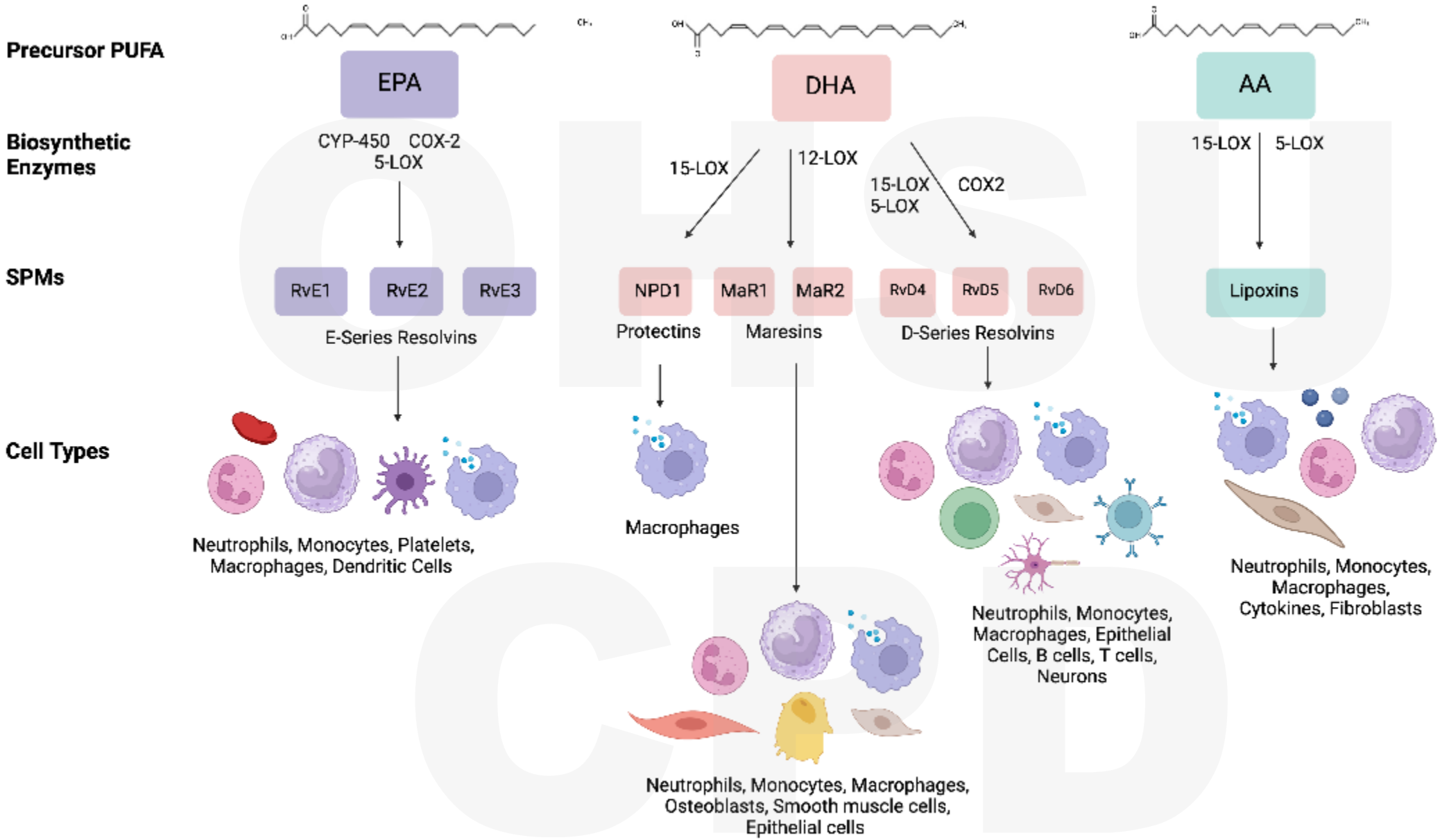
Chronic inflammatory Diseases

Pro-Resolving Mediators Activate G-protein Receptors



LX = lipoxan; LT = leukotriene; RV = resolvin; GPCR = G protein-coupled receptor; Ca = calcium; ALX/FPR2 = formyl peptide receptor 2; DRV GPR32 = G protein-coupled receptor 32; ERV = endogenous retrovirus; ChemR23 = chemerin Receptor 23; BLT1 = LTB4 receptor 1; PMN = polymorphonuclear; LX =lipoxan; TG = transgenix, KO = knockout

Chiang N, Serhan CN
Essays in Biochemistry 2020



Gold S, Martindale R Current Gastroenterology Reports 2025

SPMs and Muscle Regeneration

Muscle injury models of traumatic or surgical loss of skeletal muscle leads to chronic inflammation and fibrosis

- Macrophage and neutrophil infiltration
  - Macrophages are critical regulators of tissue repair – lack of polarization to M2
- Lack of M1 transition to M2 leads to limited regeneration

RvD1

- Limits degree of inflammation
- Enhanced regeneration
- Enhanced PMN clearance
- Modulated stem cell response

Tx with Maresin 1

- Augments macrophage polarization (conversion from M1 to M2)
- Ameliorates fibrosis
- Improved myogenesis
- Enhanced recovery of muscle strength

Resolvin D1 supports skeletal myofiber regeneration via actions on myeloid and muscle stem cells

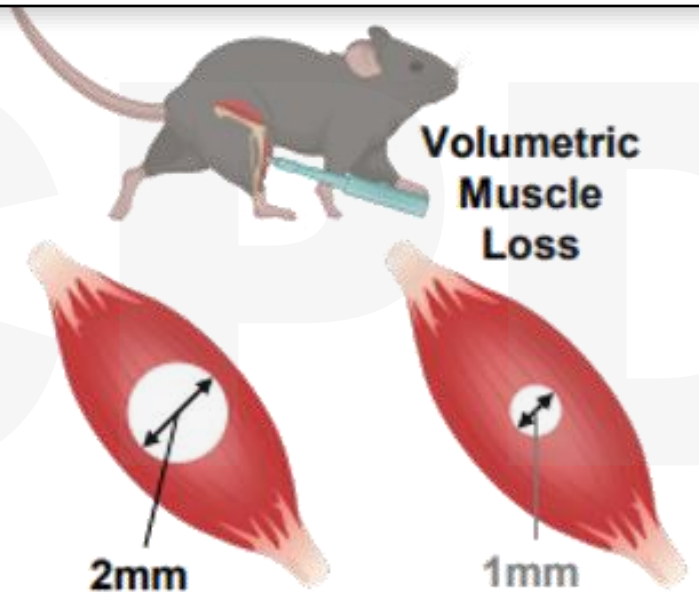
JCI Insight 2020

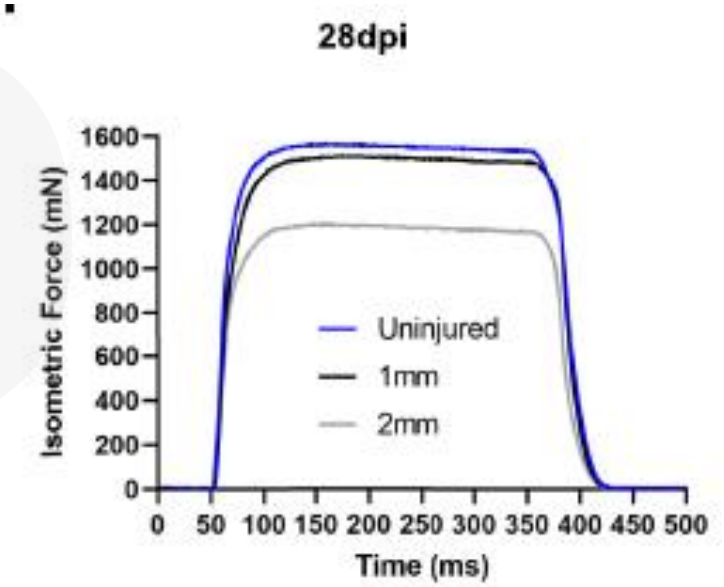
James F. Markworth,[1,2] Lemuel A. Brown,[1] Eunice Lim,[1] Carolyn Floyd,[1] Jacqueline Larouche,[3] Jesus A. Castor-Macias,[3] Kristoffer B. Sugg,[2,4] Dylan C. Sarver,[2,5] Peter C.D. Macpherson,[1] Carol Davis,[1] Carlos A. Aguilar,[3] Krishna Rao Maddipati,[6] and Susan V. Brooks[1,3]

Maresin 1 Repletion Improves Muscle Regeneration After Volumetric Muscle Loss

Jesus A. Castor-Macias[1,2,7], Jacqueline A. Larouche[1,2,7], Emily C. Wallace[1], Bonnie D. Spence[1], Alec Eames[1], Benjamin A. Yang[1,2], Carol Davis[3], Susan V. Brooks[1,3], Krishna Rao Maddipati[4], James F. Markworth[5], Carlos A. Aguilar[1,2,6,*]

eLife 2023

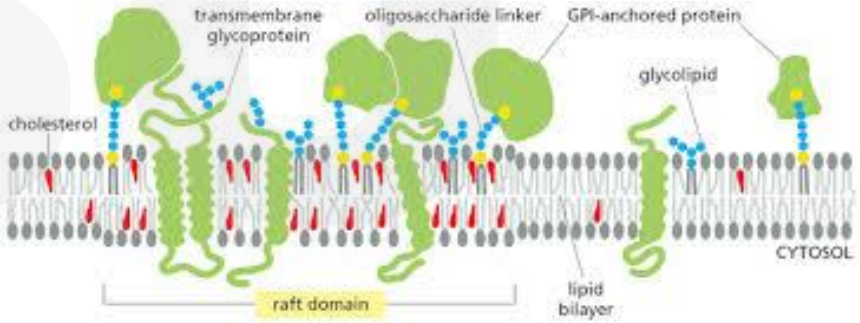


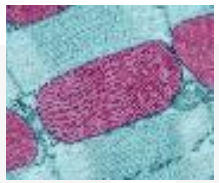


SPMs – as the downstream metabolites of DHA/EPA have multiple beneficial effects seen in muscle metabolism ?

- **Systemic effects**
  - Decrease in insulin resistance
  - Increase resolution of inflammation, via multiple mechanisms

- **Membrane and cytosolic effects:**
  - Incorporation in cell membrane lipid rafts
  - Changes in AA transport via mTOR mechanisms
  - Altering intracellular kinase activity
  - GPRC to alter and enhance pro-resolution signals
  - Dampen NFKB activity
  - Enhance polarization from M1 to M2





- **Potential mitochondrial effects:**
  - Attenuation of mitochondrial protein content and ADP-stimulated respiration with immobilization model
  - Incorporation of DHA and EPA in mitochondrial membranes alters mitochondrial protein synthesis/bioenergetics
  - Incorporation into mitochondrial membranes maintains sensitivity to ADP

Markworth JF et al JCI Insight 2020
Baker LA et al J Cellular Biochem 2018

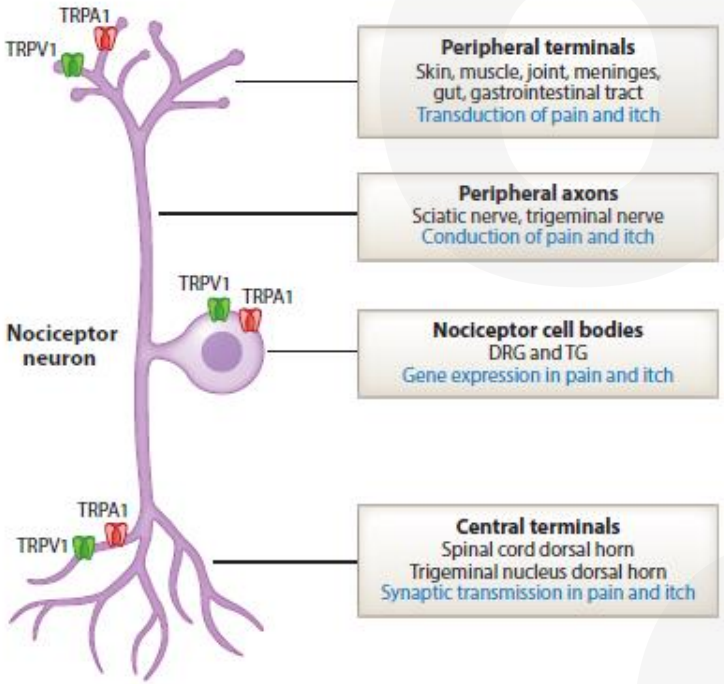
SPMs and multiple benefits in realm of pain control !

- Opioids and NSAIDS have potential detrimental side-effects post op
- Animal models:
  - Decrease pain in inflammatory models – incisional, bone fracture
  - Neuropathic pain – thoracotomy, amputation
  - Multiple models
    - RvD1 RvD2 decrease muscle incisional pain
    - RvD1 and RvD2 decrease post thoracotomy pain
    - RvD1, RvD2, and MaR1 tibial bone fracture model decrease pain
  - Systemic treatment with RvD1 prevented cognitive decline

1) SPMs do not interfere with normal pain perception
2) SPMs serve to restore homeostatic balance without suppressing physiologic pain

Ji RR Ann Rev Pharm Tox 2023

SPMs in Pain models



Ji RR. Ann Rev Pharm and Toxicology 2023

Table 1 Beneficial effects of synthetic SPMs in the control of pain, itch, and inflammatory diseases

Pain/itch model	SPM(s)	Species, route	Effect(s)	Reference(s)
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
Osteoarthritis	17(*R*)-HDHA, AT-RvD1	rats, IP	Spontaneous and mechanical pain ↓	41, 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-PD1$_{n-3}$ DPA	mice, IT	Mechanical allodynia ↓	85
Postoperative 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 and spontaneous pain ↓	96
Bone cancer pain	RvD1, RvE1	mice, IT	Mechanical and thermal pain ↓	95
Dermatitis and itch				
Eczema	LXA4	human, topical	Infantile eczema severely ↓	128
Psoriasiform itch	RvD3	mice, topical	Scratching ↓	124
Cancer itch	3-oxa-PD1$_{n-3}$ DPA	mice, IT	Scratching ↓	85

Specialized pro-resolving mediators: biosynthesis and biological role in bacterial infections

Paul M. Jordan and Oliver Werz

Department of Pharmaceutical/Medicinal Chemistry, Institute of Pharmacy, Friedrich-Schiller-University Jena, Jena, Germany

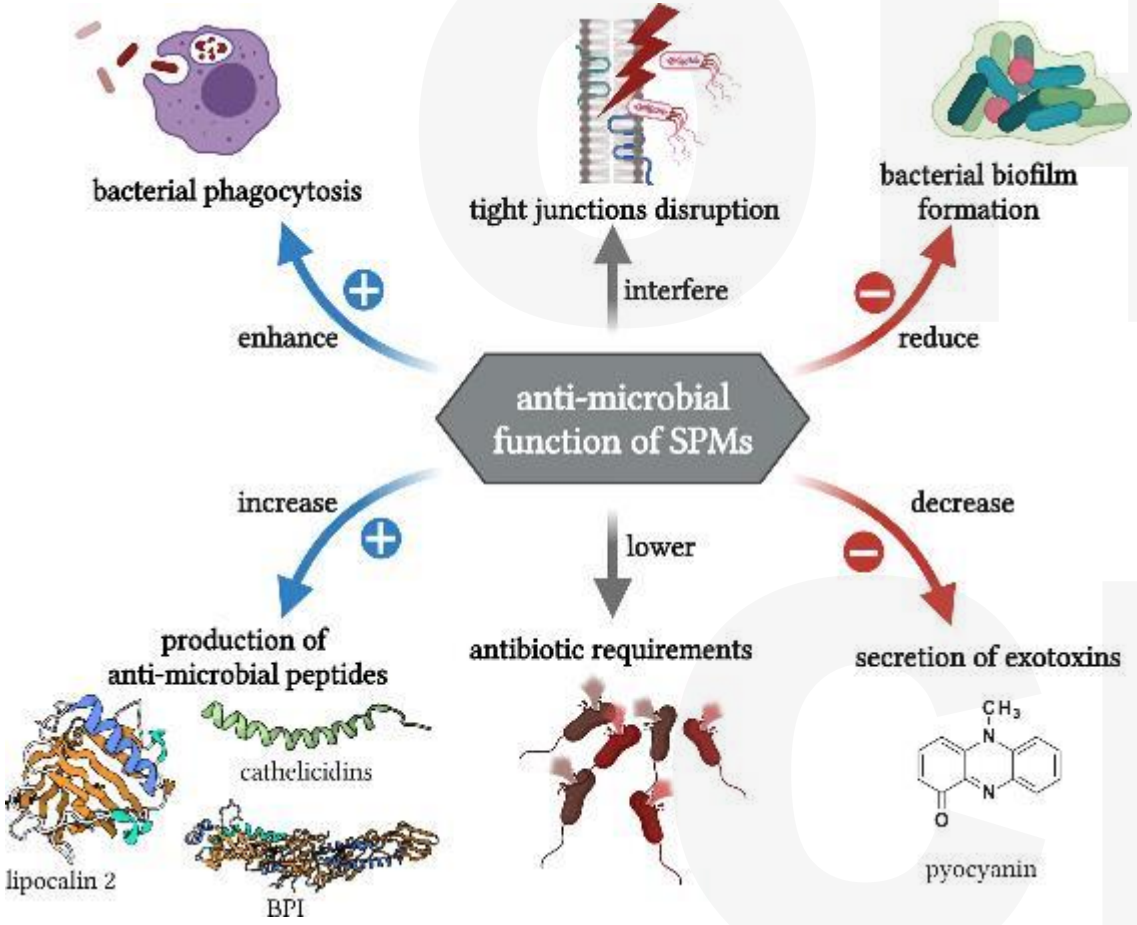
The FEBS Journal 2021

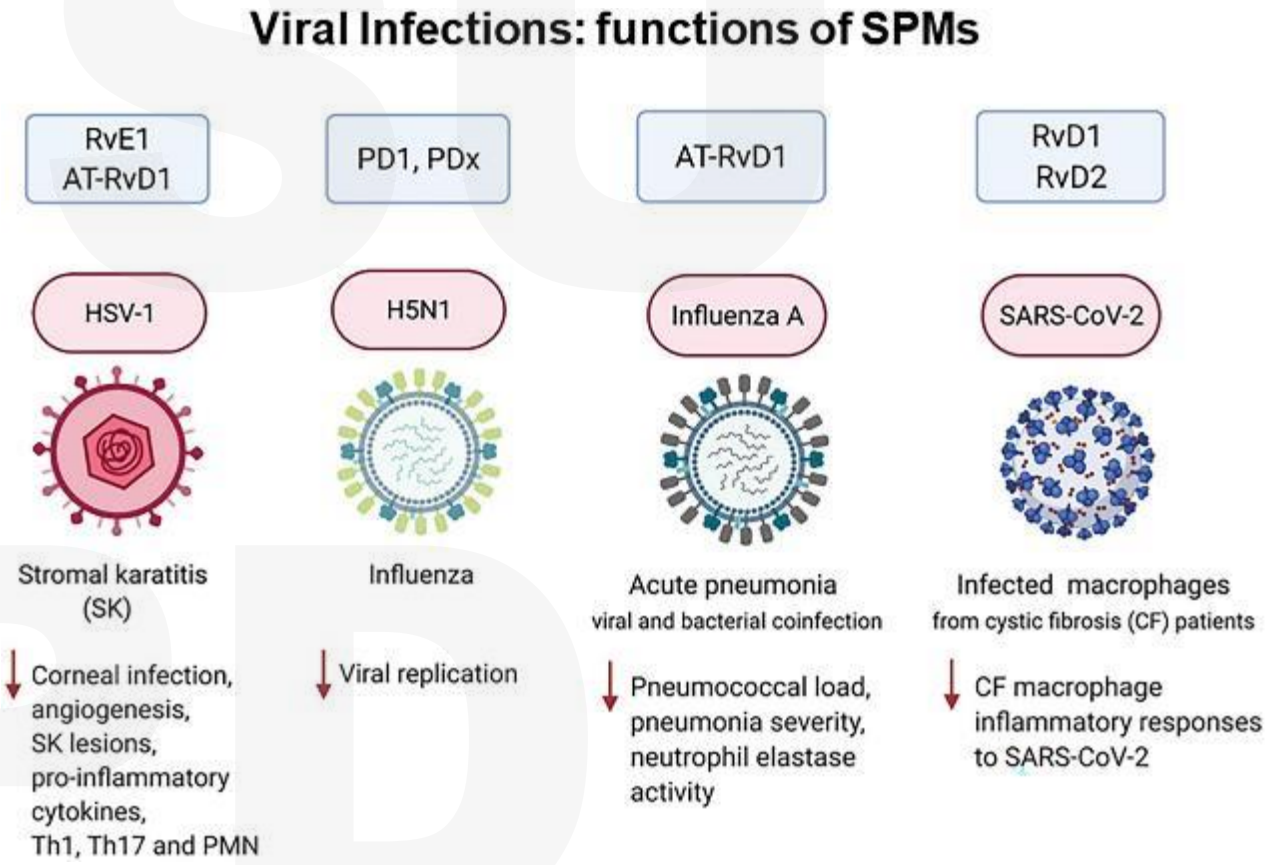
- **SPMs are physiologic immunoresolvents that actively resolve inflammation by:**
  - **Limiting neutrophil influx**
  - **Stimulating phagocytosis**
    - **Enhanced bacterial killing and clearance**
  - **Efferocytosis of apoptotic neutrophils and cellular debris by macrophages (M2)**

- **SPMs:**
  - **prevent collateral tissue damage**
  - **promote tissue repair and regeneration**
  - **lower antibiotic requirements *without* side effects**

The FEBS Journal 2021

Anti-microbial functions of SPMs





Jordan PM, Werz O. The FEBS Journal 2021
Dyall SC et al. Progress in Lipid Research. 2022

SPMs: Stroke, TBI, CNS Hemorrhage, Post-op Cognitive Decline

" Decreases Neuroinflammation"

- **SPM (NPD1) counteracts pro-inflammatory microenvironment following brain injury "Neuroprotective"**
- **SPM's Decreases:**
  - **Stroke damage**
    - **PMN entering into injured brain**
    - **induction of COX-2 and NFkB**
    - **Injury (neuronal cell death) in the penumbra**
    - **Neuroinflammation**
- **Increase CNS cell survival**
  - **Activation of pro-apoptotic pathway**
  - **Induction of pro-survival proteins**
  - **Promotes macrophage/microglia polarization to M2 phenotype**
- **Ameliorates cognitive impairment post TBI (RvD1)**
  - **Induces mitophagy**
- **Increase clearance of necrotic cells**

Terrando N et al FASEB J 2013, Asatryan A, Bazan NG J Biol Chem 2017
Bazan NG et al NY Acad Science 2017, Jun B et al Sci Reports 2017
Bhattacharjee S et al Sci Adv 2017, Valente M et al Molecules 2022
Reid MM et al Scientific Rep 2023

How inflammation in the body may explain depression in the brain

Inflammation is a pathway to depression — and a potential avenue for treatment, research suggests

By Richard Sima

Washington Post 2024

Dose-Dependent Effects of EPA Supplementation on Plasma Specialized Pro-Resolving Mediators in Major Depressive Disorder Patients with Chronic Inflammation

Jisun So [1], Stefania Lamon-Fava [2], Maurizio Fava [3], David Mischoulon [3], Andrew Nierenberg [3], Boadie Dunlop [4], Pamela Schettler [4], Becky Kinkead [4], Thomas Ziegler [4], Mark Rapaport [4]

So J et al Current Developments in Nutrition 2020

Resolution of depression: Antidepressant actions of resolvins ☆

Satoshi Deyama [a], Katsuyuki Kaneda [a], Masabumi Minami [b]

Neuroscience Research 2022

ARTICLE OPEN

Check for updates

Clinical response to EPA supplementation in patients with major depressive disorder is associated with higher plasma concentrations of pro-resolving lipid mediators

Stefania Lamon-Fava[1], Minying Liu[1], Boadie W. Dunlop[2], Becky Kinkead[3], Pamela J. Schettler[2], Jennifer C. Felger[2], Thomas R. Ziegler[4], Maurizio Fava[5], David Mischoulon[5,6] and Mark Hyman Rapaport[3,6]

Neuropsychopharmacology 2023

Diet-Derived Fatty Acids, Brain Inflammation, and Mental Health

Helen M. Melo[1†], Luis Eduardo Santos[1,2†] and Sergio T. Ferreira[1,2]*

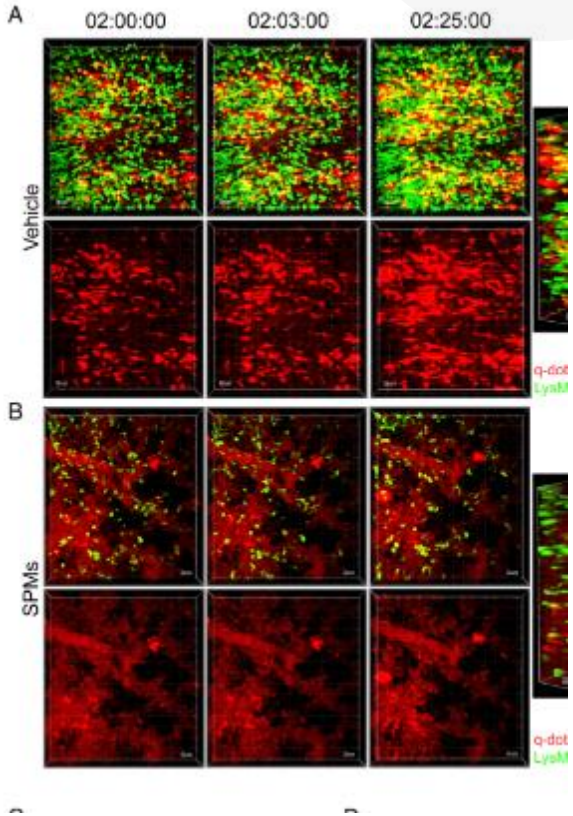
Frontiers in Neuroscience 2019

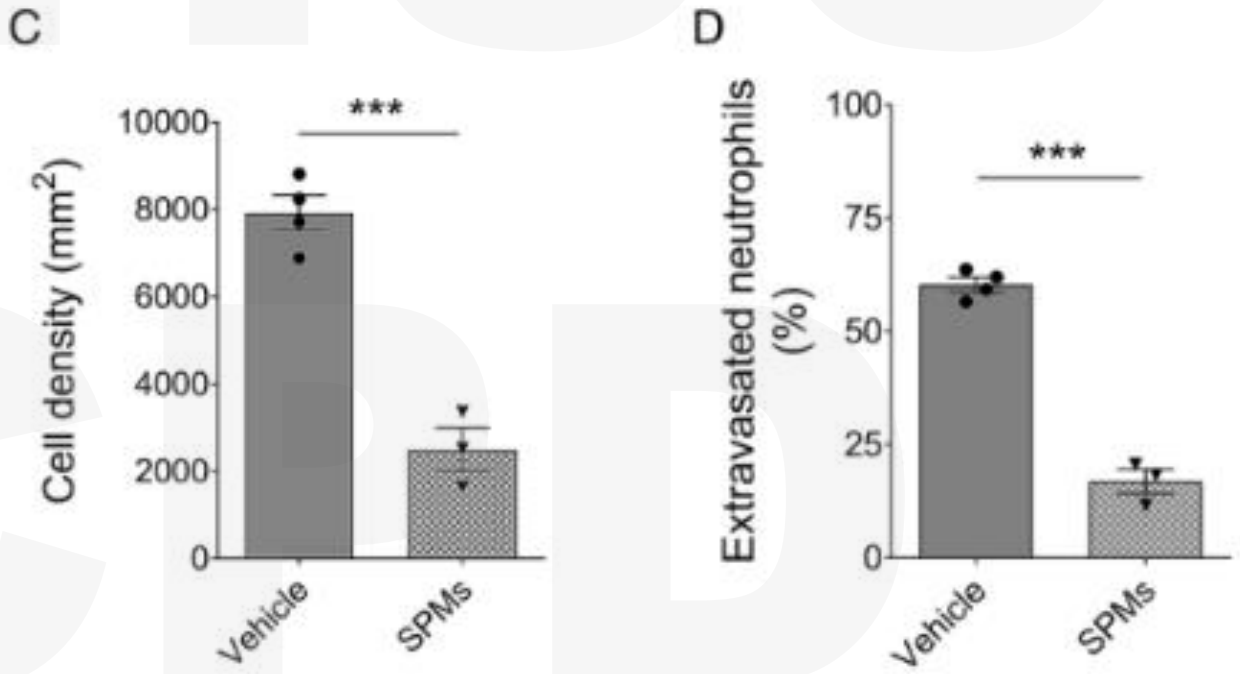
What about Transplant ?

PNAS RESEARCH ARTICLE | IMMUNOLOGY AND INFLAMMATION

Resolvin D1 prevents injurious neutrophil swarming in transplanted lungs

Wenjun Li[a,1], Hailey M. Shepherd[a,1], Yuriko Terada[a], Ashley E. Shay[b], Amit I. Bery[c], Andrew E. Gelman[a,d], Kory J. Lavine[c], Charles N. Serhan[b] and Daniel Kreisel[a,d,2]





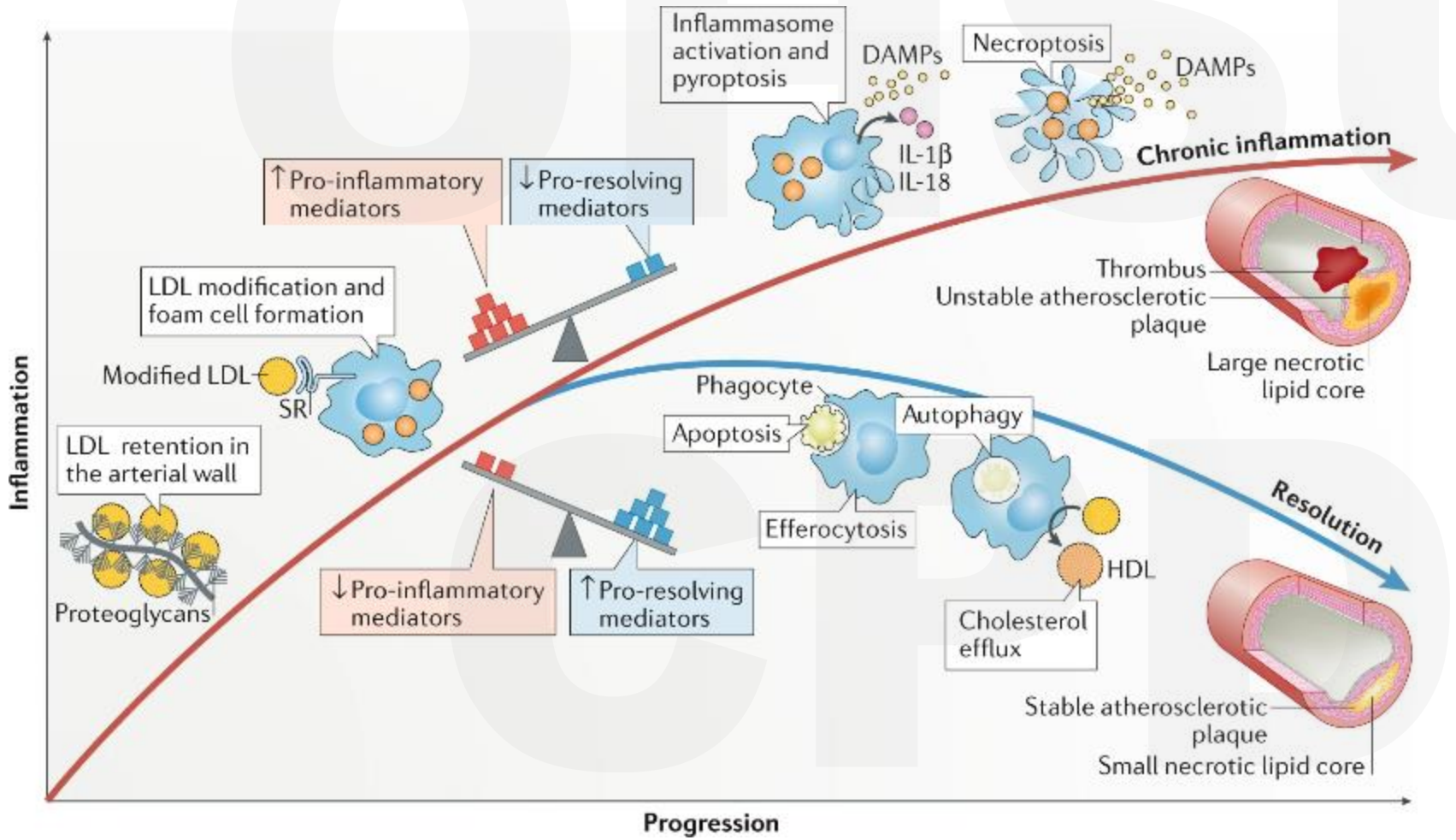
Vessels red : Neutrophils - Green
Vascular leakage diminished with RD1

Li W et al PNAS 2023

NATURE REVIEWS | CARDIOLOGY

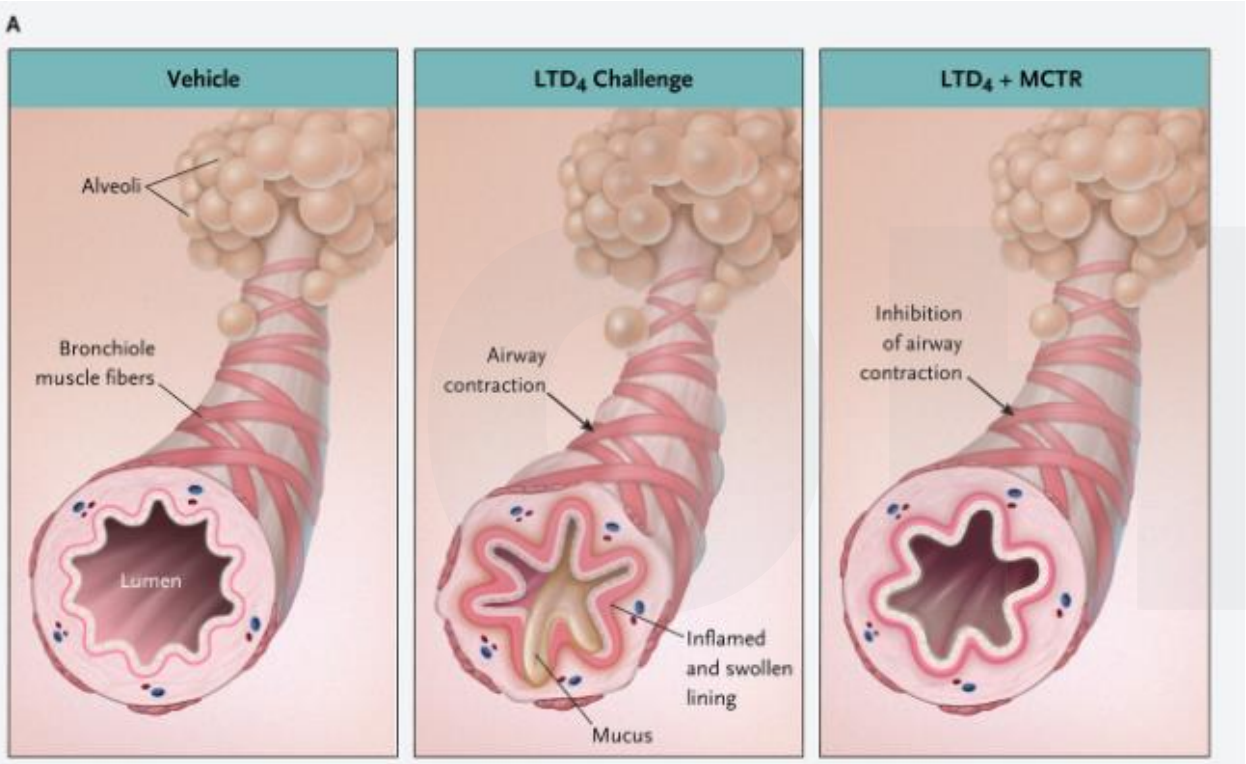
Inflammation and its resolution in atherosclerosis

*Magnus Bäck[1], Arif Yurdagul Jr[2], Ira Tabas[2], Katariina Öörni[3,4] and Petri T. Kovanen[3]**

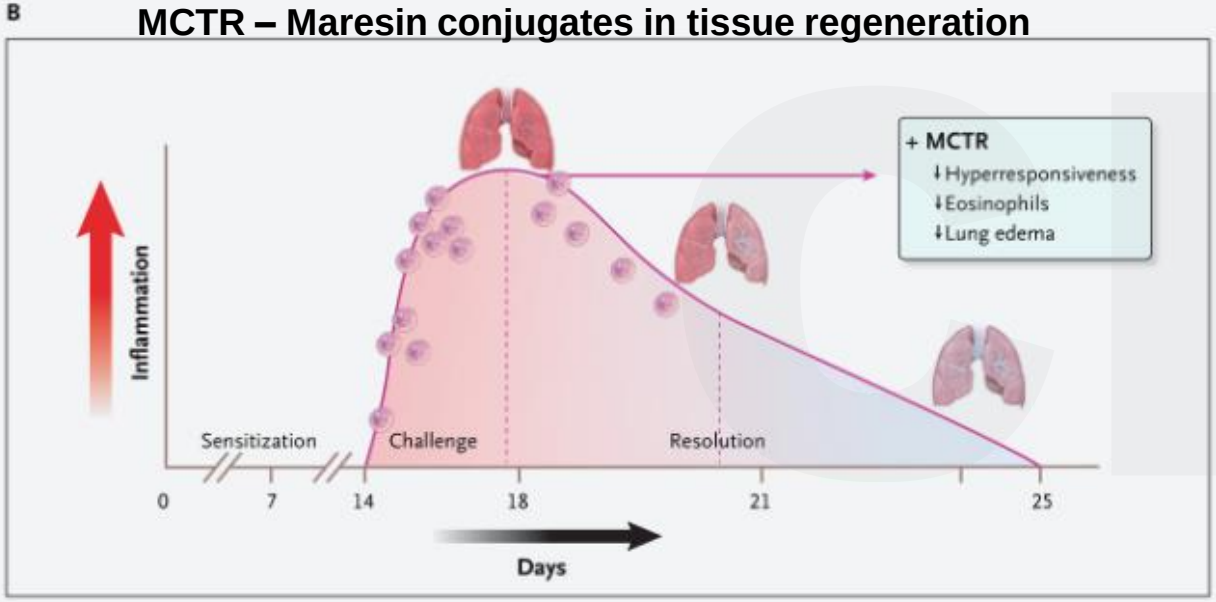


Nat Rev Cardiol. 2019;16:389-406

What about reactive airway disease ?



MCTR – Maresin conjugates in tissue regeneration



CLINICAL IMPLICATIONS OF BASIC RESEARCH

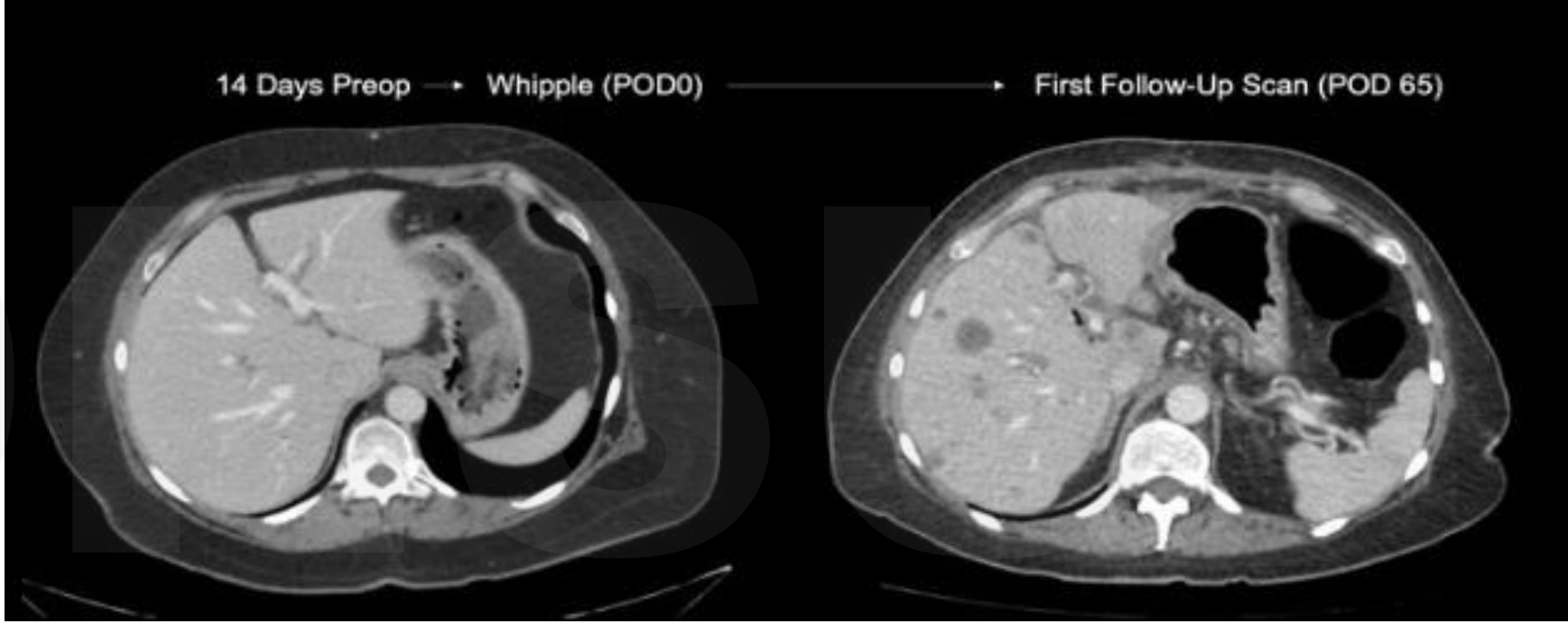
Elizabeth G. Phimister, Ph.D., *Editor*

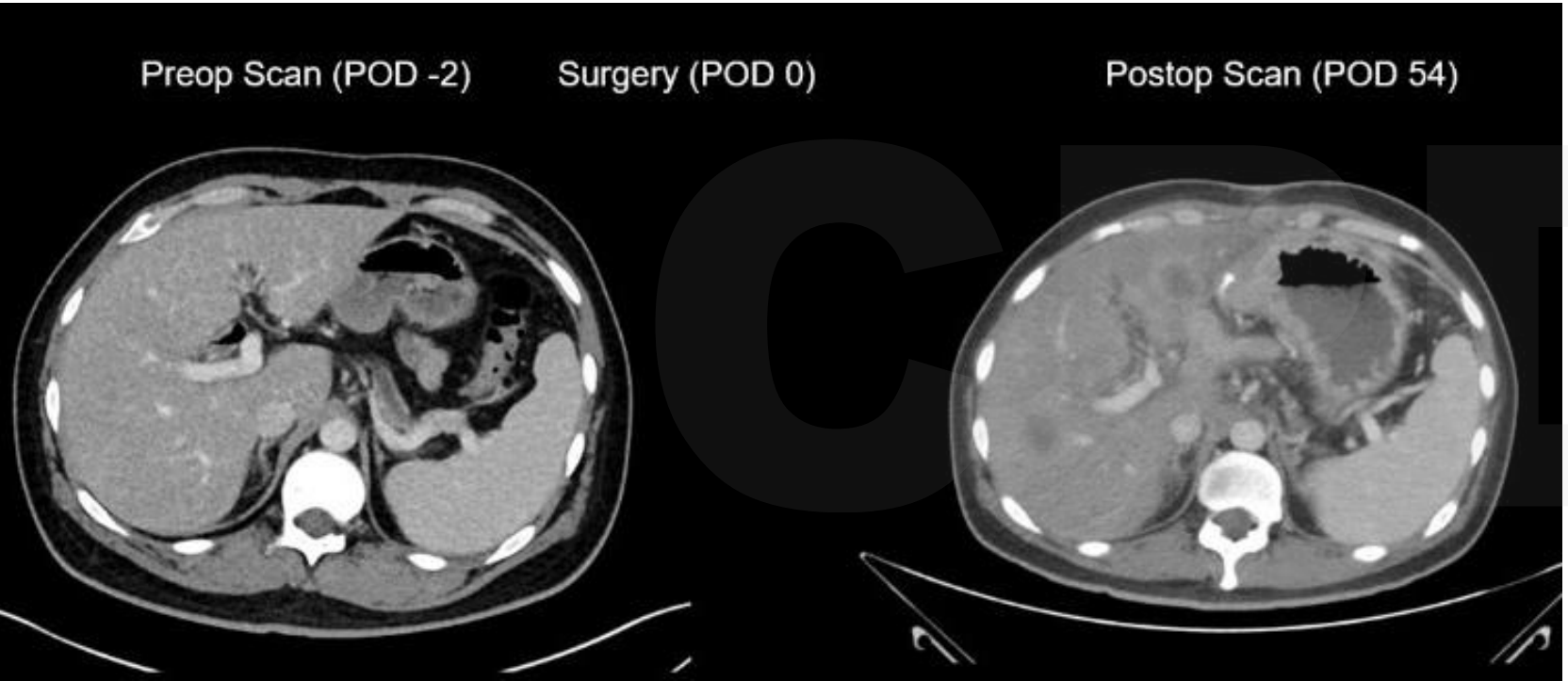
Balancing the Effect of Leukotrienes in Asthma

Catherine Godson, Ph.D.

Godson C NEJM 2020

What about SPMs and Cancer ?





Could SPMs be one of the nutritional agents to target the adverse metabolic influences of cancer ?

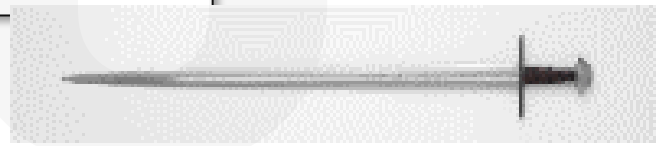
- **Possible protective role in Ca development and progression**
  - **Cancer allows or stimulates persistent inflammation**
  - **Cancer shows defective inflammation resolution signals**
- **SPMs have both direct and indirect actions in cancer**
  - **Direct on epithelial cells**
  - **Indirectly on cancer associated stroma**
- **SPM's implicated in multiple steps of neoplastic progression**
  - **Cell proliferation/survival**
  - **Inflammation**
    - **Key target for SPM**
  - **Angiogenesis**
    - **Key target for SPM -– decrease VEGF, HIF-1,**
  - **Metastasis**

Eltweri AM et al Clin Nutr 2017
Prevete N et al Pharm Res 2017
Gilligan MM et al PNAS 2019

Resolvins suppress tumor growth and enhance cancer therapy

Journal of Experimental Medicine 2018

Megan L. Sulciner,[1,2,3]* Charles N. Serhan,[4]* Molly M. Gilligan,[1,2,3]* Dayna K. Mudge,[1,2,3]* Jaimie Chang,[1,2,3] Allison Gartung,[1,2,3] Kristen A. Lehner,[1,2,3] Diane R. Bielenberg,[5] Birgitta Schmidt,[6] Jesmond Dalli,[4] Emily R. Greene,[1,2,3] Yael Gus-Brautbar,[1,2,3] Julia Piwowarski,[1,2,3] Tadanori Mammoto,[5] David Zurakowski,[7,8] Mauro Perretti,[12] Vikas P. Sukhatme,[3,9] Arja Kaipainen,[13] Mark W. Kieran,[10,11]* Sui Huang,[14]* and Dipak Panigrahy[1,2,3]*



- **Cancer treatment is a double edge sword:**
  - **Cancer therapy reduces tumor burden by killing tumor cells**
  - **Treatment creates tumor cell debris that stimulates inflammation and tumor growth**
    - **Increase metastatic disease in animal models**

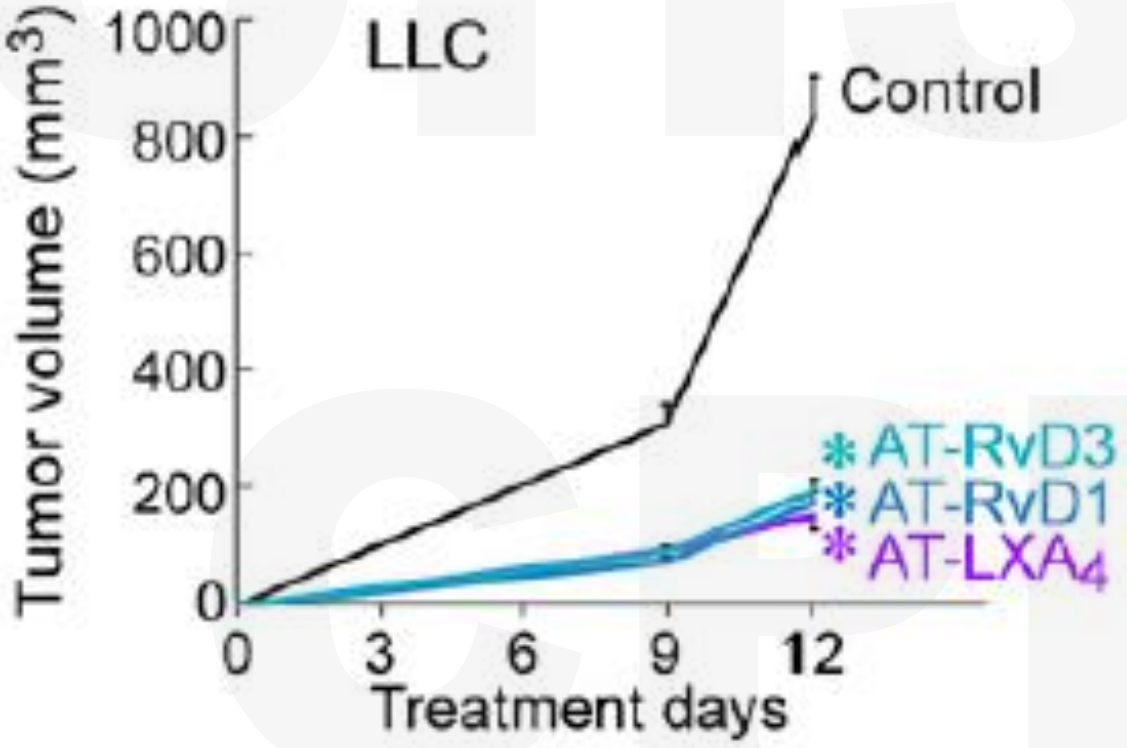
- **Debris-stimulated tumors were inhibited by anti-inflammatory and pro-resolving lipid mediators**
  - **Resolvin D1 (RvD1), RvD2, or RvE1**

- **Enhancing endogenous clearance of tumor cell debris is a new therapeutic target in cancer therapy**

Aspirin-triggered proresolving mediators stimulate resolution in cancer

Molly M. Gilligan[a,b,c,1], Allison Gartung[a,b,c,1], Megan L. Sulciner[a,b,c], Paul C. Norris[d], Vikas P. Sukhatme[c,e,f], Diane R. Bielenberg[g], Sui Huang[h], Mark W. Kieran[i,j], Charles N. Serhan[d,2], and Dipak Panigrahy[a,b,c,2]

PNAS 2019

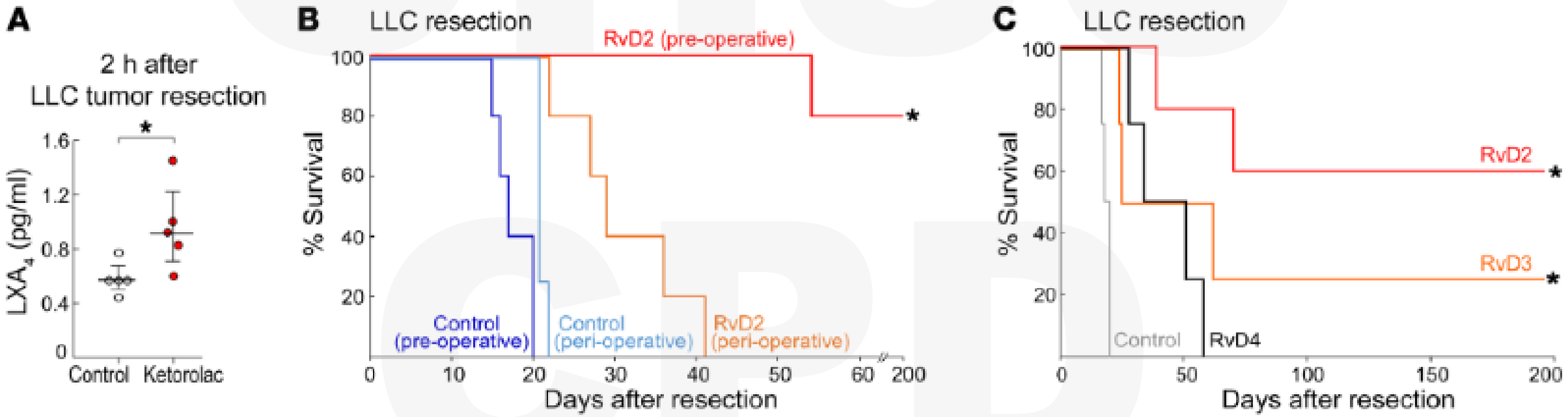


Differentiating between suppression and resolution of inflammation is highly relevant in cancer biology

SPMs represent a new class of endogenous antitumor mechanisms

Preoperative stimulation of resolution and inflammation blockade eradicates micrometastases

Dipak Panigrahy,[1,2,3] Allison Gartung,[1,2,3] Jun Yang,[4] Haixia Yang,[1,2,3] Molly M. Gilligan,[1,2,3] Megan L. Sulciner,[1,2,3] Swati S. Bhasin,[5] Diane R. Bielenberg,[6] Jaimie Chang,[1,2,3] Birgitta A. Schmidt,[7] Julia Piwowarski,[1,2,3] Anna Fishbein,[1,2,3] Dulce Soler-Ferran,[1,2,3] Matthew A. Sparks,[8] Steven J. Staffa,[9] Vidula Sukhatme,[10] Bruce D. Hammock,[4] Mark W. Kieran,[11,12] Sui Huang,[13] Manoj Bhasin,[5] Charles N. Serhan,[14] and Vikas P. Sukhatme[3,5,15]



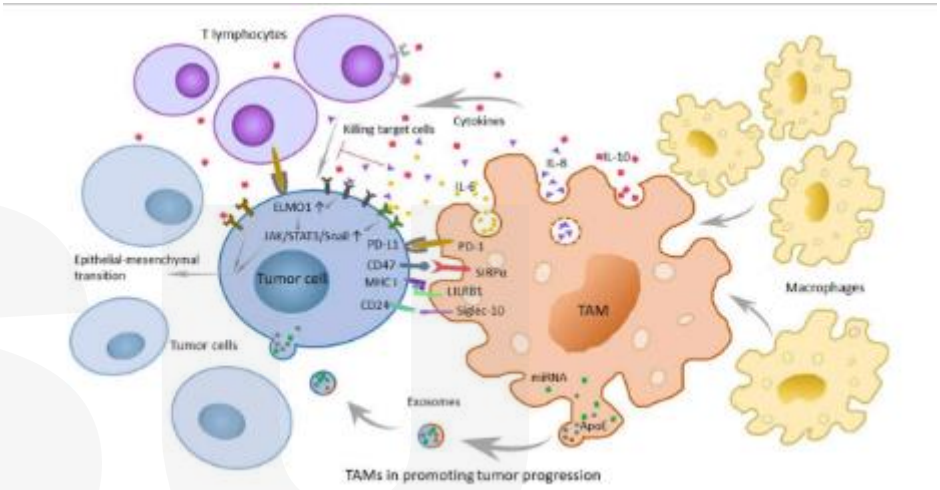
LLC=Lewis lung carcinoma Mouse model

JCI 2019

Specialized Pro-Resolving Mediators Mitigate Cancer-Related Inflammation: Role of Tumor-Associated Macrophages and Therapeutic Opportunities

Frontiers in Immunology 2021

Margot Lavy[1], Vanessa Gauttier[1], Nicolas Poirier[1], Sophie Barillé-Nion[2†] and Christophe Blanquart[2*†]*



Multiple mechanisms of TAMs including the “do-not-eat-me” signal SIRP/CD47
TAMs promote development via exosomes

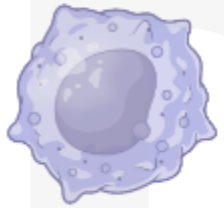
- **Chronic inflammation creates a favorable environment that fuels carcinogenesis and cancer progression**
  - **Macrophages are key actors of both inflammation and its active resolution due to their plastic phenotype**
- **Conventional cancer therapy (chemo/radiation) increases cancer-related inflammation by inducing massive tumor cell death, and activation of TAMs. TAMs can support tumor progression and immune escape, or therapy resistance. Exosomes seems to be one of mechanisms**
- **SPMs can promote inflammation resolution in cancer and improve anticancer treatments, limiting the ability of the TAMs to support tumor**
- **TAMs’ re-education toward an antitumor phenotype by using SPMs this creates a new line of endogenous mediators in cancer treatment**

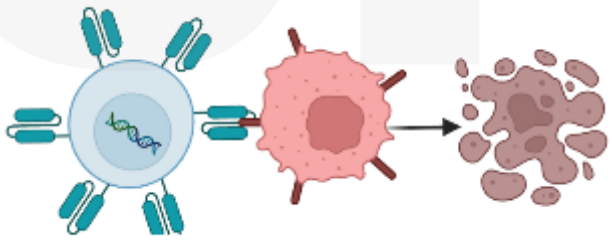
TAM = tumor-associated macrophage

Where are we in regards to SPMs in cancer management ?

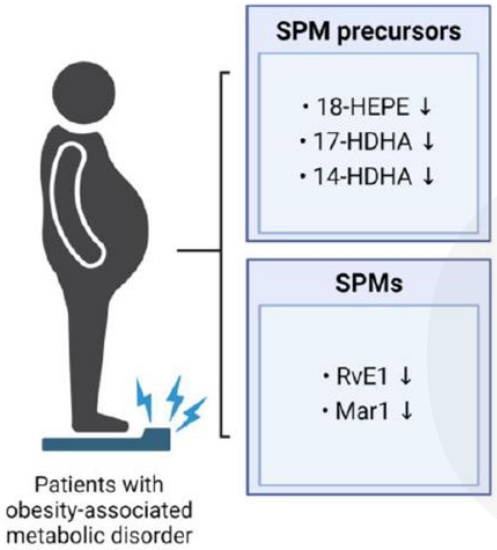
- **SPM can play crucial role in controlling inflammatory process and inhibiting angiogenesis**
  - **Altering neoplastic progression via cell proliferation**
  - **Inflammatory control**
  - **Altering angiogenesis**
  - **Changing metastatic potential**

- **Significant potential for SPMs in cancer prevention and therapy**
- **Prevention via modulating "tumor environment"**
  - **Macrophage phenotype M1, decrease VEGF, TAMs etc**
  - **Chemo, radiation, surgery**
    - **Preventing metastasis**
    - **Clearing tumor debris**





Prevete N et al Pharm Res 2017
Greene ER, Serhan CN et al Prostaglandins Lipid Mediators 2011
Sulciner ML et al J Experimental Medicine 2018
Ungaro F et al Cancers 2020
Panigraphy D et al JCI 2019



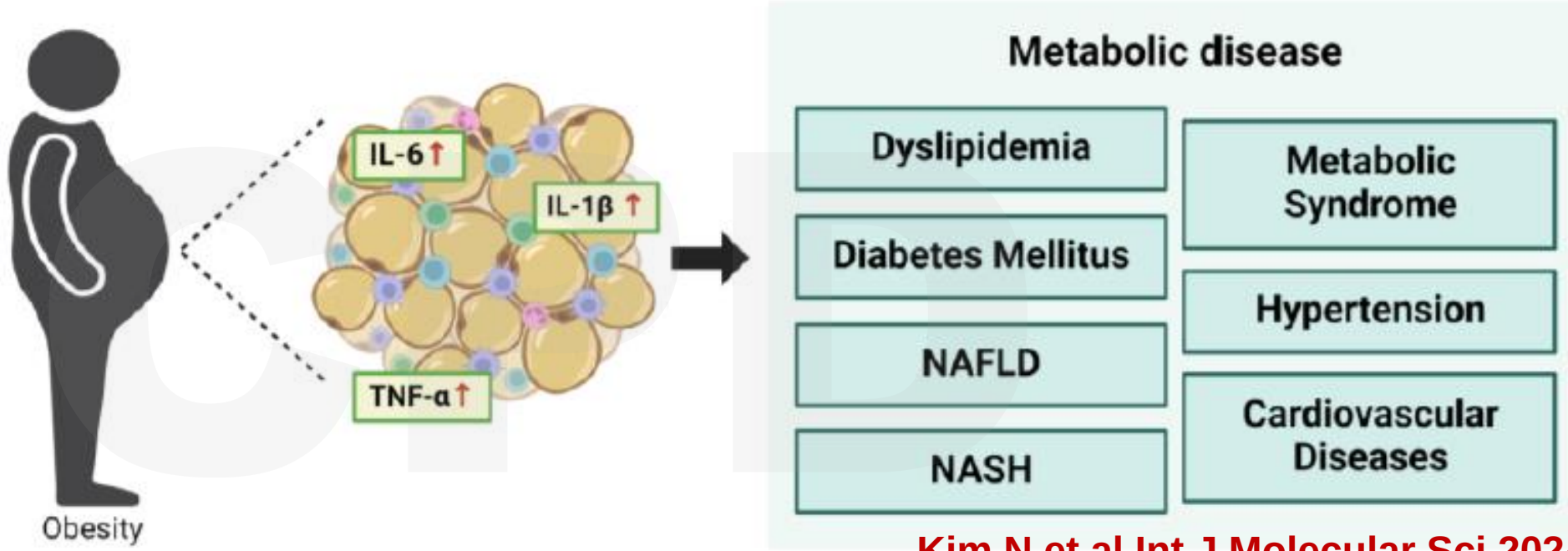
Obese individuals have decrease in serum and neutrophils SPMs

High fat diets decrease SPMs and weight loss increases SPMs

Animal models RvD1 and D2 appear to have most potent activity against metabolic diseases associated with obesity

-reducing inflammation

-enhancing insulin sensitivity



Kim N et al Int J Molecular Sci 2024

Al-Shaer AE et al J Nutrition 2022

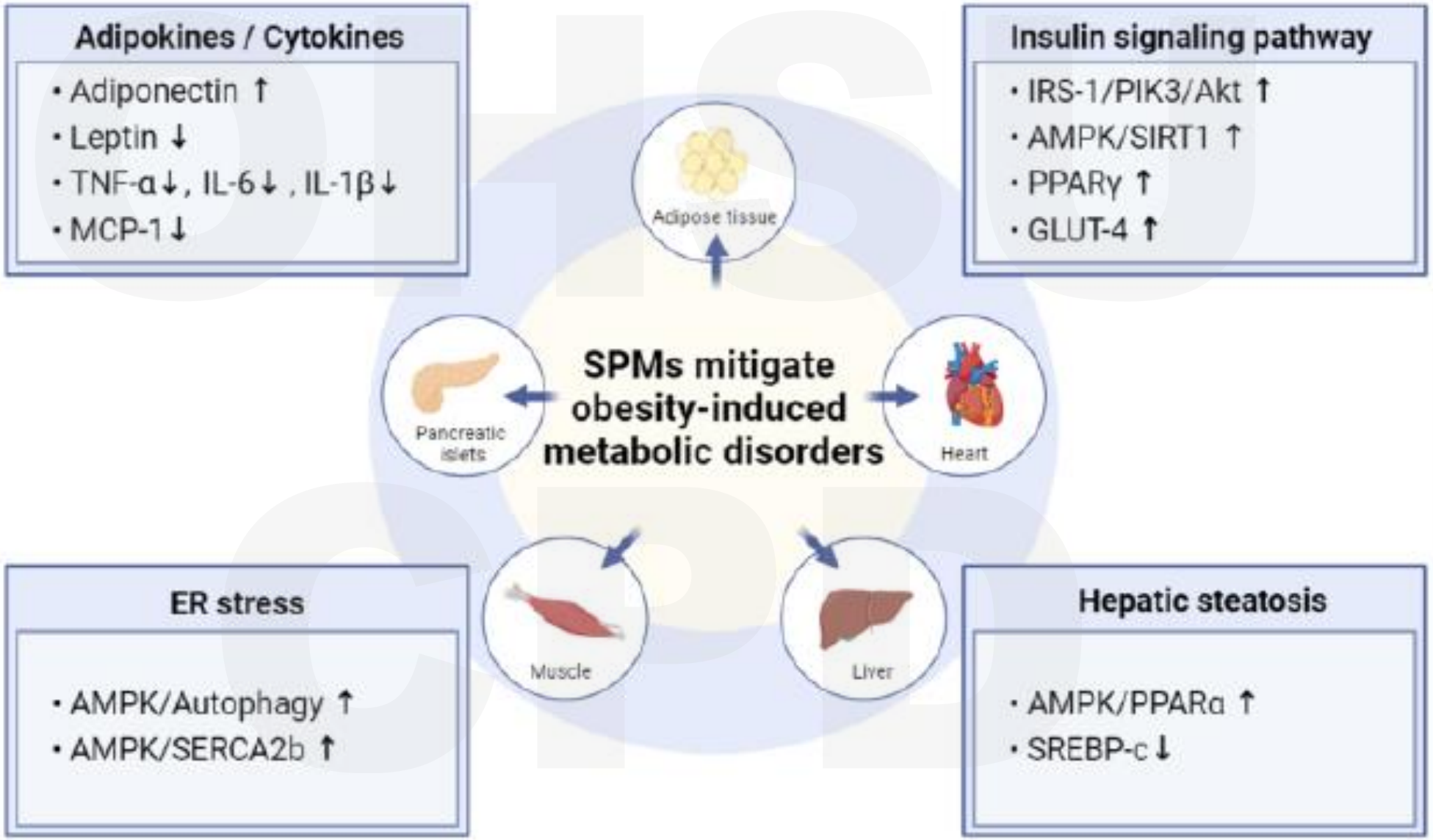
n-3 PUFA supplement (EPA and DHA)

Metabolic change

- SPM levels ↑
- Pro-inflammatory cytokines ↓
- Waist circumference ↓
- TG levels ↓
- Lipogenesis ↓
- Insulin senstivity ↑

Kim N et al Int J Molecular Sci 2024

Deciphering the Potential Role of Specialized Pro-Resolving Mediators in Obesity-Associated Metabolic Disorders

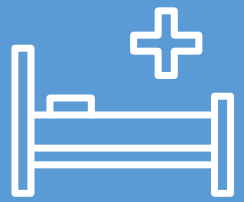


Kim N et al Int J Molecular Sci 2024

The role of lipid emulsions containing omega-3 fatty acids for medical and surgical critical care patients

Christian Stoppe[1,2*], Robert G. Martindale[3], Stanislaw Klek[4], Philip C. Calder[5,6], Paul E. Wischmeyer[7] and Jayshil J. Patel[8]

Critical Care Medicine 2024



Shorter ICU stay

ICU length of stay significantly reduced by 1.95 days[27]

Shorter hospital stay

Hospital length of stay significantly reduced by 2.14 days[27]

Lower relative risk of infections

40% significant reduction in relative risk of infection rate in non-ICU and ICU patients[27]

Lower relative risk of sepsis

56% significant reduction in the risk of sepsis[27]

27. Pradelli L et al. JPEN J Parenter Enteral Nutr. 2020;44(1):44-57

ICU, intensive care unit; PN, parenteral nutrition

Can oral intake of Fish Oils or SPMs alter tissue concentration to a clinically relevant levels ?

Eicosapentaenoic and docosahexaenoic acid derived specialised pro-resolving mediators: Concentrations in humans and the effects of age, sex, disease and increased omega-3 fatty acid intake

Philip C. Calder [a, b, *]

Biochimie 2020

"the relationship of specific intakes of EPA and DHA to enhancement in the appearance of specific SPMs is not clear and needs a more thorough investigation"

Pharmacokinetics and Changes in Lipid Mediator Profiling after Consumption of Specialized Pro-Resolving Lipid-Mediator-Enriched Marine Oil in Healthy Subjects

Irun P et al Molecular Sciences 2023

by Pilar Irún [1,2,3,*], Patricia Carrera-Lasfuentes [1,2,4], Marta Sánchez-Luengo [2,5], Úrsula Belio [3,6], María José Domper-Arnal [1,2,5], Gustavo A. Higuera [3,6], Malena Hawkins [3,6], Xavier de la Rosa [3,6,*] and Angel Lanas [1,2,3,5,7]

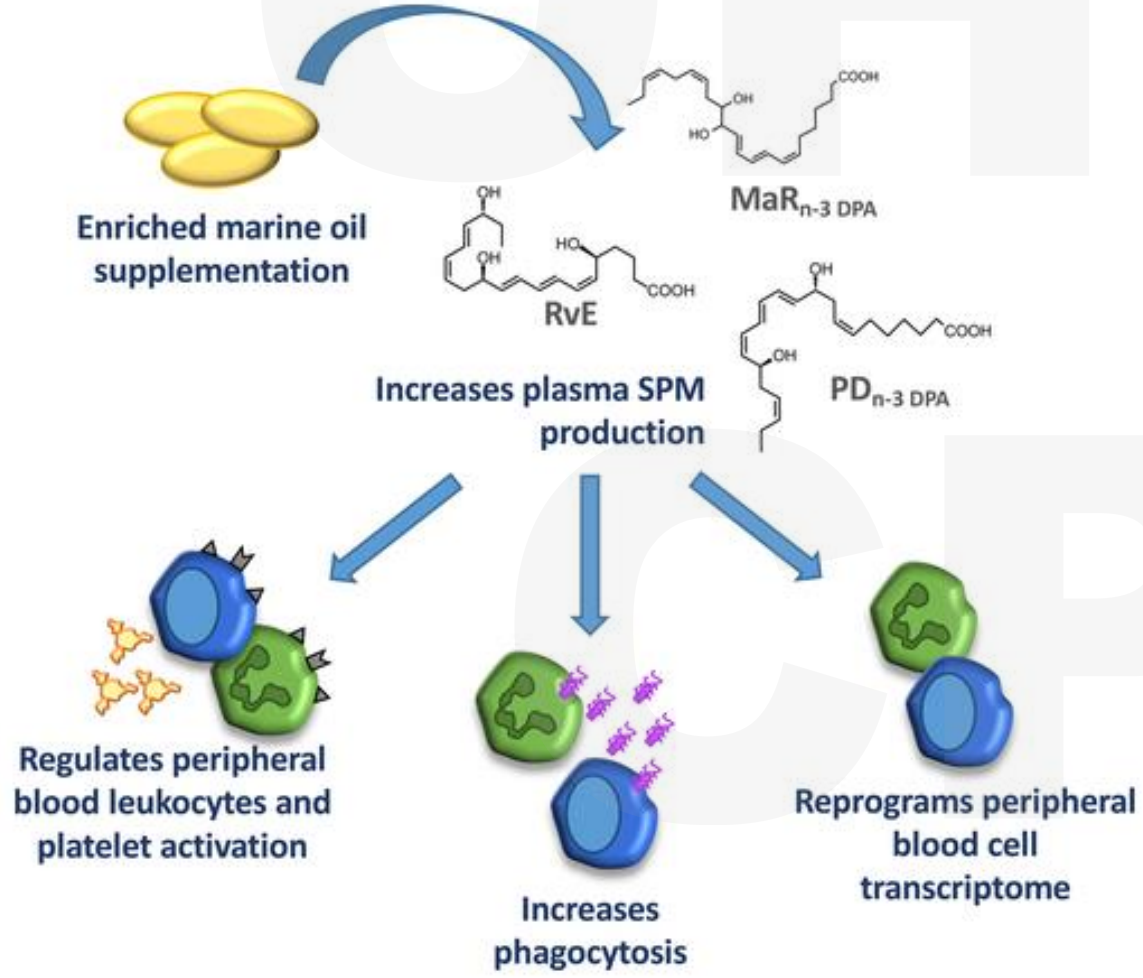
pilot study in which ten healthy subjects enrolled and received a single dose of 6 g of an oral SPM-enriched marine oil emulsion

Enriched Marine Oil Supplements Increase Peripheral Blood Specialized Pro-Resolving Mediators Concentrations and Reprogram Host Immune Responses

A Randomized Double-Blind Placebo-Controlled Study

Circulation Research 2020

Patricia R. Souza, Raquel M. Marques, Esteban A. Gomez, Romain A. Colas, Roberta De Matteis, Anne Zak, Mital Patel, David J. Collier and Jesmond Dalli



Findings:

Time and dose dependent increase in blood SPMs

Dose dependent increase in neutrophil and monocyte phagocytosis

Reduction in adhesion molecule expression

What about IVLE options for lipid delivery ?

- **SMOF** (FDA approved in USA 2016) (soy, MCT, olive oil, fish oil)
  - 15% fish oils
- **Omegaven** (FDA approved in children 2018)
  - 100% fish oils

Intravenous Fish Oil Lipid Emulsion Promotes a Shift Towards Anti-Inflammatory-Pro-Resolving Lipid Mediators

Am J Physiol Gastrointestinal Liver Physiology 2013

Brian T. Kalish[1], Hau D. Le[1,2], Jonathan M. Fitzgerald[3], Samantha Wang[4], Kyle Seamon[4], Kathleen M. Gura[5], Karsten Gronert[4], and Mark Puder[1*]

Lipid emulsion rich in n–3 polyunsaturated fatty acids elicits a pro-resolution lipid mediator profile in mouse tissues and in human immune cells

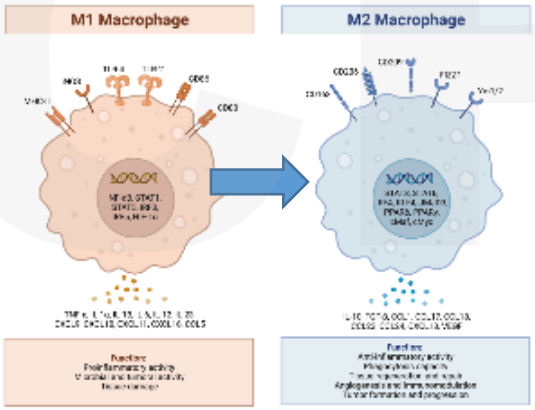
American J Clin Nutrition 2022

Nazek Noureddine,[1,2] Ivan Hartling,[1,2] Paulina Wawrzyniak,[1] Pakeerathan Srikanthan,[1] Phing-How Lou,[3] Eliana Lucchinetti,[3] Stefanie D. Krämer,[4] Gerhard Rogler,[5] Michael Zaugg,[3,6] and Martin Hersberger[1,2]

Intralipid vs Omegaven vs control

What is the evidence that SPM's have a role in the concept of immunonutrition ?

- Decreases postop edema pain, neuropathic pain, cancer pain etc (1)
- SPM serum profiles linearly correlated with outcomes in obesity, pregnancy and ICU(2)
- SPMs are key to appropriate host response both viral and bacterial infections (3, 4)
  - Enhance bacterial killing by macrophages and neutrophils
  - Increase antimicrobial peptides
  - Disrupts biofilm production
  - Potentiates action of antibiotics
- Accelerates removal of inflammatory and necrotic debris (5,6)
  - Seen in cancer therapy (radiation and chemo) trauma, and surgery
- RvD1 reported to decrease post-op cognitive decline (7)
- Enhances conversion M1 to M2 macrophages (resolution macrophages) (8)



1. Ji RR et al Ann Rev Pharm and Toxicololgy 2022
2. Dalli J Molecular Biol 2017, Dali J CCM 2017
3. Chiang N et al Essays in Biochem 2020
4. Thornton JM et al Molecules 2021
5. Baidoo JNE Int J Molecular Sci 2021
6. Sulcinar ML et al J Exp Med 2018
7. Terrando N et al FASEB J 2013
8. Shay AE et al PNAS 2021

What do we do in our surgical nutrition clinic TODAY ?

- Depending on timing we start Mediterranean Diet
  - High fiber foods
  - Anti-inflammatory diet
  - Commercially available probiotic yogurt and / or kefir
  - Relative increase in protein
- 30 days before surgery start 4 to 5 gm / day EPA/DHA
- Preop immune/metabolic modulating formula 5 days preop
- Aggressive individualized resistance exercise program

Resolution Physiology Will Become Part of Clinical Practice

Specialized pro-resolving mediators as modulators of immune responses

Walker A. Julliard [a, 1], Yu Par Aung Myo [b, 1], Apostolos Perelas [c], Peter D. Jackson [c], Thomas H. Thatcher [c], Patricia J. Sime [c]

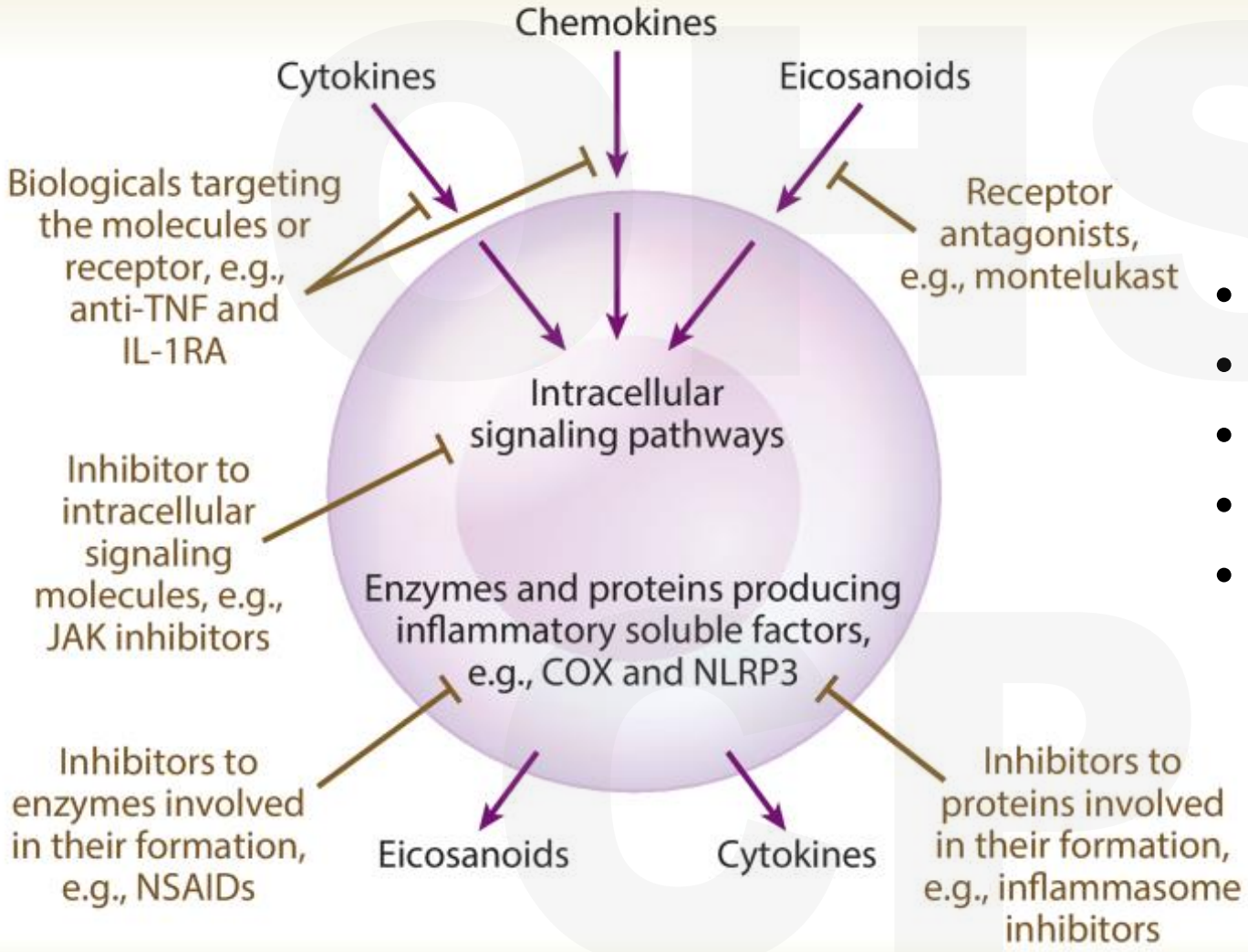
Seminars in Immunology 2022

The goal of resolution physiology is to stimulate the host innate response to accelerate microbial clearance, limit collateral tissue damage and stimulate tissue regeneration.

Personalized profiling of resolution metabolomes and subsequent specific SPM treatment could provide precision focused immune modulation and metabolism

Small M, Serhan CN et al Seminars in Immunology 2022

Multiple attempts to block response to cellular response to toxic stimuli



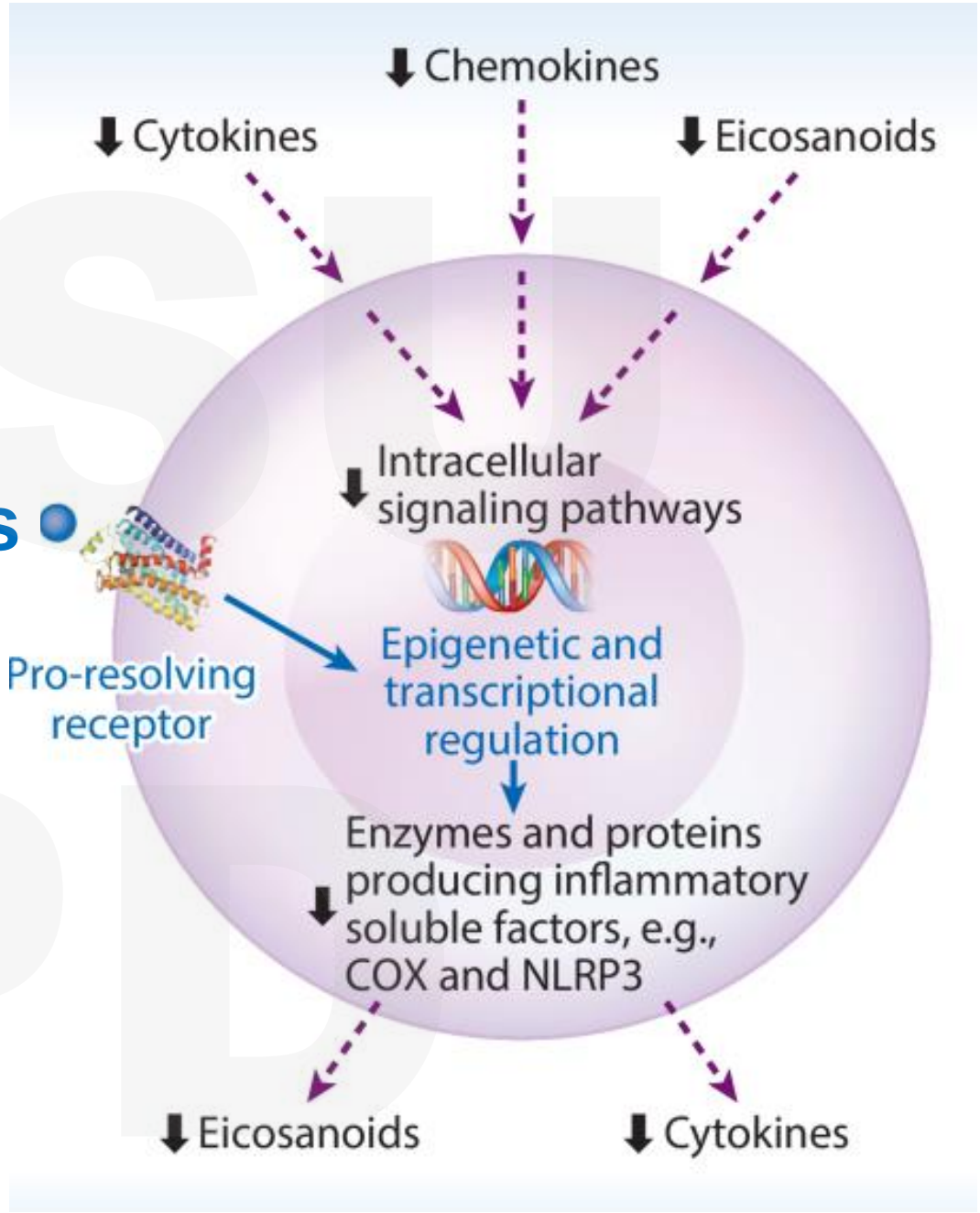
Limitations:

- **Excess inhibition**
- **leading to immunosuppression**
- **Tissue/organ damage**
- **Autoantibodies to biologics**
- **Partial response in patients**

Slide courtesy of Jes Dalli

Perretti and Dalli J Annu Rev Pharmacol Toxicol. 2023 Jan 20;63:449-469.

SPMs via their receptors Reprogram Immune Cells responses to limit inflammation and repair tissues



Slide courtesy of Jes Dalli

Perretti and Dalli Annu Rev Pharmacol Toxicol. 2023 Jan 20;63:449-469.

Future Targeting of Resolution Pathways

CV Disease

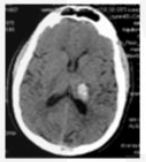
Cancer

Intensive Care

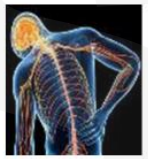
General Surgery

Trauma

Burns



Traumatic Brain Injury, Neurosurgery, Neurodegenerative diseases, Postop cognitive function



Pain

Bacterial and viral Infections/ sepsis

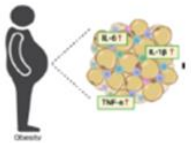
Orthopedic Surgery

Tissue regeneration

IBD

Rheumatoid

Asthma



Obesity

Chronic inflammatory Diseases

- ARDS
- Ischemia reperfusion
- Firefighters/ military personnel exposed to toxic smoke
- Ongoing COVID-19 –Data already available
- Cancer management during surgical and medical treatment
- Obesity associated proinflammatory omental tissue
- “fibromyalgia”

Key Take Home Messages

- **Inflammation is killing us**
- **Inflammation resolution is biosynthetically active process**
- **Initiating and enhancing *inflammation resolution* is now well described with multiple mechanisms of action, methodically proven via human biosynthetic models and studies.**
  - **Anti-inflammation does not equal pro-resolution**
- **SPMs yield a plausible answer to many unresolved questions regarding down stream mechanisms for omega 3 fatty acids (immunonutrition)**
- **Use of Bioactive lipids will yield an entire new set of precision immune and metabolism focused nutritional therapeutics (my opinion)**

Thank You!

martindr@ohsu.edu

What about harm---Fish oils and coagulopathy: Yes – No- Maybe ?

- Agren JJ et al Prost Leuko EFA 1997
  - supplement at moderate levels no effect on coags (in-vitro)
- Bender NK et al J Thrombosis and Thrombolysis 1998
  - Placebo controlled PRT – dose response of FO in patients on warfarin (3gm and 6gm)
  - No difference on coags in subjects receiving warfarin
- Hvas AM (Center for Haemophila and Thrombosis) Danish Med J 2017
  - Meta-analysis of 52 studies: 32 in healthy subjects, 20 in patients undergoing surgery
  - In-vitro in healthy subjects minor reduction in platelet aggregation
  - In surgical patients: NO increase in bleeding and no increase in transfusion requirements during or after surgery
- Akintoye E et al Circulation: CV Quality Outcomes 2018
  - N=1516 pts, PRPCT 8 to 10 gm/day preop then 2gm/d post-op
  - NO increase in perioperative bleeding, reduced # of PRBC transfusions
    - The higher levels of omega-3 FA had lower bleeding
- Jeansen S et al Clinical Nutrition 2018
  - Meta-analysis of 8 clinical trials, n > 600, doses up to 10gms per day is safe
  - No evidence of concern of bleeding, no adverse bleeding episodes
- Nicholls SJ et al JAMA 2020
  - PRPCT 4 gm EPA/DHA in patients on statins, significant # on anti-plt therapy (n=13,078 randomized multinational trial)
  - No effect on bleeding risk
  - No benefit in decreasing number of adverse cardiac events
- Javaid M et al J Am Heart Association 2024
  - Meta-analysis of RCTs – N=120,643 patients from 11 RCTs
  - Omega-3 supplements ***not*** associated with increase bleeding
  - Antiplatelet therapy made no difference in bleeding
  - Very high dose purified EPA may have slight increase bleeding, modest clinical significance