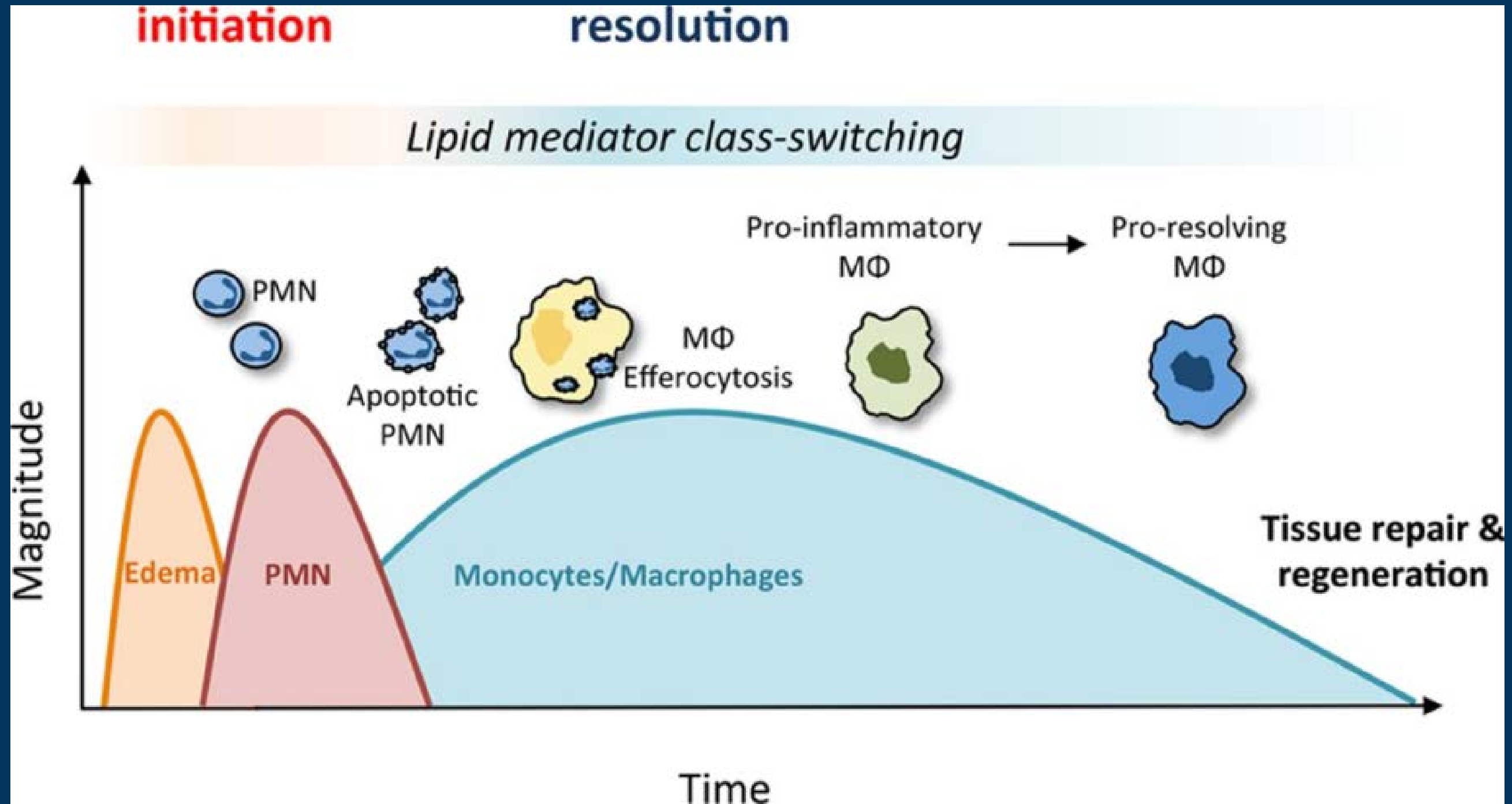


Start the Resolution



Robert G. Martindale MD, PhD

Chief, Division of General and Gastrointestinal Surgery

Medical Director Hospital Nutrition Service

Oregon Health and Science University

Portland, Oregon

Evolving Paradigms in Metabolic Modulation

- **Earliest Paradigm:**
- 1970's epidemiologic studies suggesting reduced cardiac disease in Greenland Inuits with high FO consumption
- **Clinical Paradigm: attenuating catabolism , gut protection**
- 1970's Barbul reports arginine enhances wound healing
- 1980's Wilmore group starts the glutamine “revolution”
 - Conditionally EAA, primary fuel enterocyte, N donor DNA / RNA syn, HSP, insulin resistance

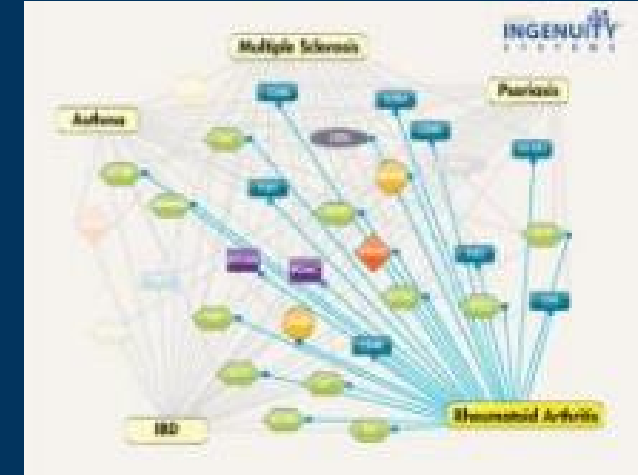


Evolving Paradigms in Metabolic Modulation

- 1990's Wes Alexander shows improved outcome in burns:
 - Arginine, fish oils, RNA
- 1980 to 2012 most clinical trials report benefit
 - Chronic vs acute situations
 - Majority of positive data benefit in perioperative surgical and traumatic ICU populations
 - Both inpatient and outpatient data very mixed
- **Newest paradigm: Focused on inflammation “resolution physiology”**
 - Resolving inflammation and prevention of transition to chronic inflammation

Inflammation:

When physiology turns to pathology



- Acute inflammation is a normal healthy response
- Triggers of inflammation share common pathways
 - Chronic inflammation is a destructive process
 - Mechanisms of chronic inflammation overlap
 - “Healthy” inflammation resolves “naturally”
- Omega 3 FAs are reported to reduce inflammation
 - Specialized pro-resolving mediators (SPMs) endogenously produced from Omega-3 accelerate resolution



**“Many types of injury
produce a similar
inflammation”**

**Hunter J (1794) A treatise on
blood, inflammation and
gunshot wounds**

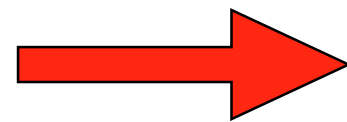
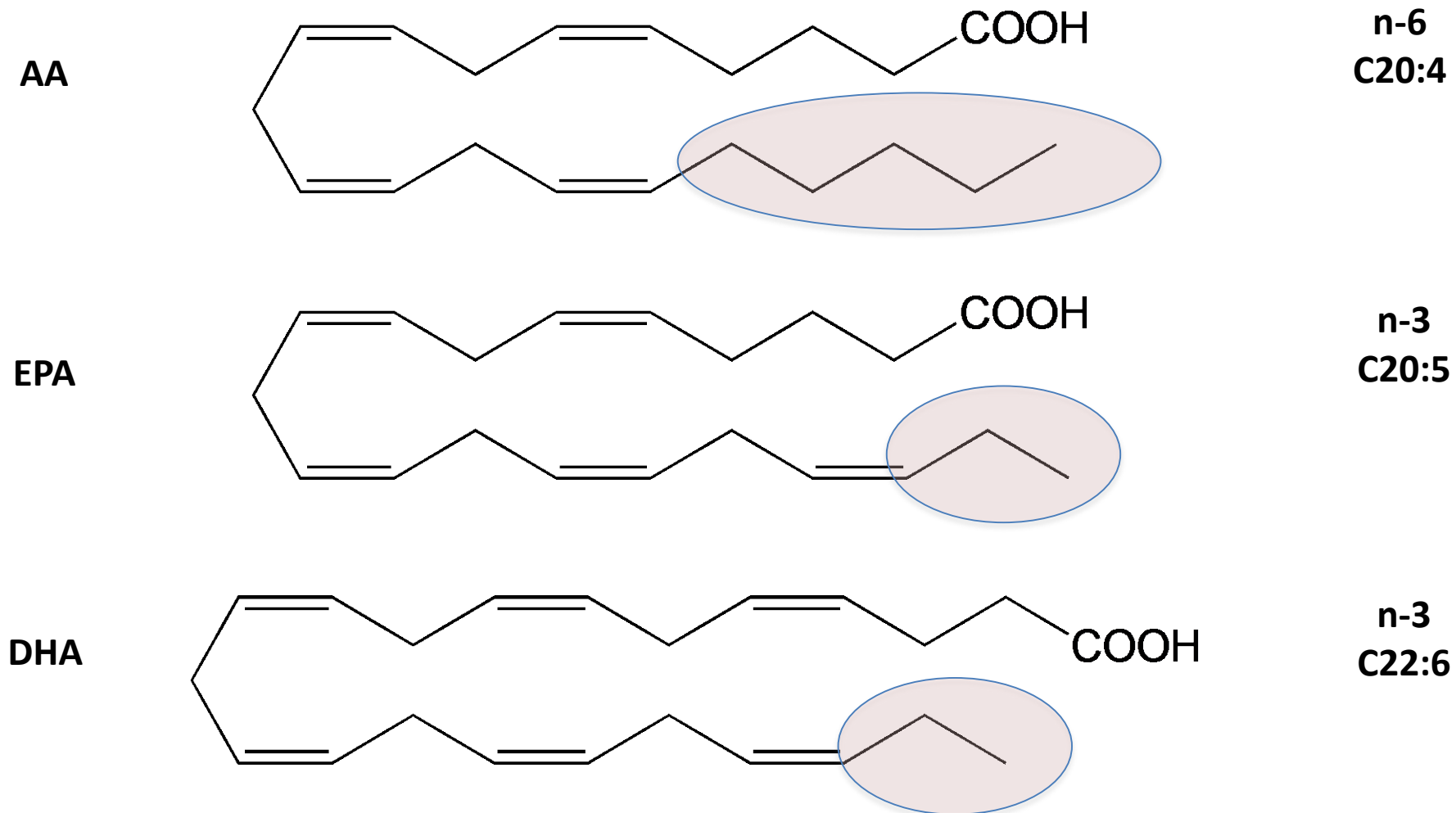


We have been lost in
trying to prevent
inflammation

we forgot resolution
inflammation

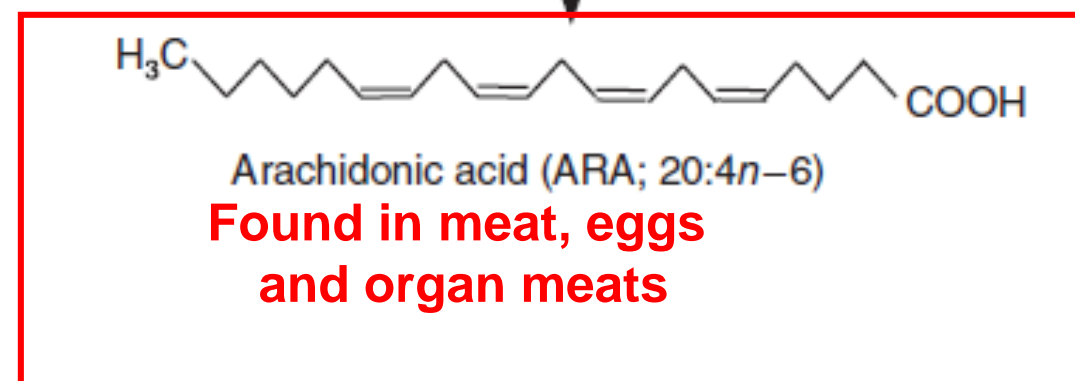
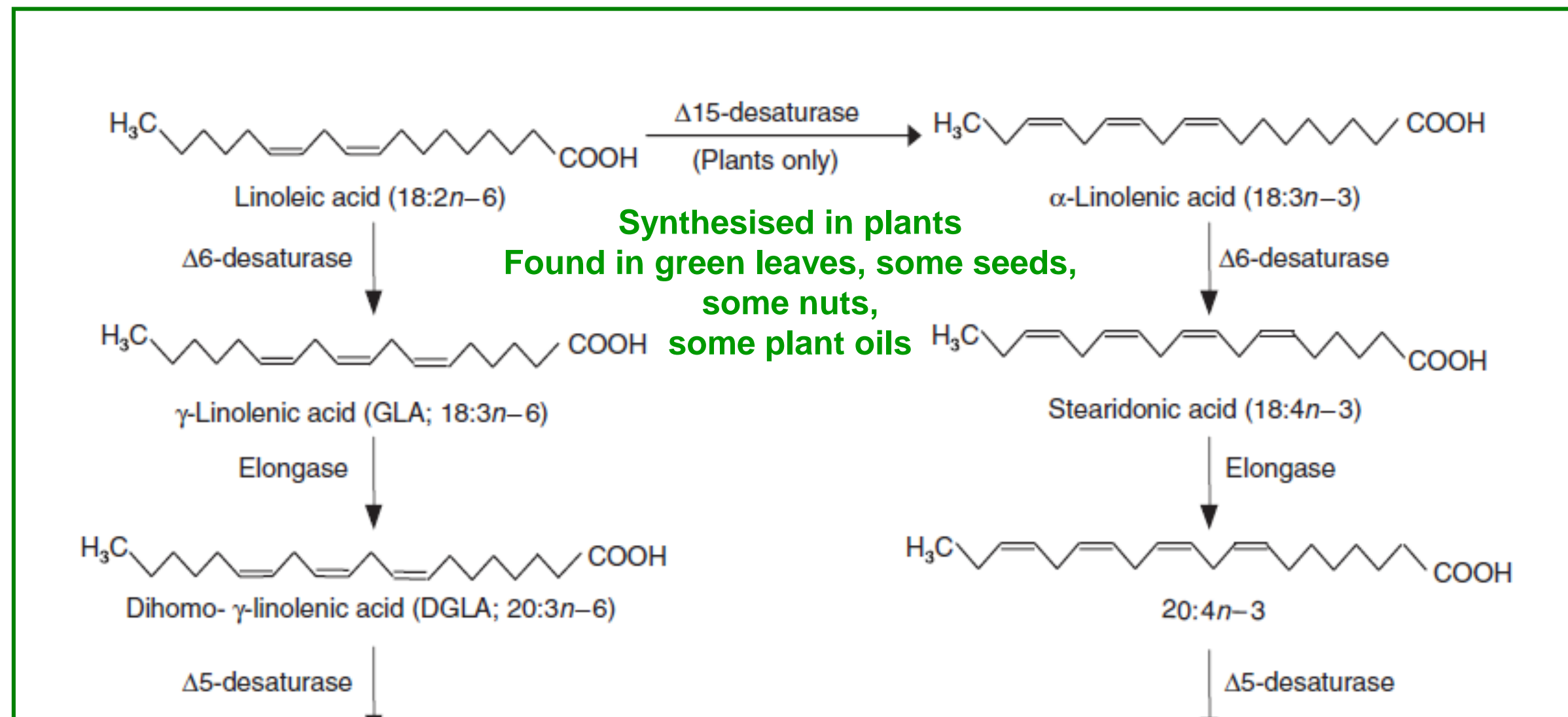


PUFA n-6 & n-3

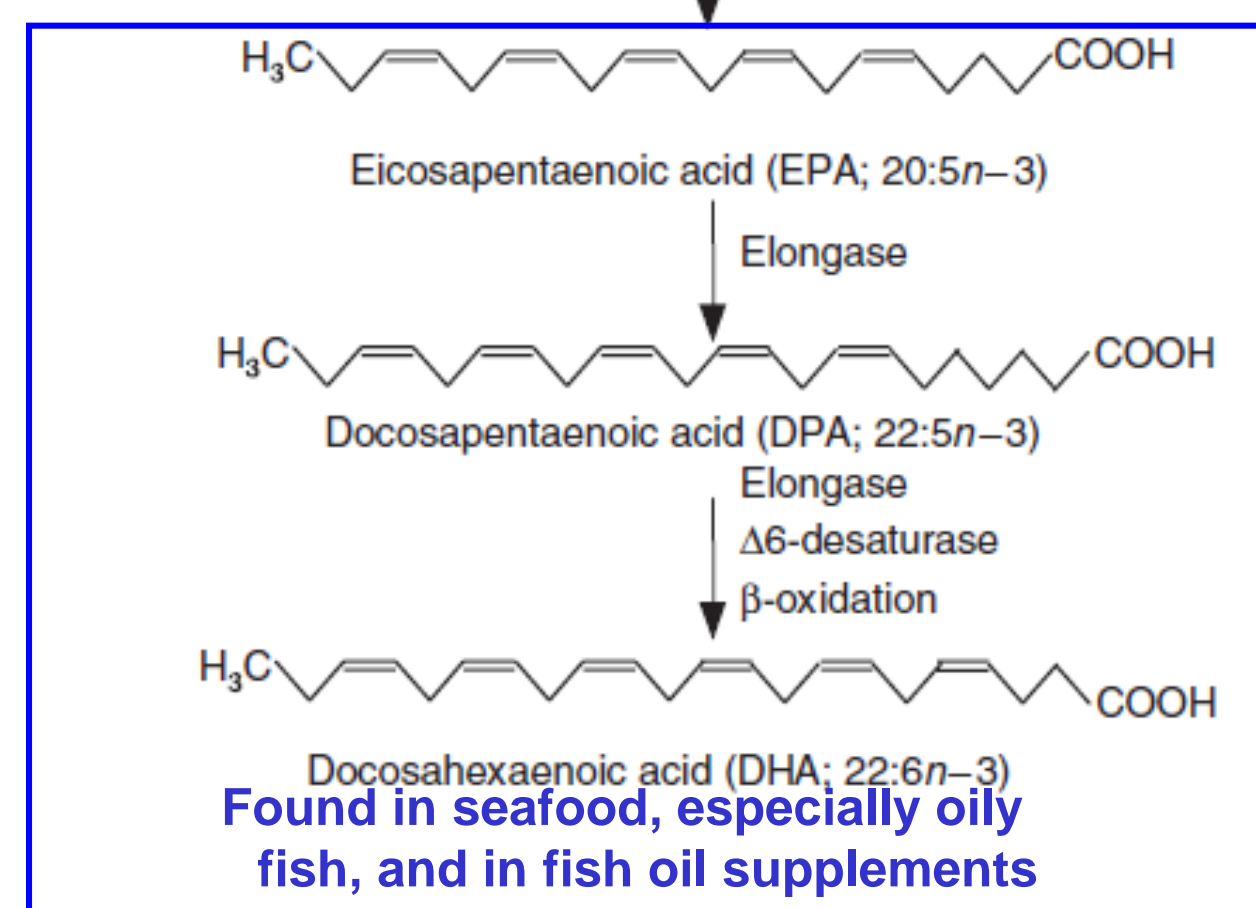


Theory
Compete
for AA

Essential fatty acids: They exert critical functions in human health
Not produced by human cells
Obtained from our diet



**In most human cells EPA and
DHA is low
compared to omega-6**



ω -6 and ω -3 PUFA contents of phospholipids of human white (mononuclear) cells

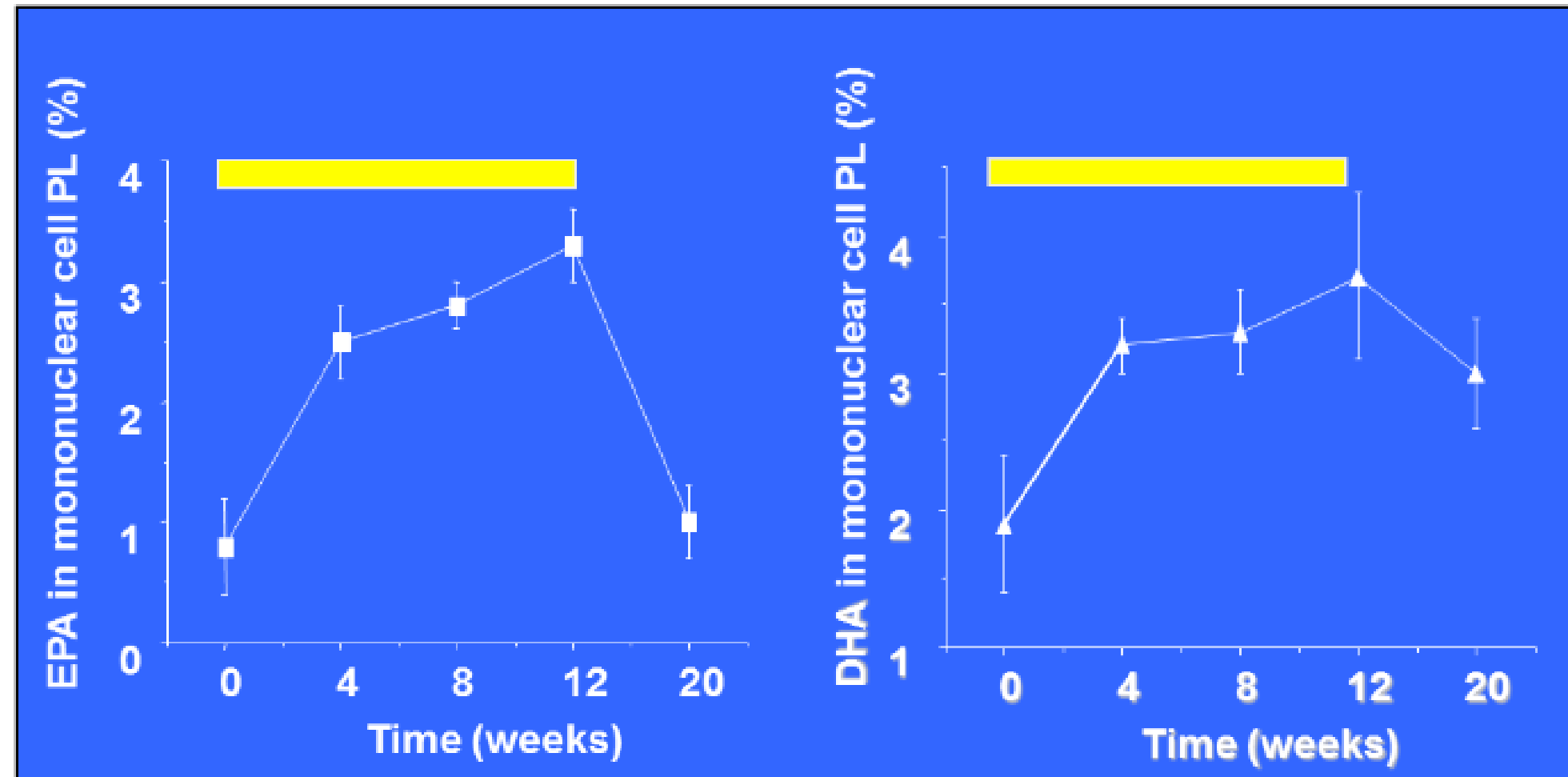
	% of total fatty acids	
Linoleic acid (18:2 ω -6)	10	
DGLA (20:3 ω -6)	1.5	
Arachidonic acid (20:4 ω -6)	20	
<hr/>		
α -Linolenic acid (18:3 ω -3)	< 0.5	
EPA		1.0
DHA		2.5

Yaqoob et al. (2000) Eur. J. Clin. Invest. 30, 260-274

But increasing EPA+DHA intake [supply] increases the EPA and DHA content of blood lipids, blood cells, and many tissues including liver, heart & skeletal muscle – effect is dose, time and tissue dependent



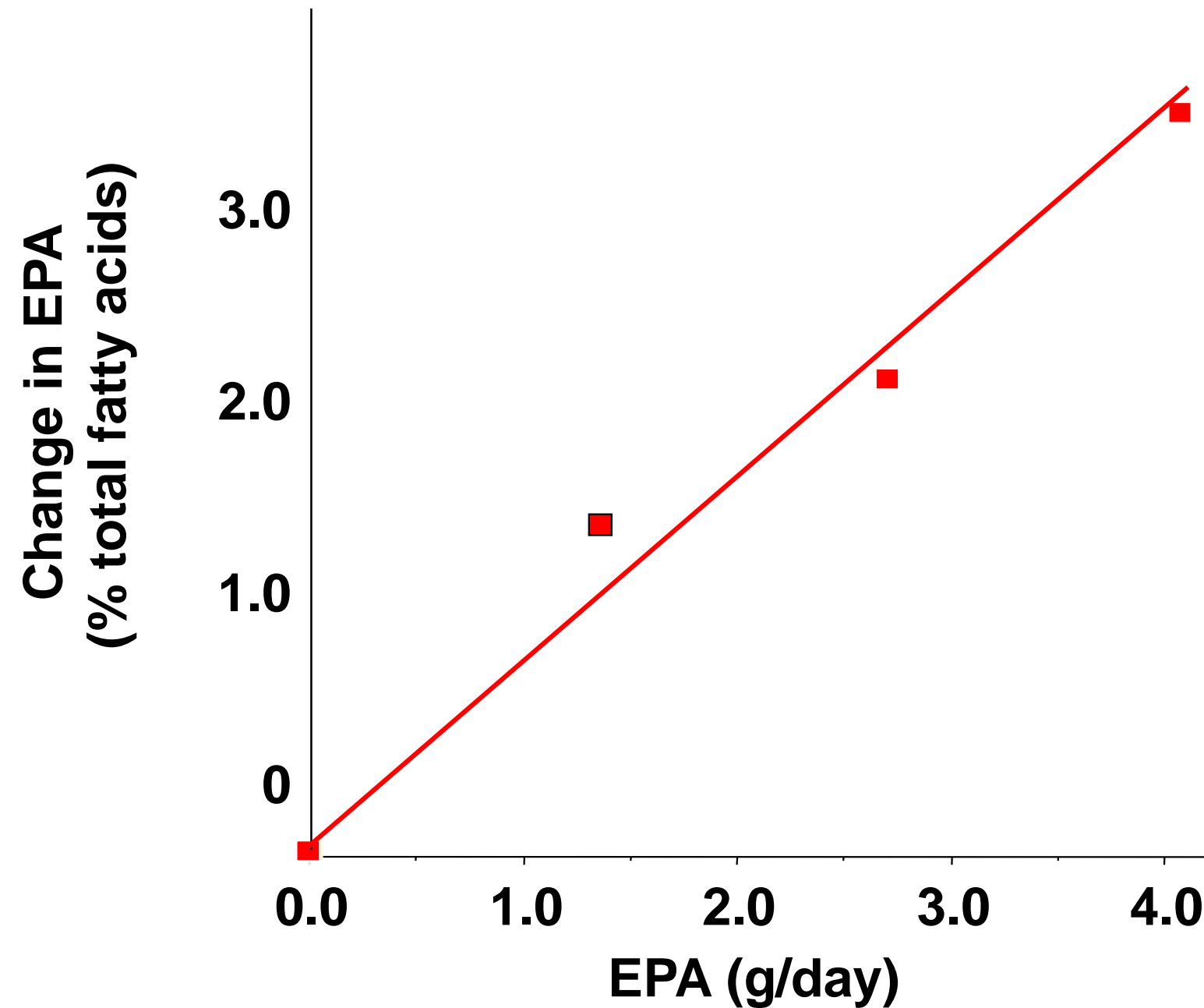
Time course of incorporation of EPA and DHA into human immune cell phospholipids



Healthy volunteers given fish oil (2.1 g EPA and 1.1 g DHA/day) for 12 weeks

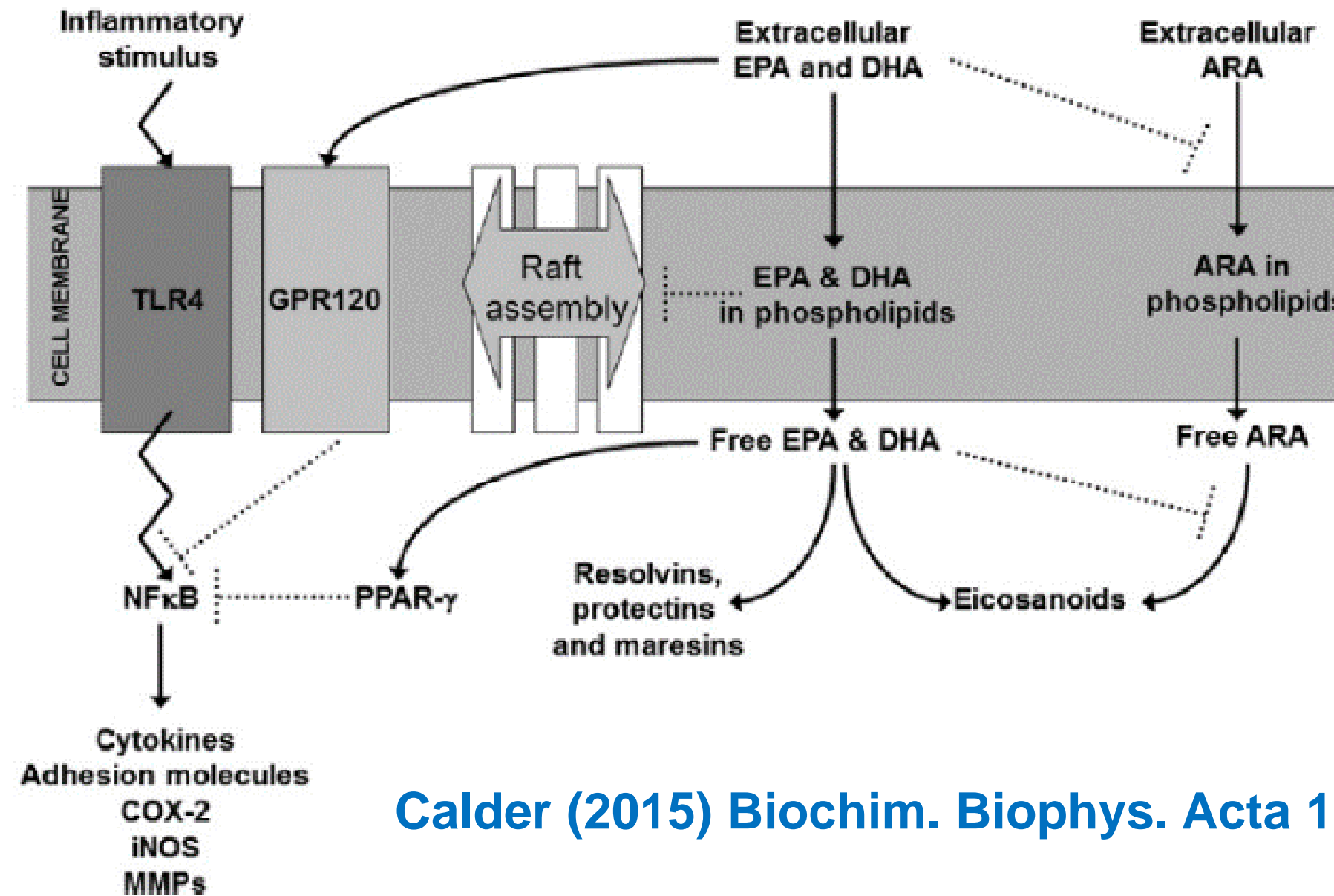
Yaqoob et al. (2000) Eur. J. Clin. Invest. 30, 260-274

Dose response of incorporation of EPA into human mononuclear cells



Rees et al. (2006) Am. J. Clin. Nutr. 83, 331-342

Mechanisms by which increased EPA and DHA status affect inflammatory processes



Calder (2015) Biochim. Biophys. Acta 1851, 469-484

Reported benefits of EPA and DHA in clinical settings



- ◆ Cardiovascular Ds
- ◆ Cardiac Arrhythmias
- ◆ Rheumatoid Arthritis
- ◆ Psoriasis
- ◆ IBD
- ◆ Renal Transplant
- ◆ Multiple Sclerosis
- ◆ Glucose tolerance
- ◆ Lupus
- ◆ ARDS
- ◆ Cystic Fibrosis
- ◆ Psychiatry
 - ◆ Depression, suicide
- ◆ etc etc etc

In excess of >4000 clinical trials showing benefits of fish oil or omega 3 fatty acids in clinical medicine !!!



Omega 3 Fatty Acids: Acute Care Setting



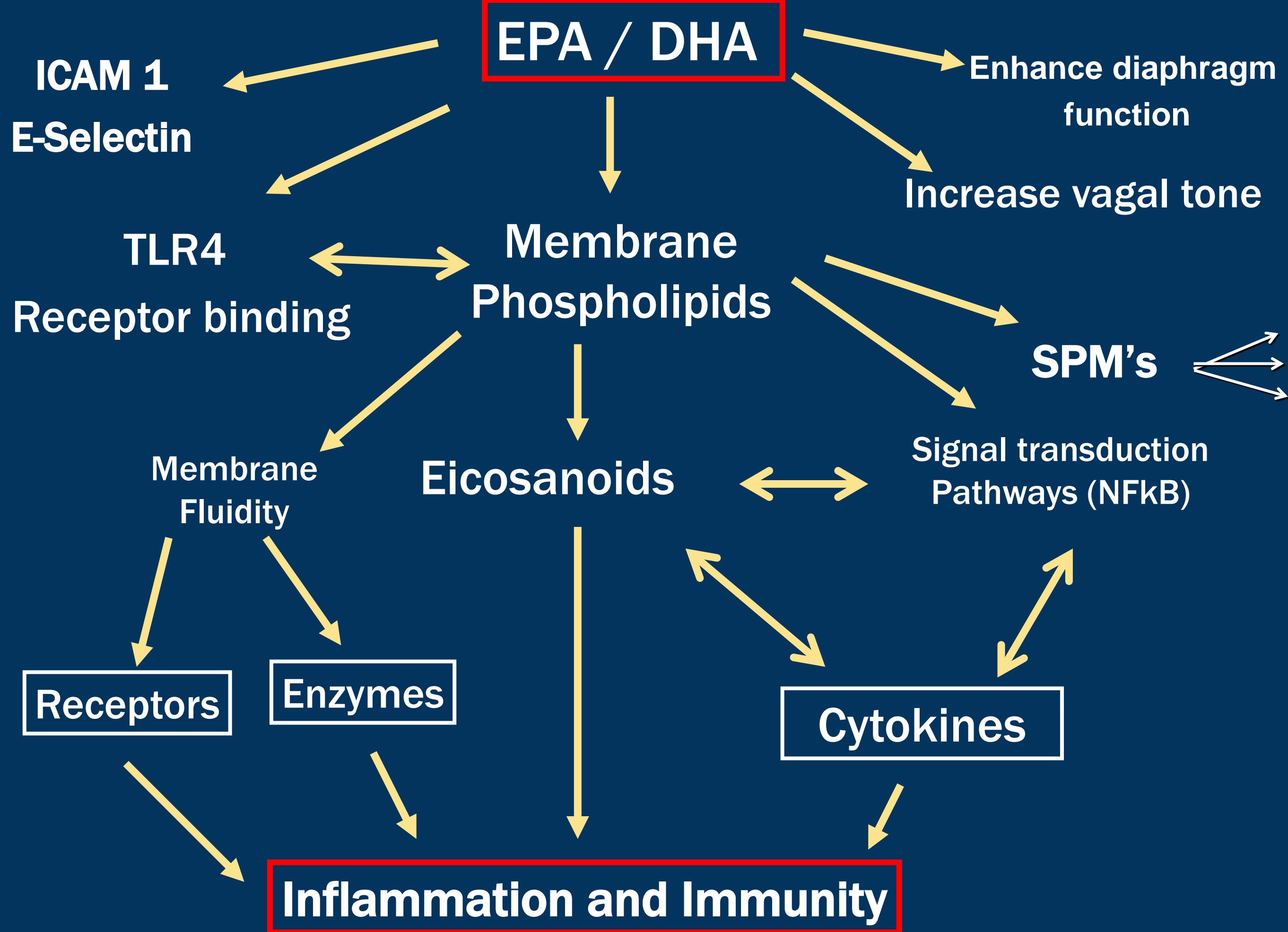
◆ Clinical Data

- ◆ ↓ inflammatory response
- ◆ ↓ cardiac arrhythmias
- ◆ ↑ tissue microperfusion
- ◆ ↑ graft function
- ◆ ↓ cancer in cell lines
- ◆ Limits omega-6 immune suppression
- ◆ Maturation of CNS
- ◆ ↑ clearance

◆ Biochemical Data

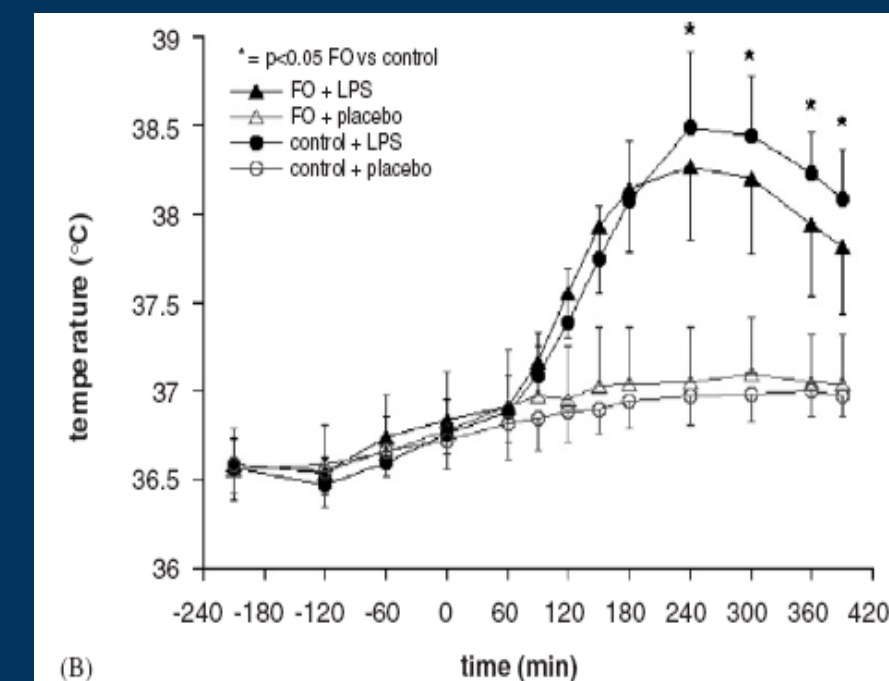
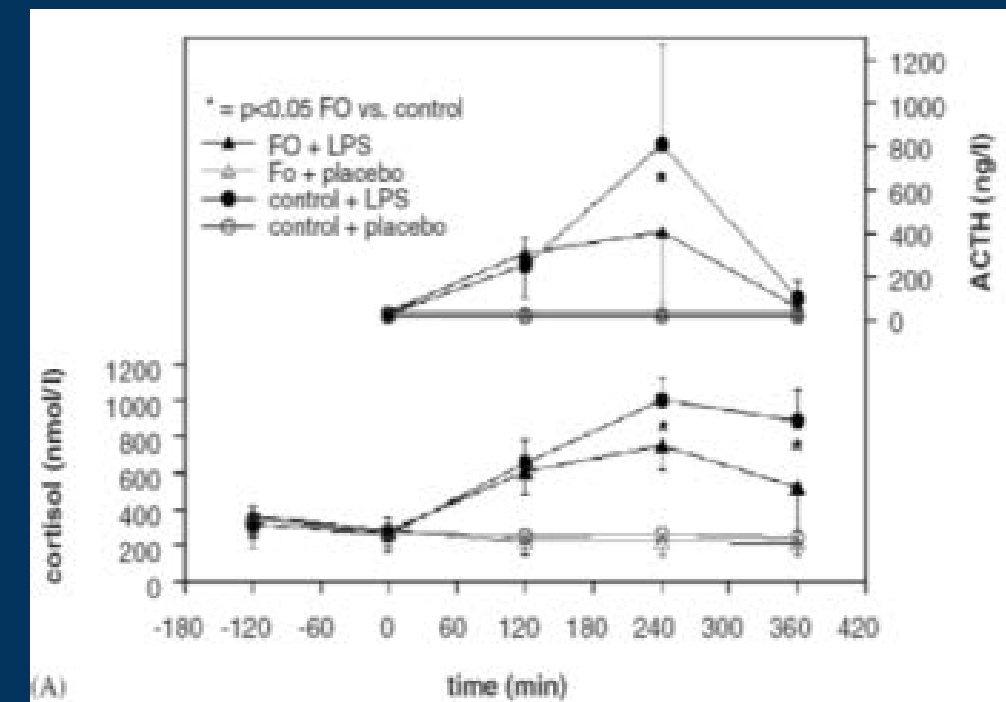
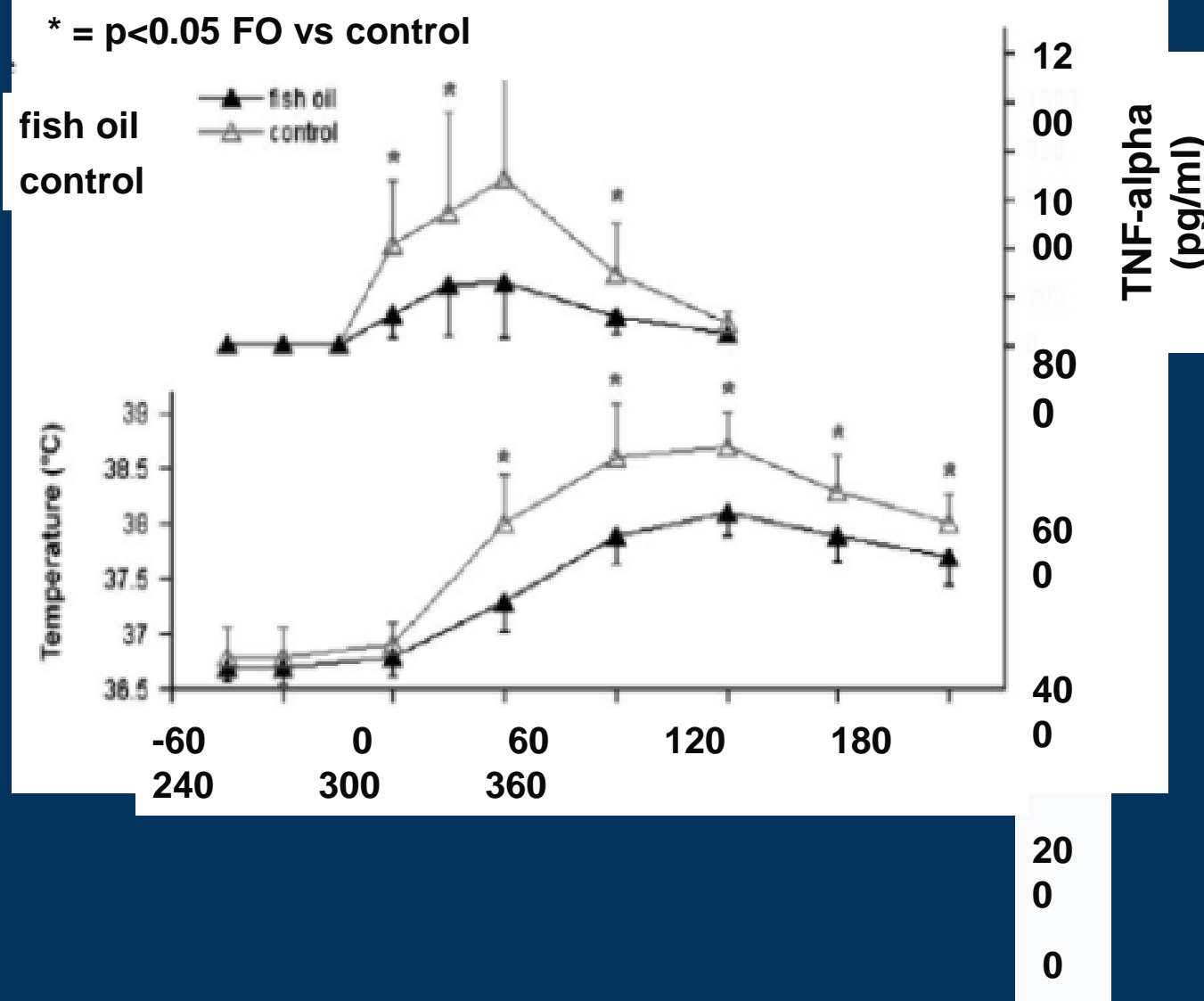
- ◆ Biological regulators
- ◆ Cell membrane structure and function
- ◆ Influences membrane fluidity
- ◆ Alters receptors activity
- ◆ Eicosanoid metabolism
- ◆ Cytokine production
- ◆ Gene expression

*Effects noted within 1-3 hours via
parenteral route 1-3 days via enteral*



Thomas-Thi Pluess
Daniel Hayoz
Mette M. Berger
Luc Tappy
Jean-Pierre Revelly
Burkhard Michaeli
Yvon A. Carpentier
René L. Chioléro

Intravenous fish oil blunts the physiological response to endotoxin in healthy subjects



Michaeli B. et al Clin Nutrition (2007) 26, 70-77

Pluess TT et al Intensive Care Med (2007) 33:789-797

Three short perioperative infusions of n-3 PUFAs reduce systemic inflammation induced by cardiopulmonary bypass surgery: a randomized controlled trial¹⁻³ **Am J Clin Nutr 2013**

- **PRBCT Evaluation influence of FO infusion in immediate peri-operative period in CABG**
 - N=28 equal groups
 - Three 2 hour infusion with/in 12 pre-op period
- **Results: FO showed;**
 - Pilot study not powered for clinical outcome
 - No change in mortality, clinical outcome, endogenous glucose production
 - Trend toward decrease APACHE, SOFA
 - Improved glycemic control
 - Decrease in lactate
 - Decrease in IL-6

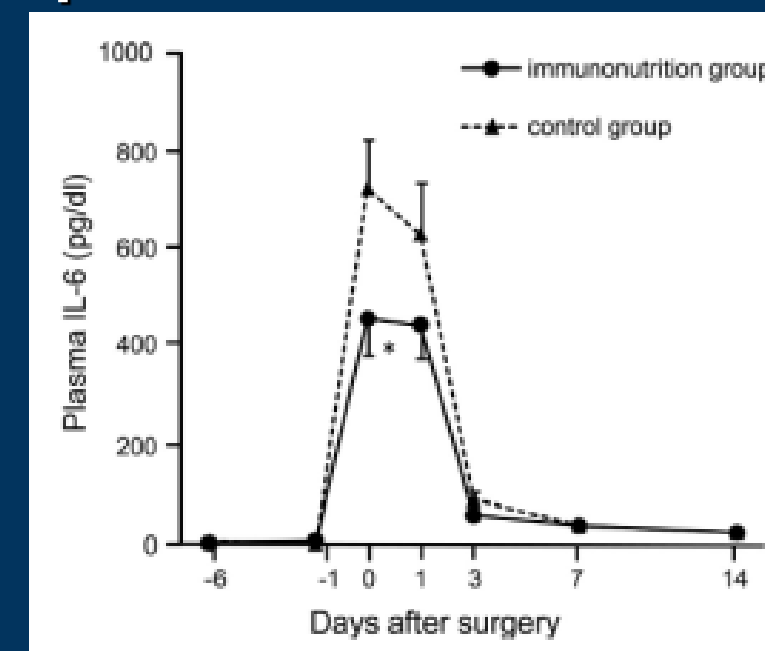
Berger M et al Am J Clin Nutr 2013

Preoperative immunonutrition decreases postoperative complications by modulating prostaglandin E₂ production and T-cell differentiation in patients undergoing pancreatoduodenectomy **Surgery 2014**

- **N=50 RCT**
 - PO 5 days preop



- **Outcome**
 - Attenuates metabolic response to surgery
 - Decrease infection
 - Decrease severity of complications



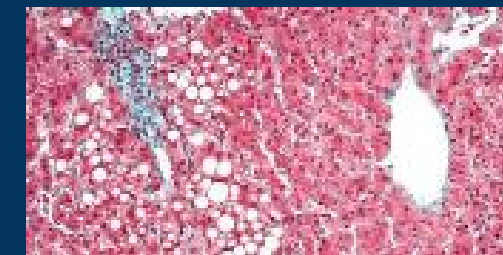
Aida T et al Surgery 2014

Not all the data is positive or consistent !

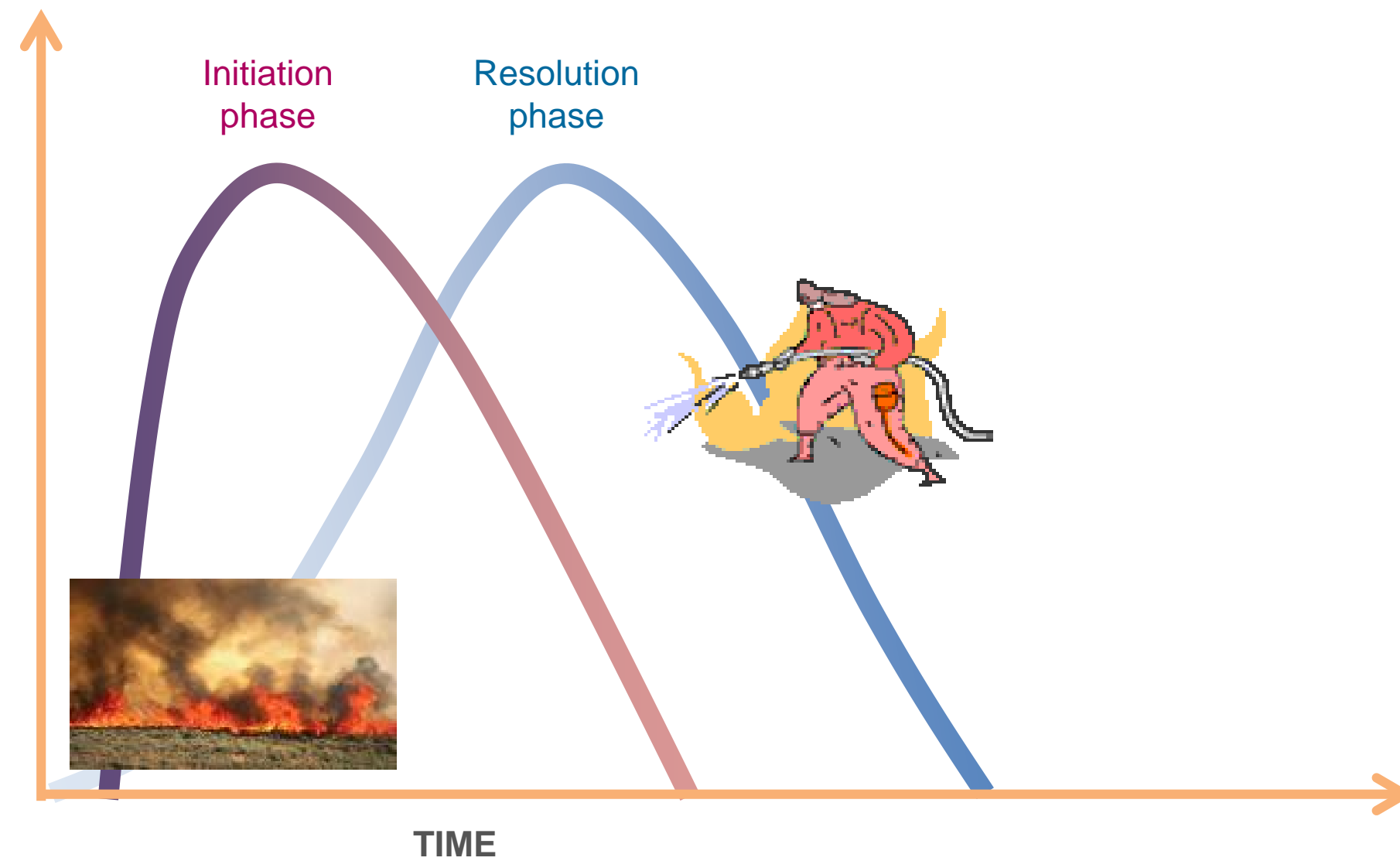
Fish Oils use in the ICU / Trauma:

Clinical Outcome Dependent on Several Factors:

- **ARDS / ALI (variable)**
 - Dependent upon;
 - Route of feeding (EN v PN)
 - Bolus versus continuous
 - Background nutrition
- **Cardiac rhythm stabilization(variable)**
 - Dependent upon
 - Timing of delivery
 - Background cardiac status
- **Prevention of hepatic steatosis**
 - Anytime
- **Early recovery after traumatic brain injury**
 - Well developed in animal studies
 - As early as possible following injury
 - Dependent on timing of injury



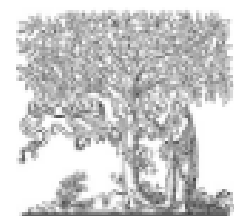
Inflammation has two phases: initiation and resolution



Lipid mediator class switching during acute inflammation: signals in resolution

Bruce D. Levy, Clary B. Clish, Birgitta Schmidt, Karsten Gronert and Charles N. Serhan

Nature Immunology 2001

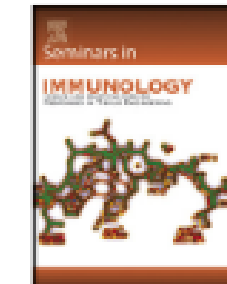


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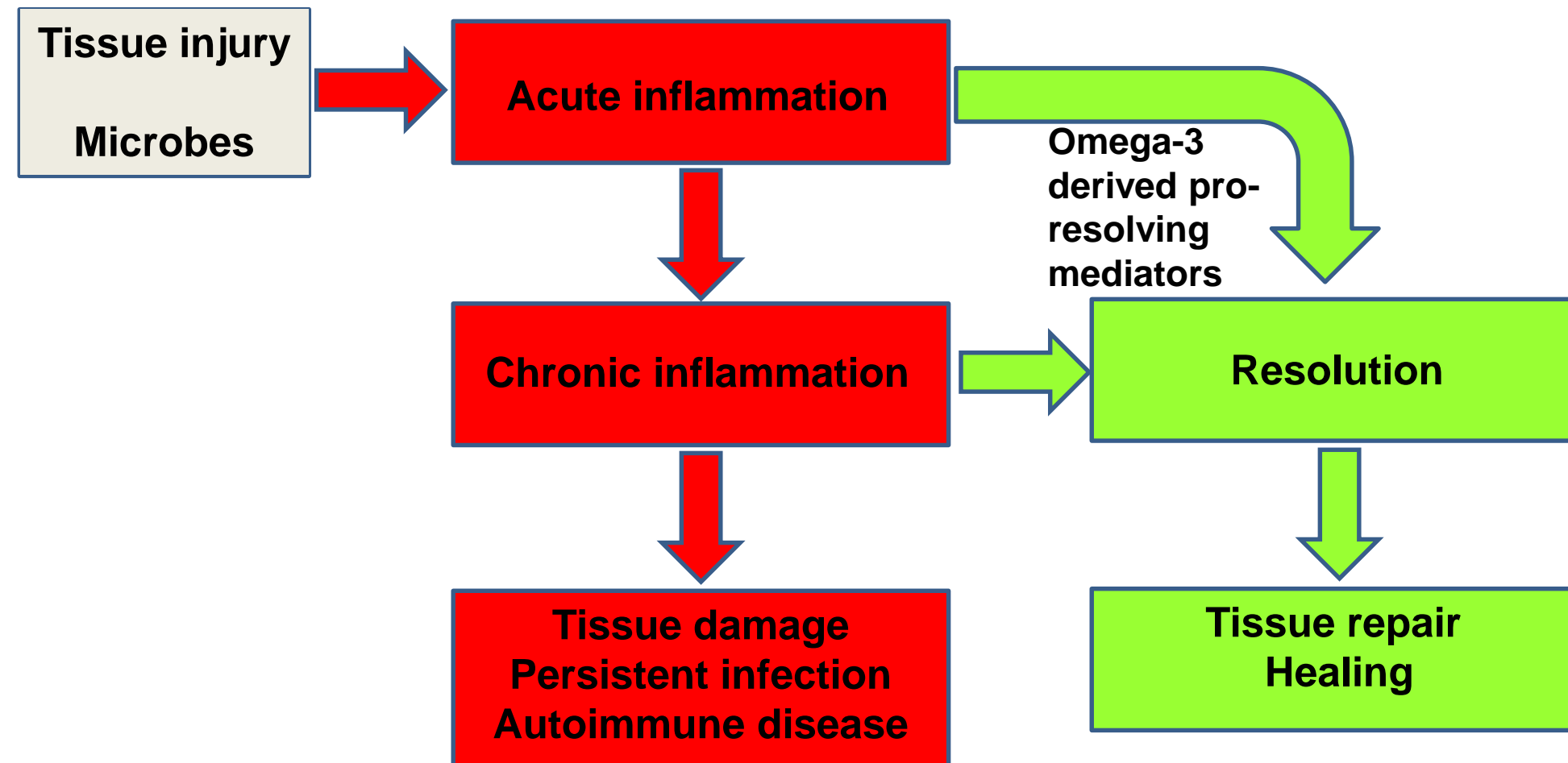
Review

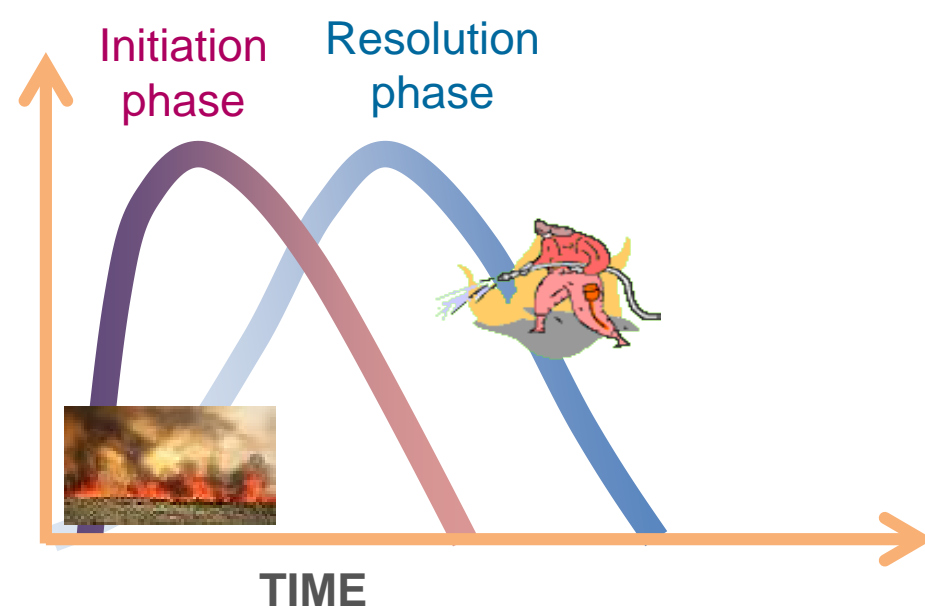
The resolution code of acute inflammation: Novel pro-resolving lipid mediators in resolution

Charles N. Serhan*, Nan Chiang, Jesmond Dalli



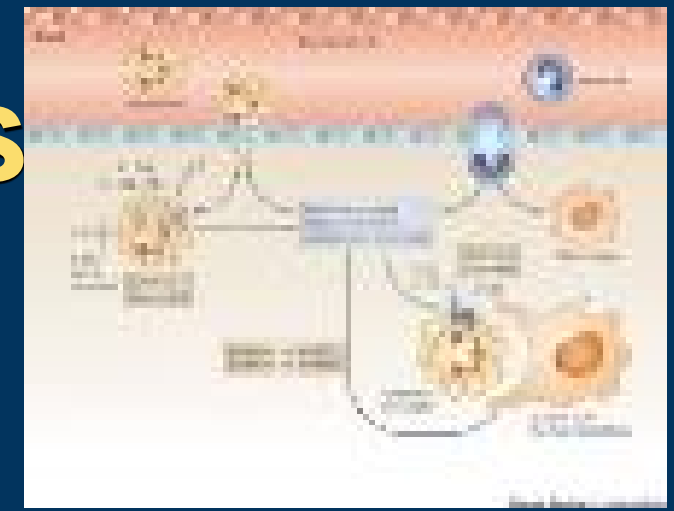
Seminars in Immunology (2015) 27, 200-215





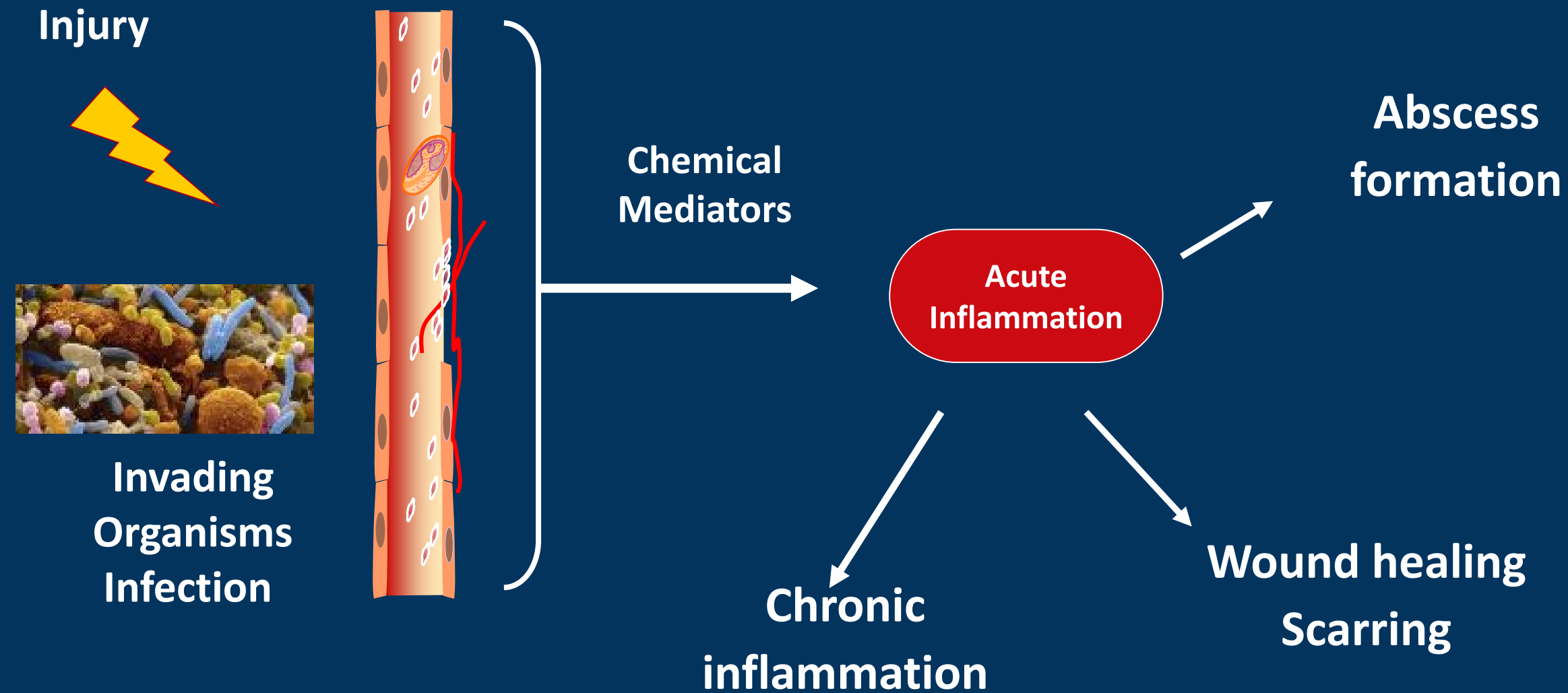
	EPA+DHA	SPMs
Are naturally occurring	✓	✓
Present in the diet	✓	✗
Synthesised endogenously in humans	✓	✓
Anti-inflammatory	✓	✓
Inflammation resolving	✗	✓
Concentration range for activity	micromolar	nanomolar/ picomolar

SPM's present in most tissues tested to date

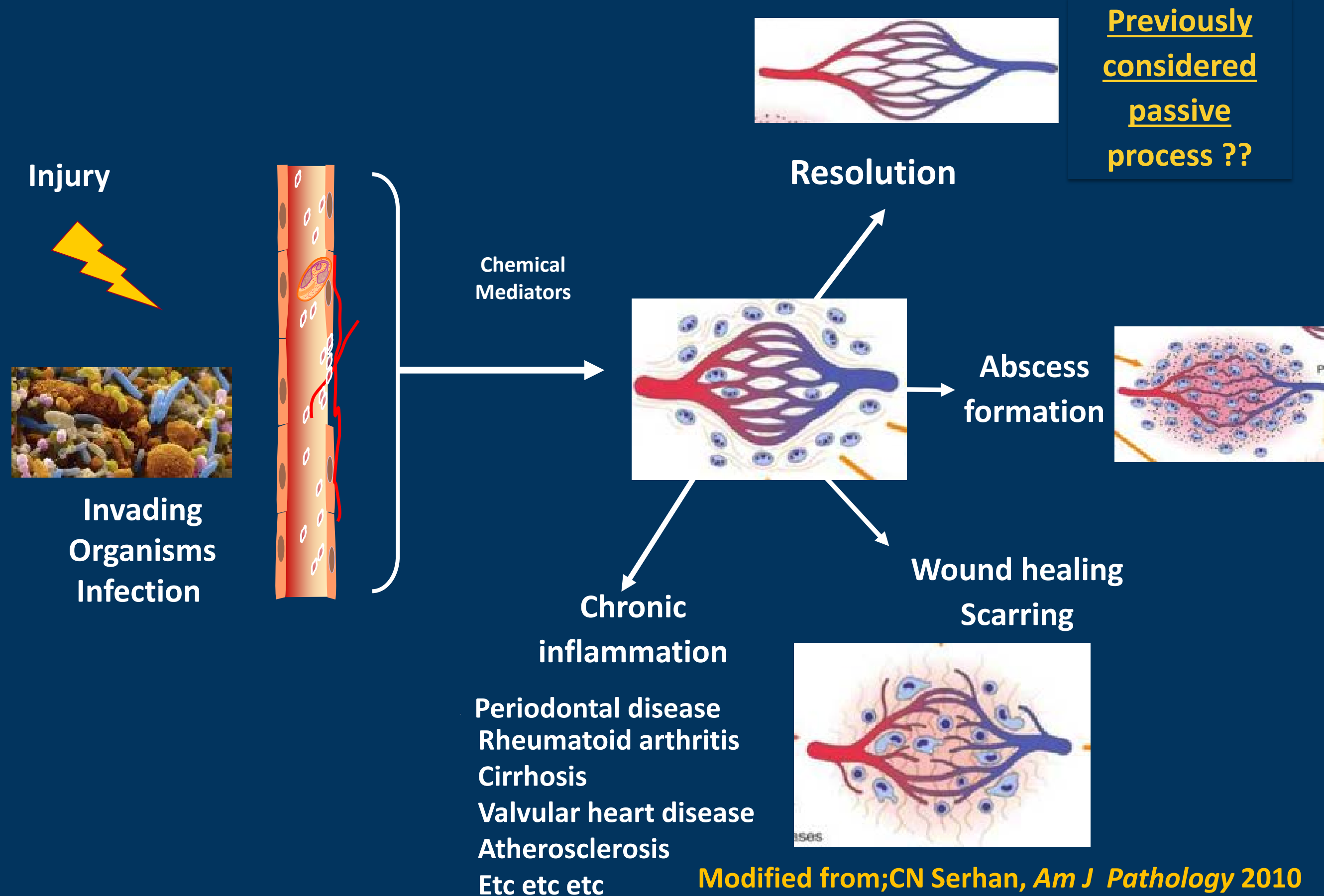


- **Bioactive at levels of 20 to 200 picomolar**
 - Serum in range of pg/ml (10^{-12})
- **Serum** (Serhan C et al Am J Physiol 2014)
- **Human milk** (Weiss et al 2013 Lipids in Health and Disease)
- **Urine** (Sasaki et al 2015 Annals Bioanal Chem)
- **Lymph nodes** (Colas et al 2014 Am J Physiology)
- **Adipose tissue** (Claria et al 2013 Am J Physiol Cell Physiol)

Acute or Chronic Inflammation

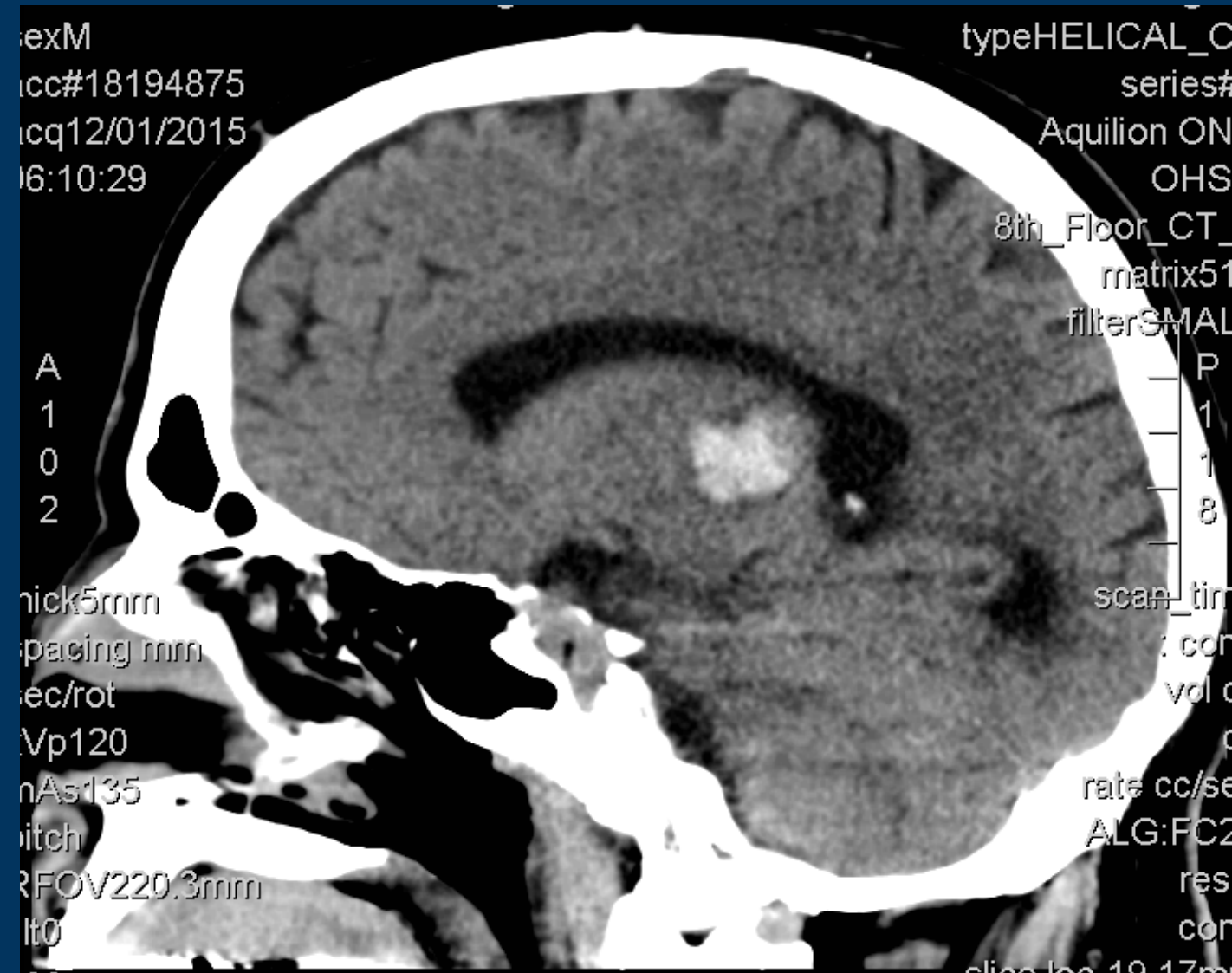
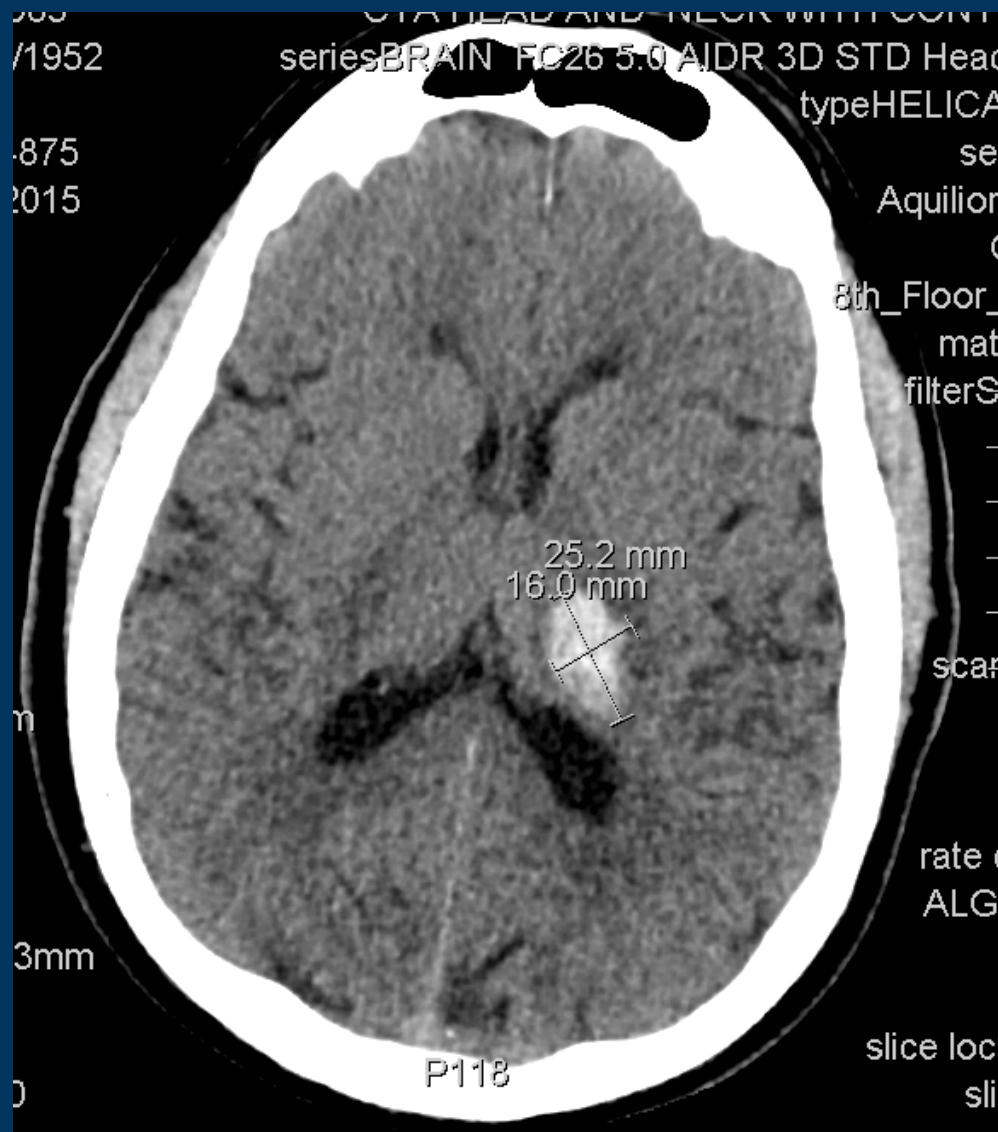


Acute, Chronic, or Resolution of Inflammation



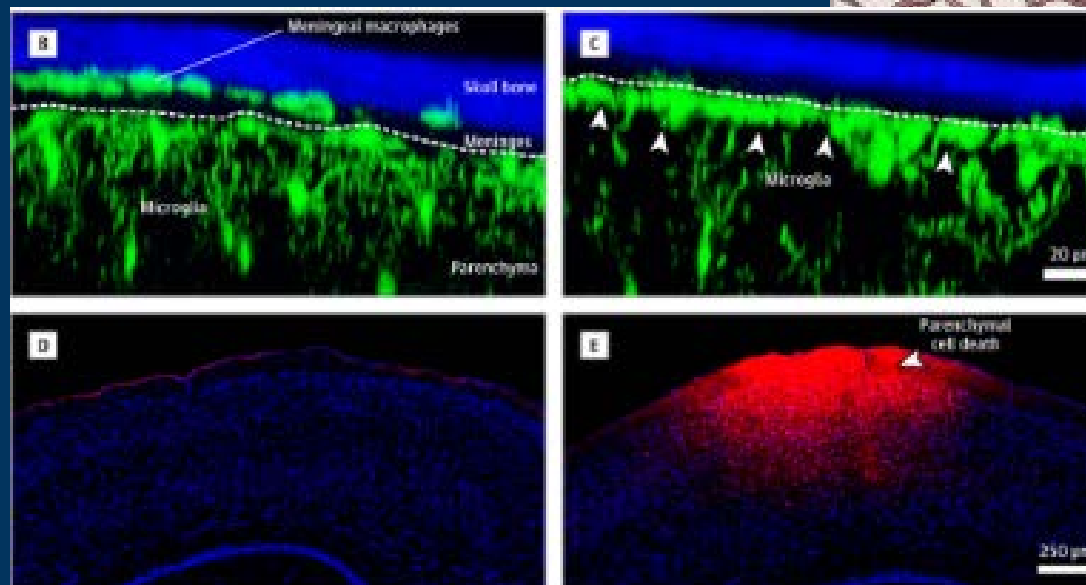
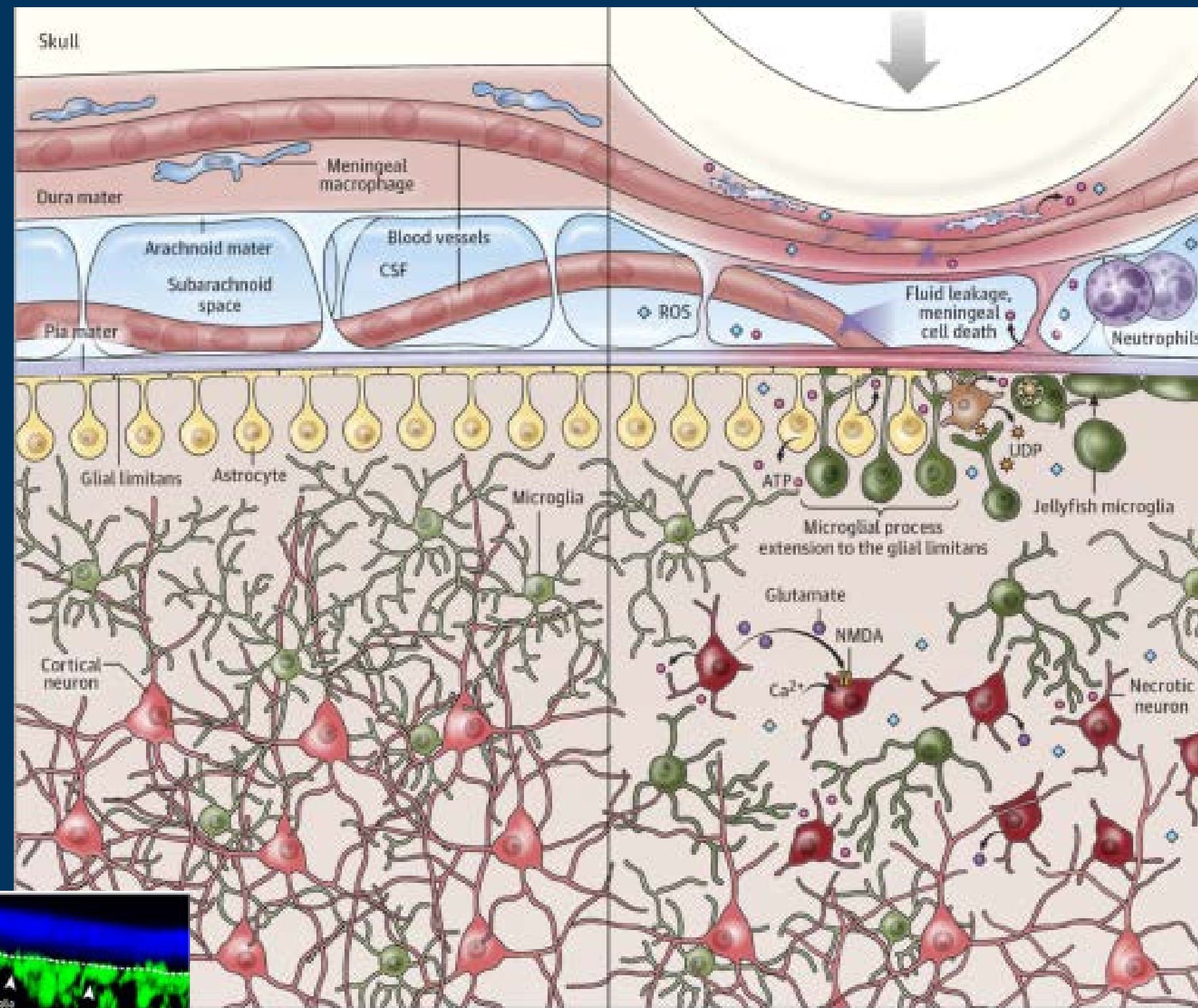
Case study

- 63 yo male relatively healthy male with mild HTN, untreated. Sustains hypertensive intracranial hemorrhage in thalamus at border of caudate nucleus.



**CNS inflammation following bleed is significant.
Now What ?**

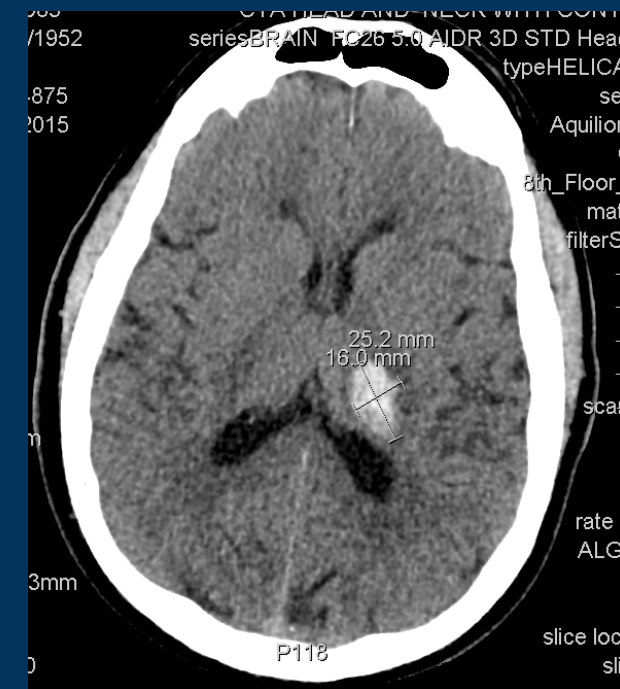
Inflamed Brain



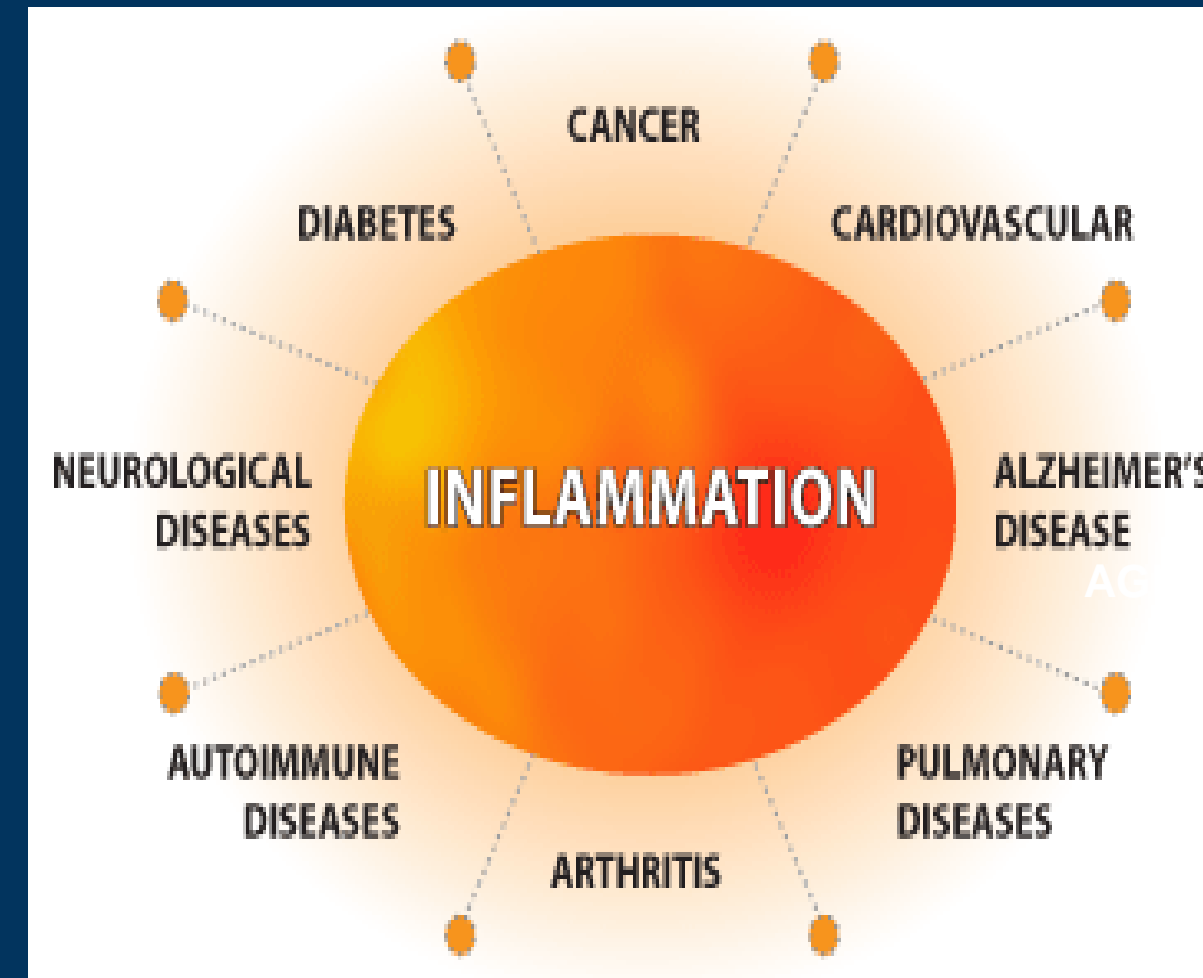
JAMA –Neurology 2015
Inflammation and Neuroprotection

Multiple compounds now reported to be active in “resolution” of inflammation

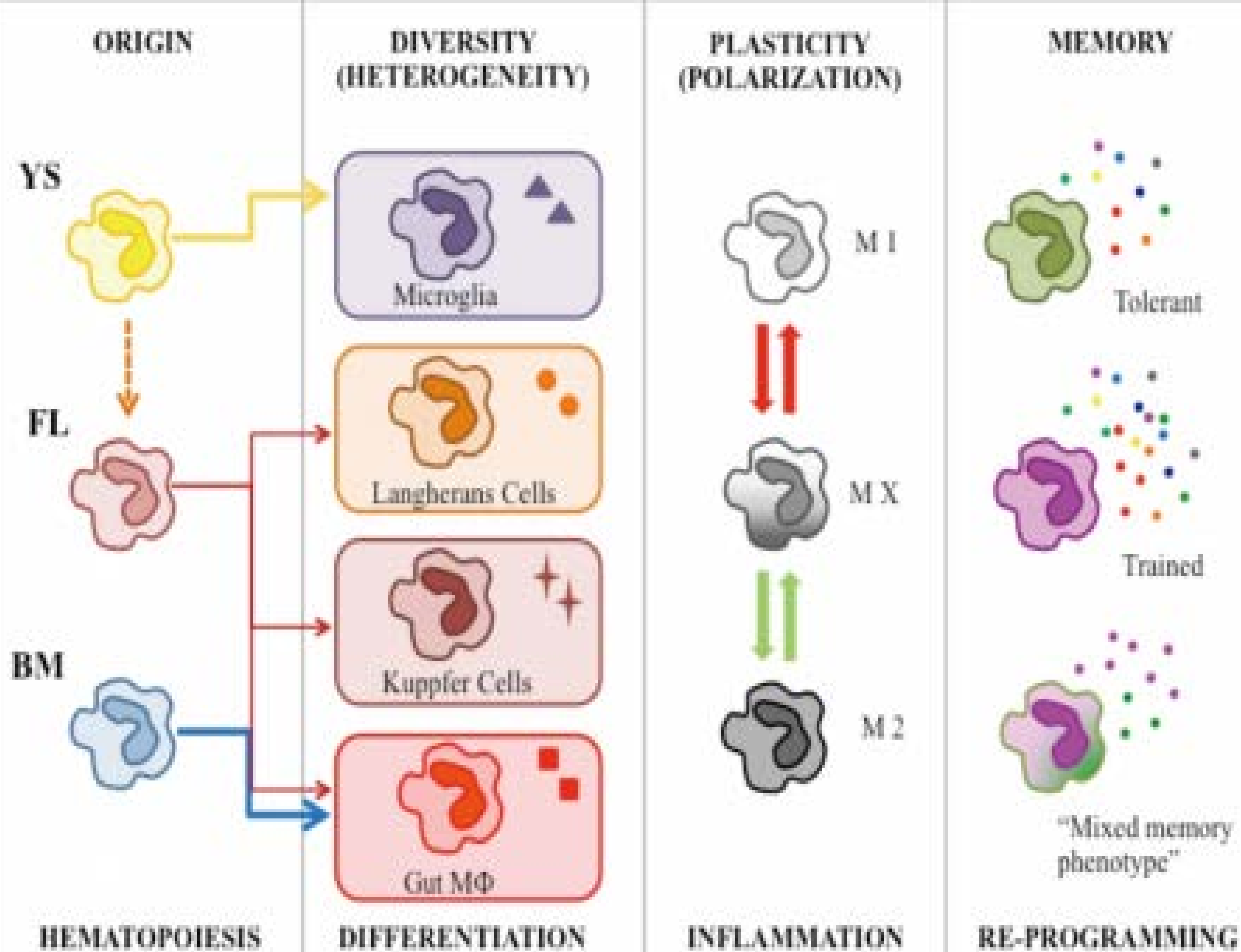
- SPM's
 - Lipoxins, resolvins, protectins, maresins
- Proteins and peptides
 - Annexin A1
 - Leikina E et al Sci Rep Nat 2015 (most work in muscle)
- Gaseous mediators
 - NO, CO, H₂S
 - Zheng Y et al Acta Pharm 2015
- Adenosine
 - » Jacobson KA et al Neuropharmacology 2015
- Vagal release of neuropeptides / HPA axis
 - Boonen E et al Int Care Med 2015



SPM's could they be the answer to unmet promises of immunonutrition ?

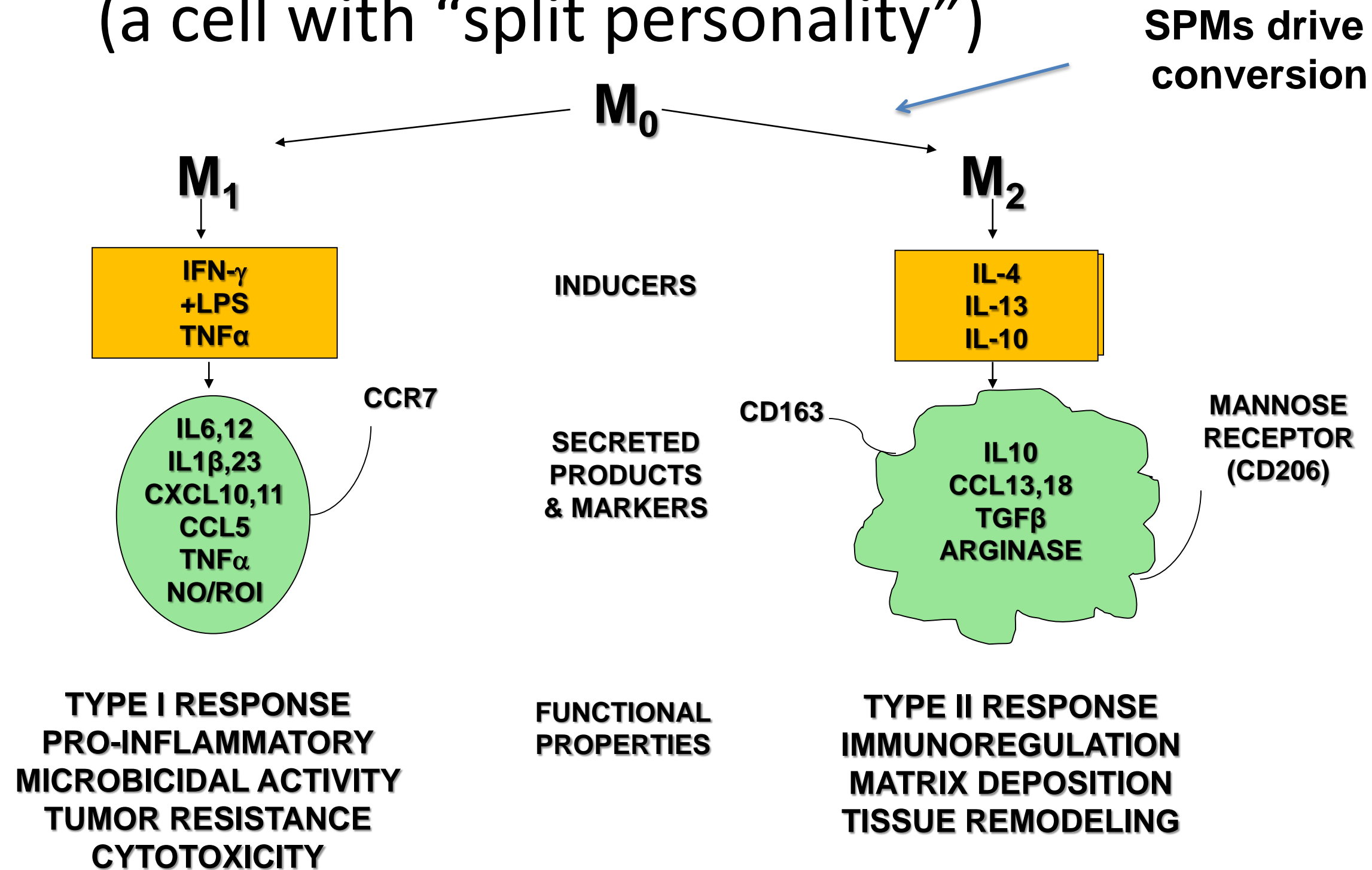


Acute and Chronic
Inflammatory States

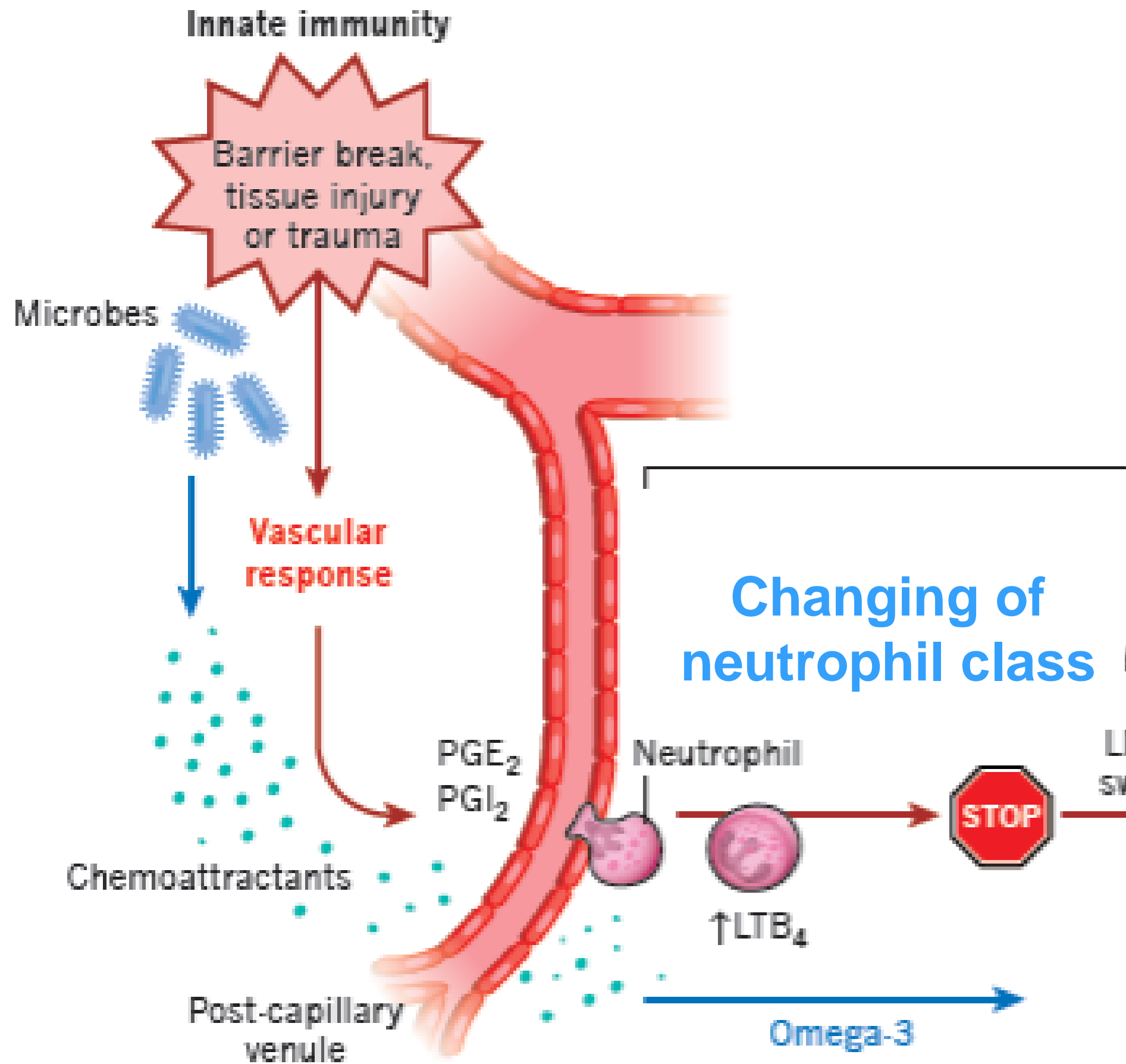


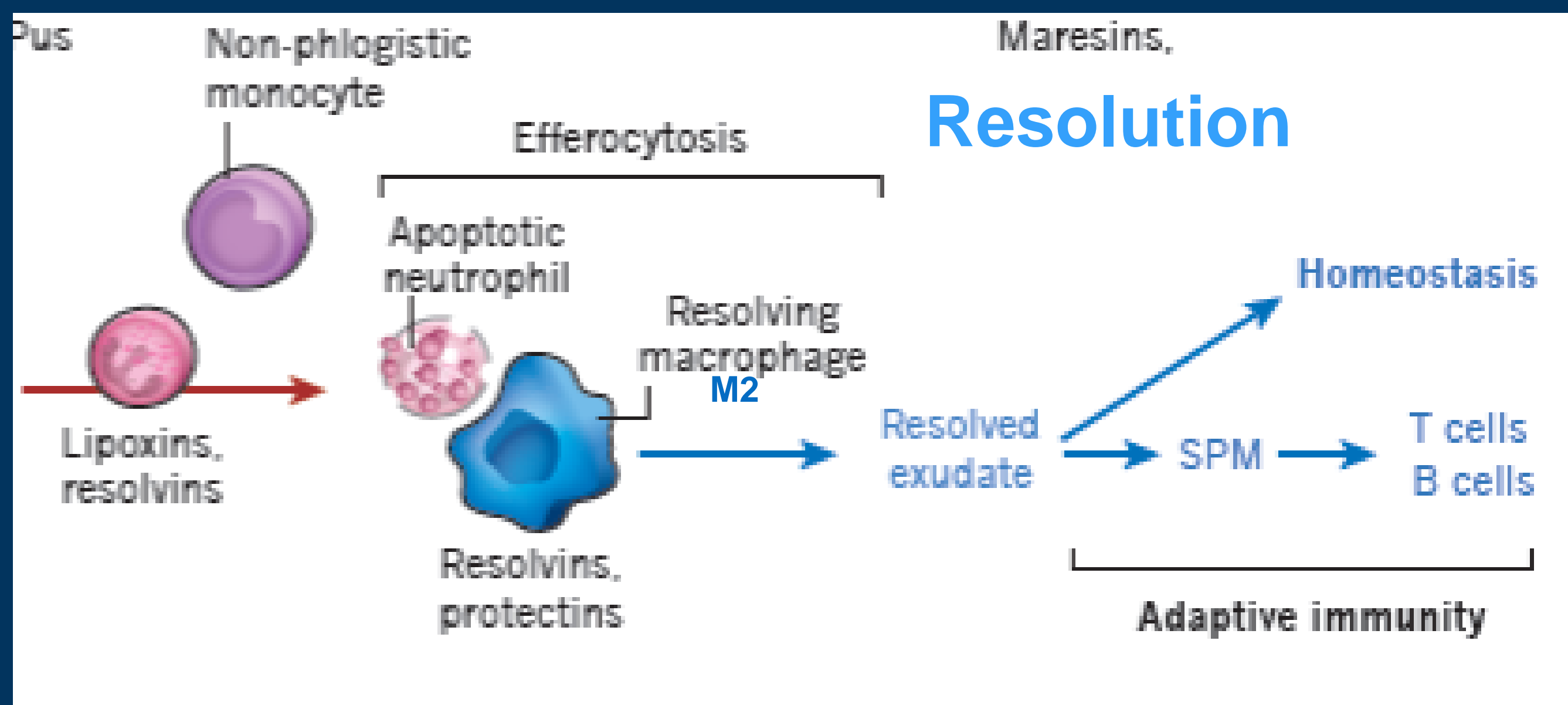
Macrophage Heterogeneity

(a cell with “split personality”)



Adapted from: Mantovani A, et al.
Trends Immunol. 2004;25:677.





When macrophages ingest apoptotic neutrophil
the change phenotype from M1 to M2
(M2 macrophages resolution phase macrophage)

Efferocytosis-(Effere-Latin “to take to the grave”)
Dead cells are are engulfed before cell membranes are breached

SPM: specific pro-resolving mediators
LM: Lipid mediators

Serhan C Nature 2014

Biological Systems: On and Off Signals

- **Radically changed concept of inflammation**
 - Concept stimulated by his own experience
 - » Active vs passive resolution of inflammation
 - 1984 Lipoxins – stopped inflammation
 - 1992 ASA stimulated lipoxin
 - 2000 mouse abscess model
 - Resolvins, Protectins and Maresins
- **Actively stimulate cardinal signs of resolution, namely;**
 - Cessation of leukocytic infiltration
 - Counter regulation of pro-inflammatory mediators
 - Stimulate the uptake of apoptotic neutrophils
 - Clearance of cellular debris



Charlie Serhan



Taber's Cyclopedic Medical Dictionary

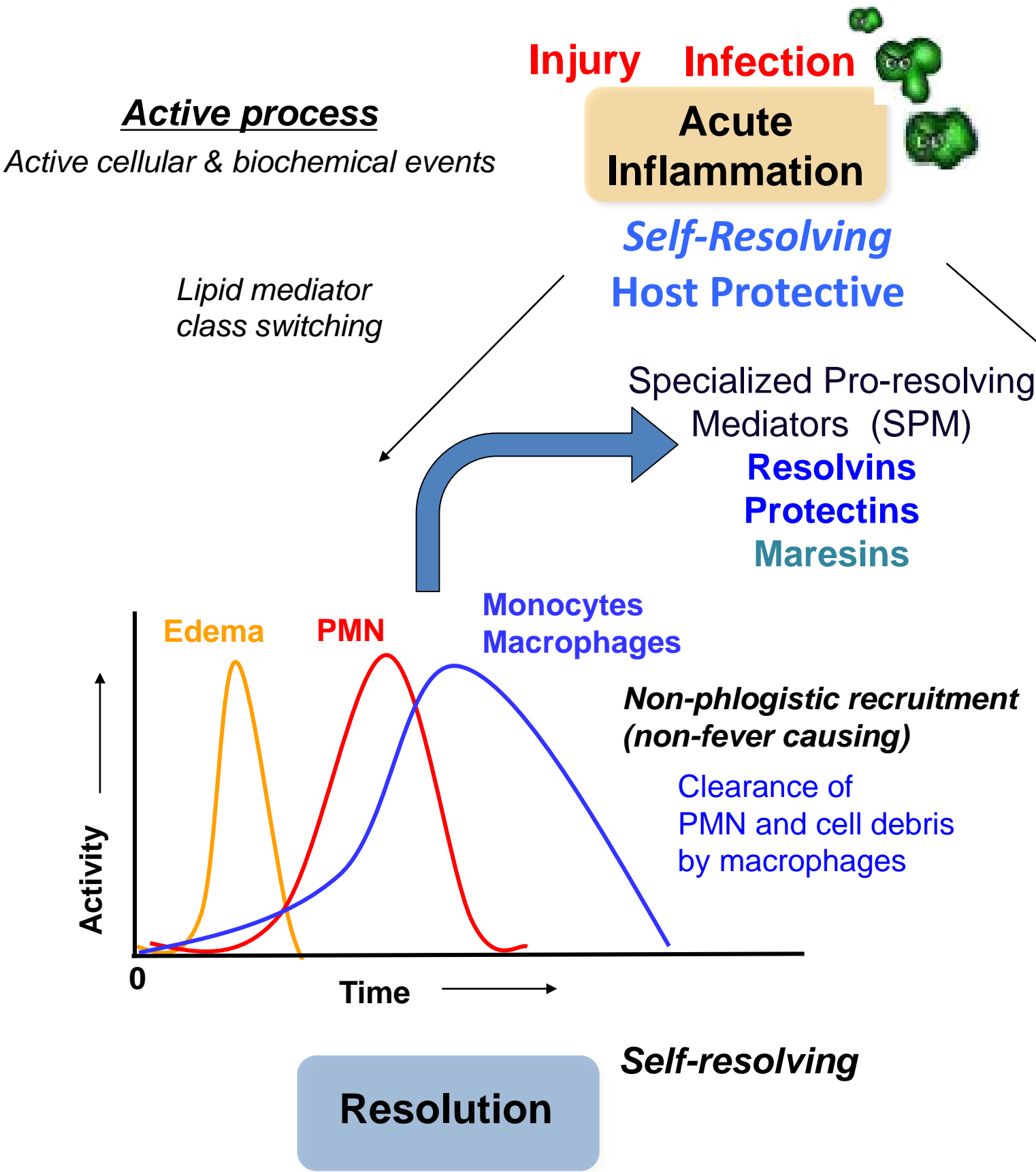
resolution 1. Decomposition; absorption or breaking down of the products of inflammation. 2. Cessation of inflammation without suppuration. The return to normal.

resolvent 1. Promoting disappearance of inflammation. 2. That which causes dispersion of inflammation.

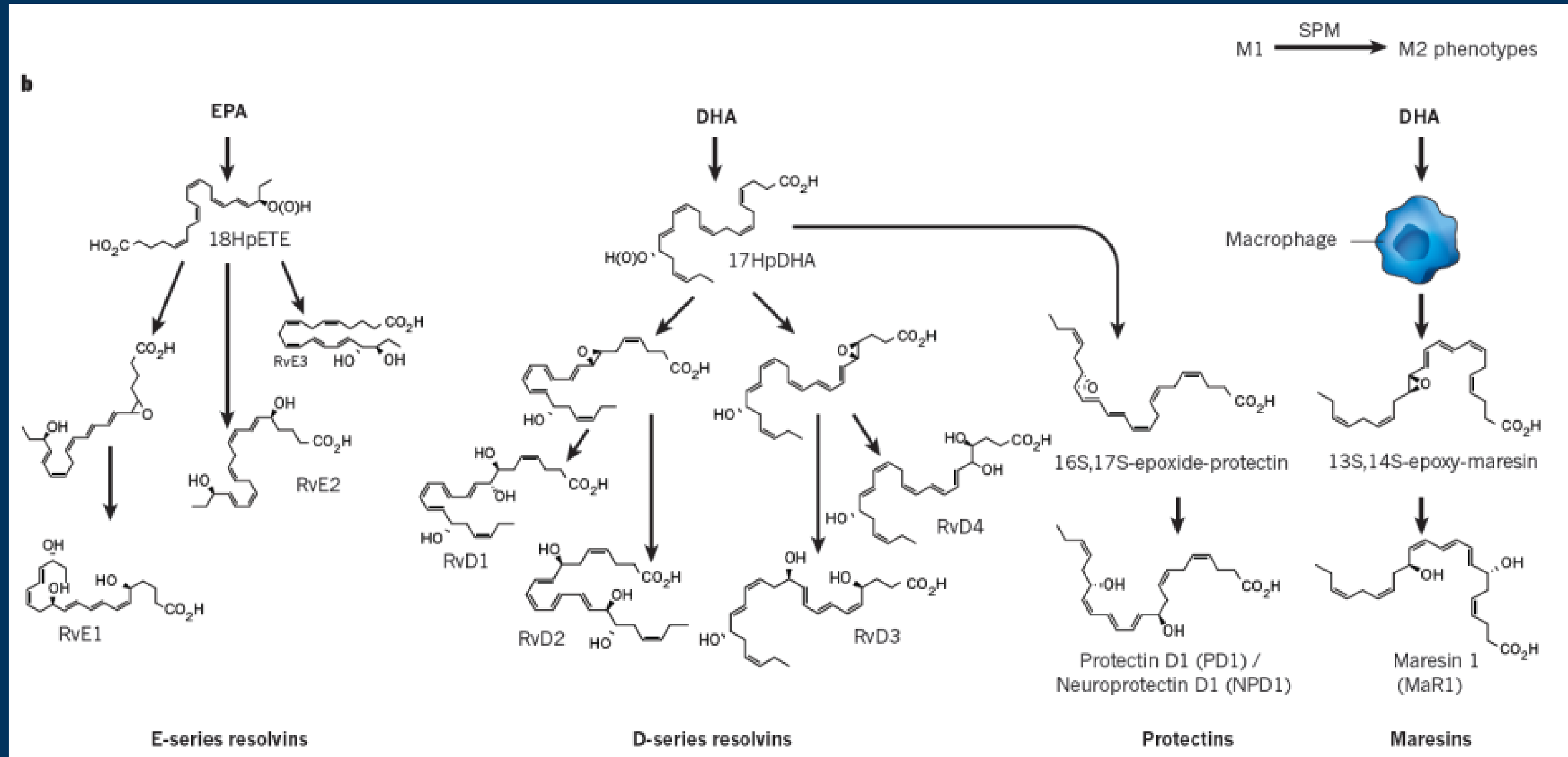
“Immunoresolvent : endogenous mediator or agent that stimulates resolution”

**Serhan, CN
2005**

Resolution of Inflammation vs Prevention of Inflammation



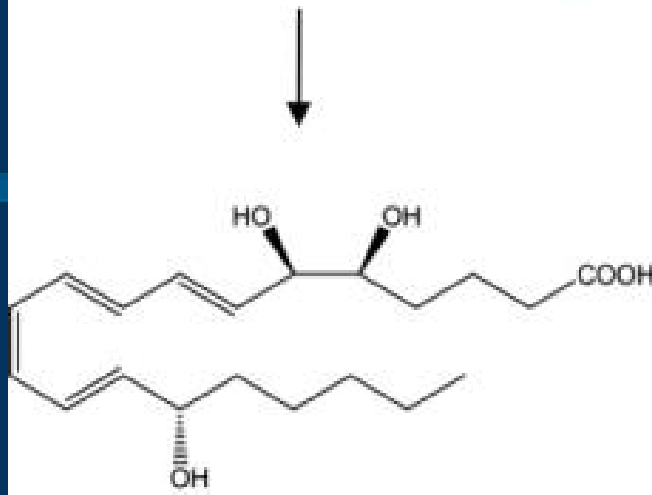
Multiple SPM classes, each with specific end action, may answer some of the questions regarding EPA / DHA variable clinical responses



SPM: Specialized pro-resolving mediators

Serhan C Nature 2014

**Arachidonic acid
(AA)**



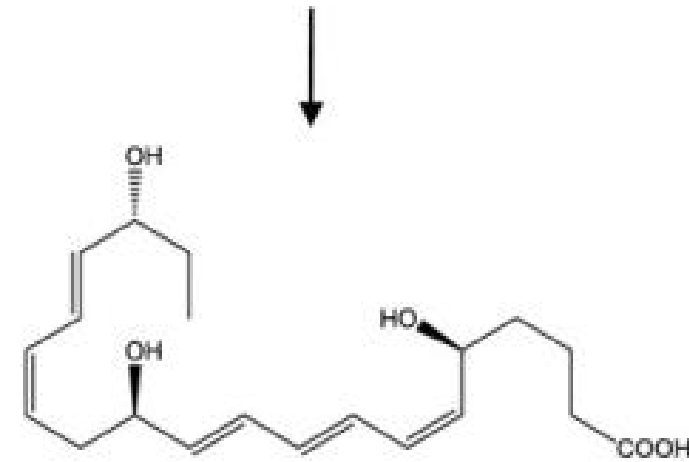
Lipoxin A₄



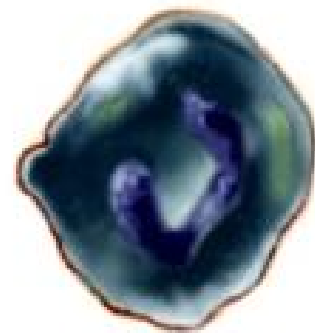
**Monocytes/
Macrophages**

↑ Phagocytosis &
IL-10 production
↓ Pro-inflammatory
cytokines

**Eicosapentaenoic acid
(EPA)**



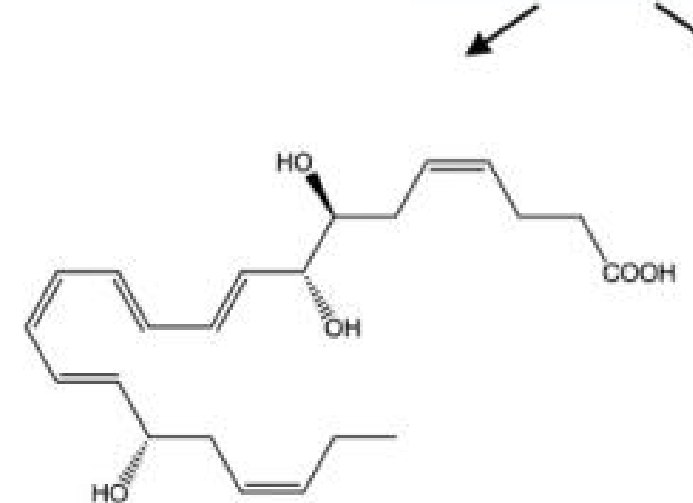
Resolvin E1



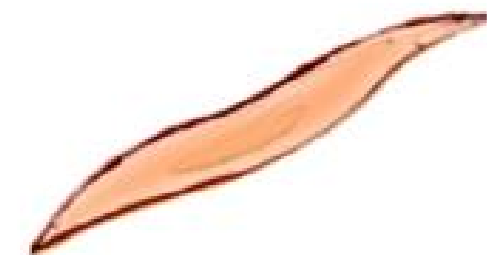
**Neutrophils
(PMN)**

↓ Activation,
Adhesion & ROS
↑ Microbial
clearance

**Docosahexaenoic acid
(DHA)**

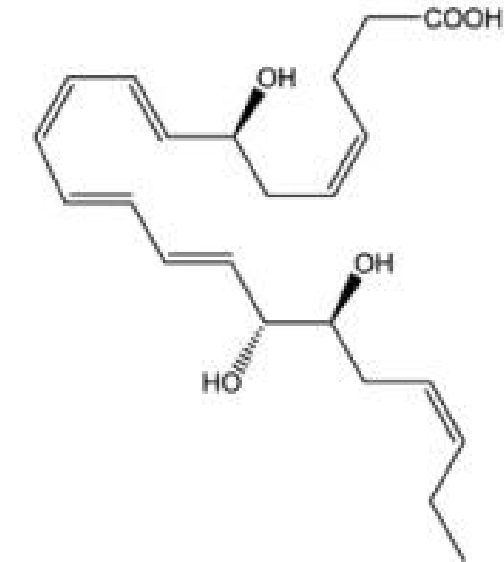


Resolvin D1

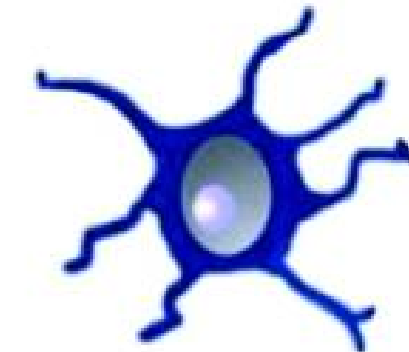


Endothelial cells

↑ Nitric Oxide and Prostacyclin
↓ Adhesion receptors,
ROS generation &
Pro-inflammatory cytokines



Resolvin D2



Dendritic cells

↓ Migration
↓ IL-12 production

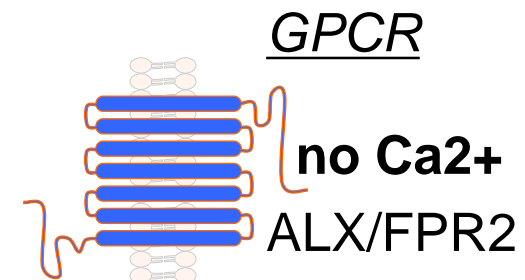
Pro-Resolving Mediators Activate GPCR

Ligand : Agonist

TG mice

KO mice

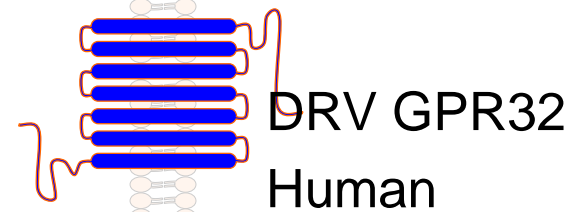
LXA₄,
RvD1, 0.1nM



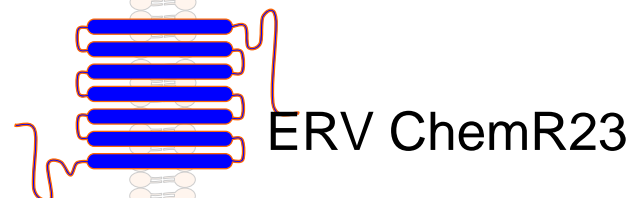
Accelerates
resolution with
LXA₄ and RvD1

RvD1 actions is
abolished

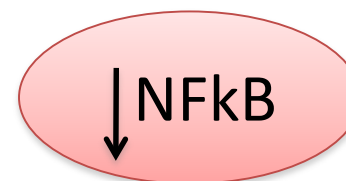
RvD1, RvD3, RvD5
nM



RvE1, RvE2 (partial)
nM

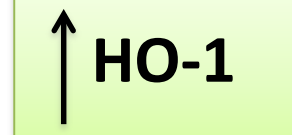
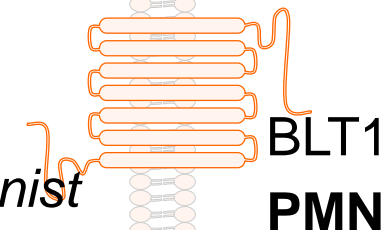


Potentiates RvE1
action in limiting PMN
protecting bone loss



Agonist: LTB₄

Antagonist: Partial Agonist
RvE1, RvE2

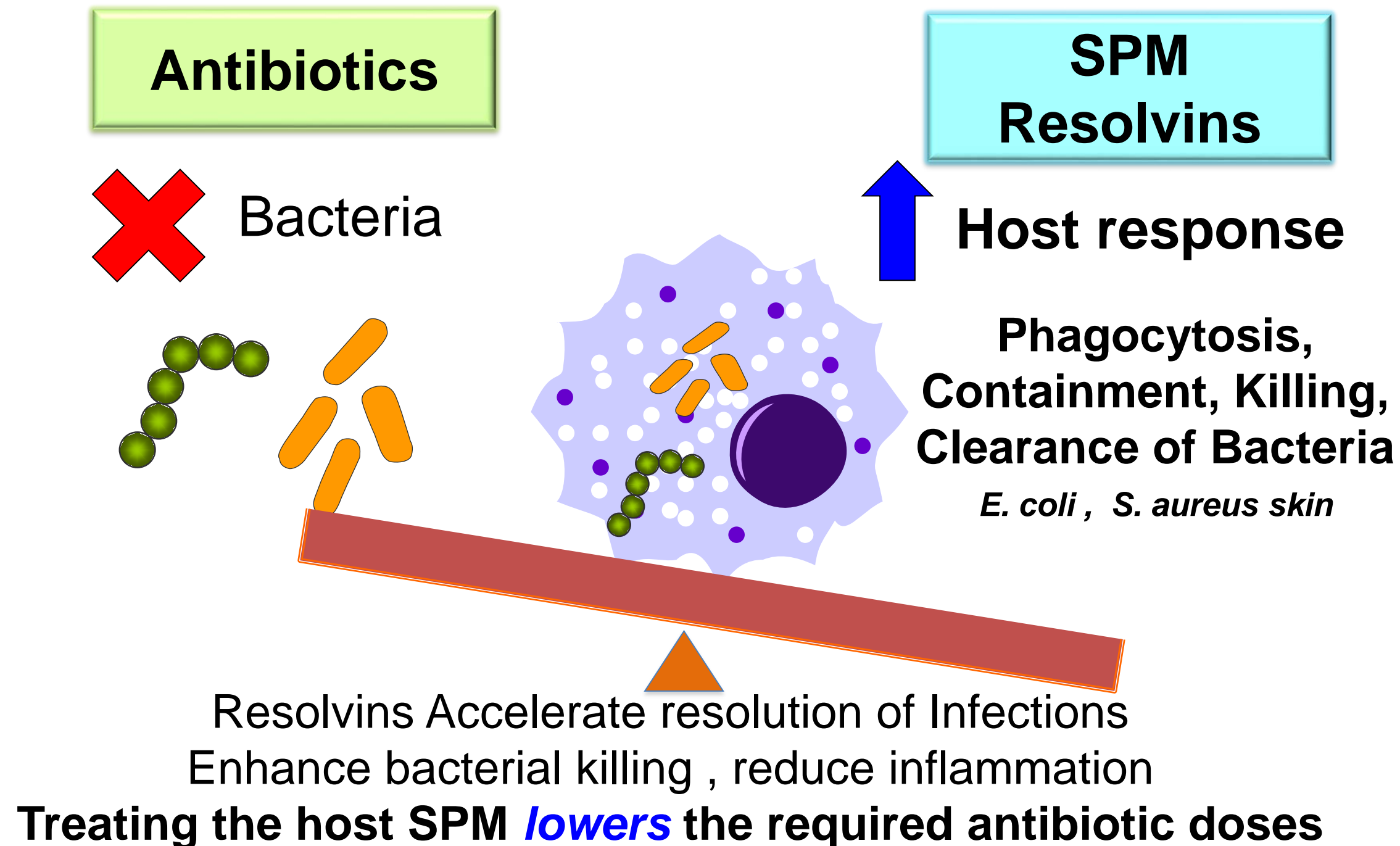


RvE1 regulate
PMN infiltration
& Apoptosis

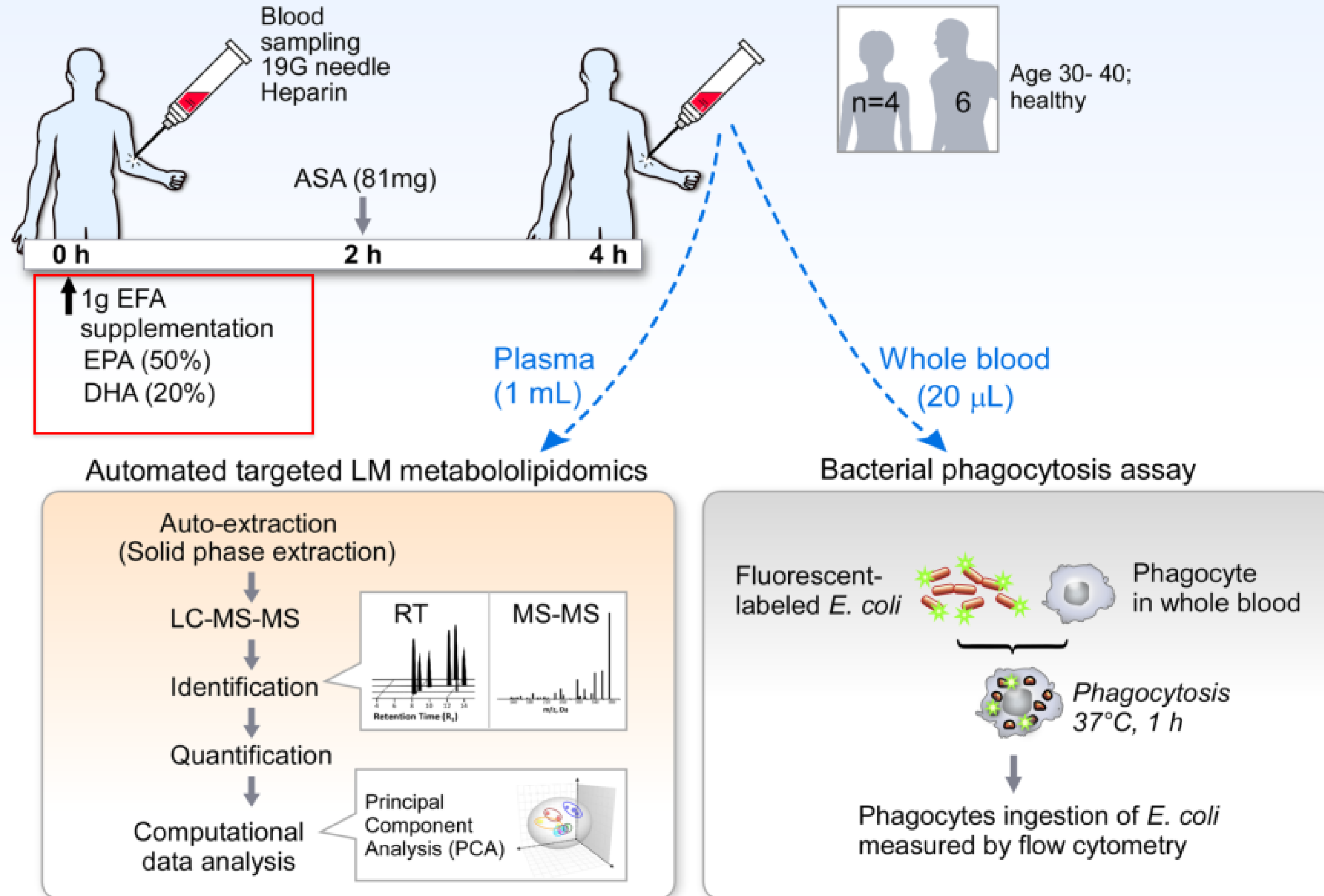
Infection regulates pro-resolving mediators that lower antibiotic requirements

Nature 2012

Nan Chiang¹, Gabrielle Fredman¹, Fredrik Bäckhed², Sungwhan F. Oh¹, Thad Vickery¹, Birgitta A. Schmidt¹ & Charles N. Serhan¹



Demonstration : Human SPM Production & Assessment of Function



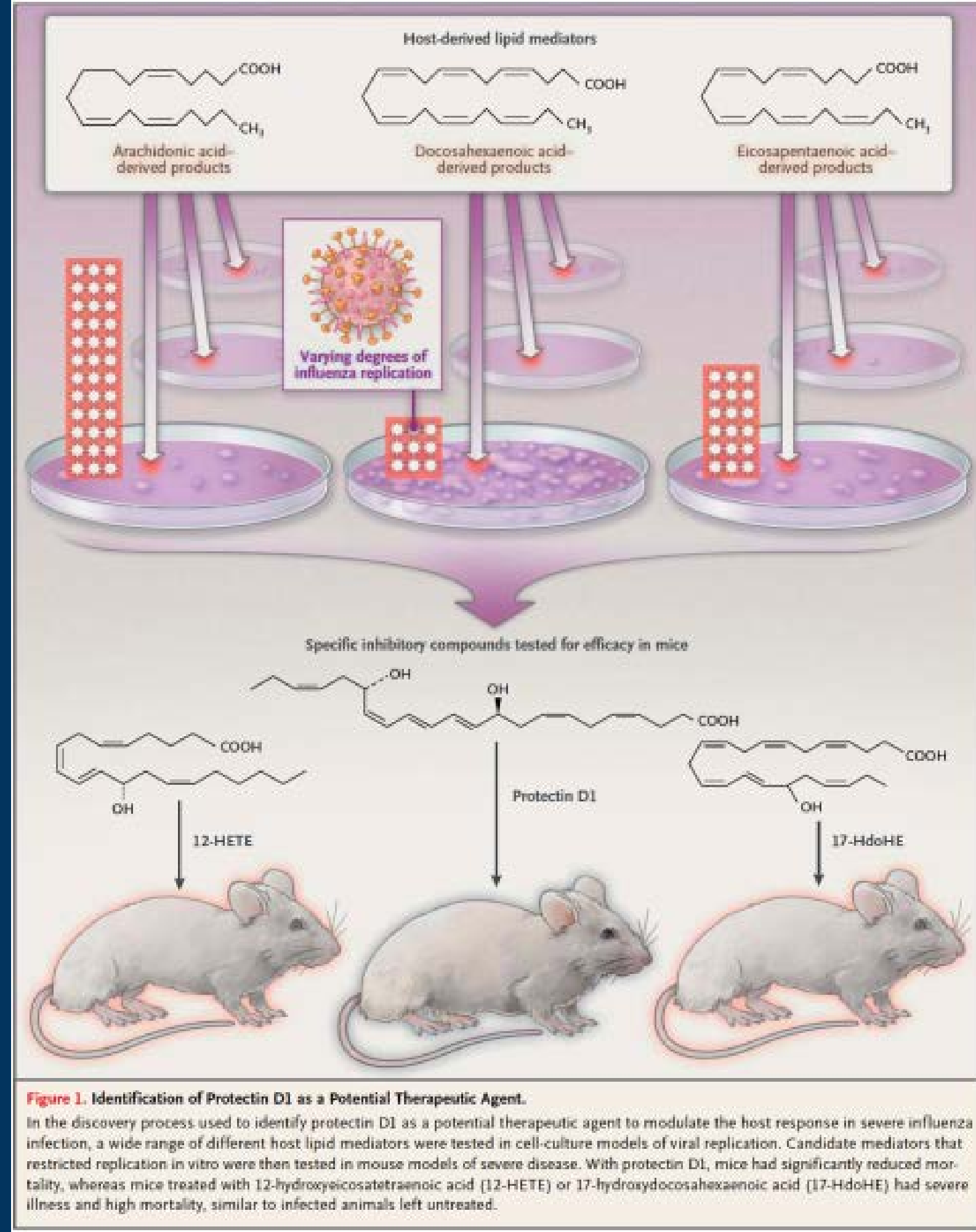
CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Primister, Ph.D., Editor

Influenza — Time to Target the Host?

J. Kenneth Baillie, M.D., Ph.D., and Paul Digard, Ph.D.

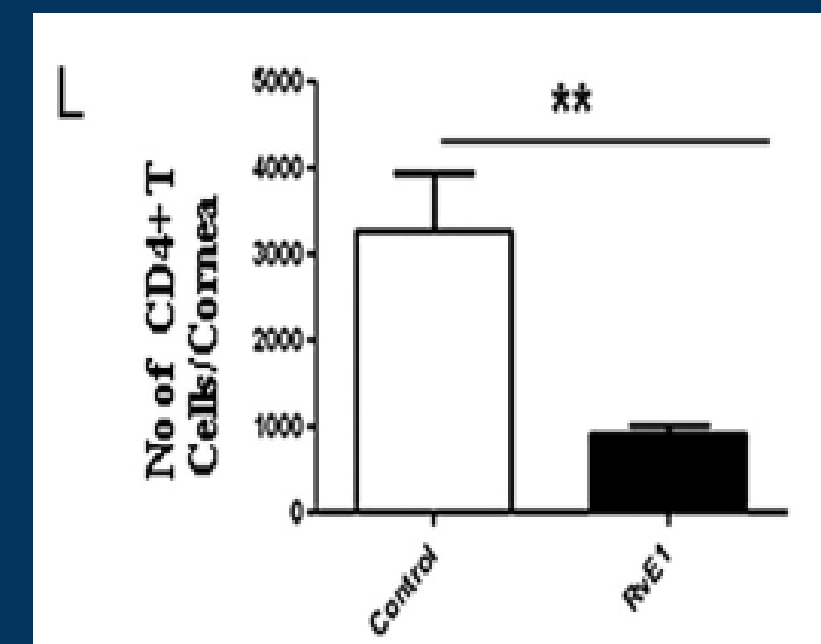
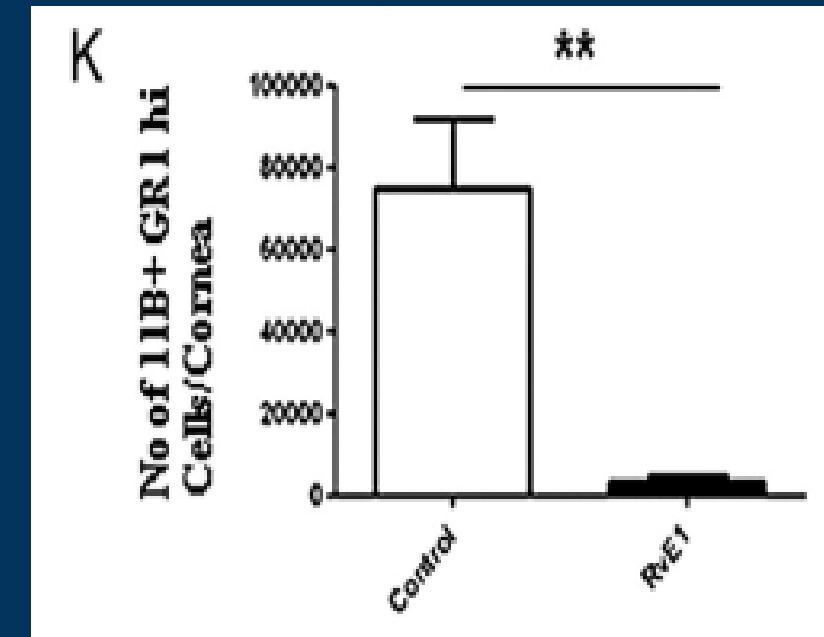
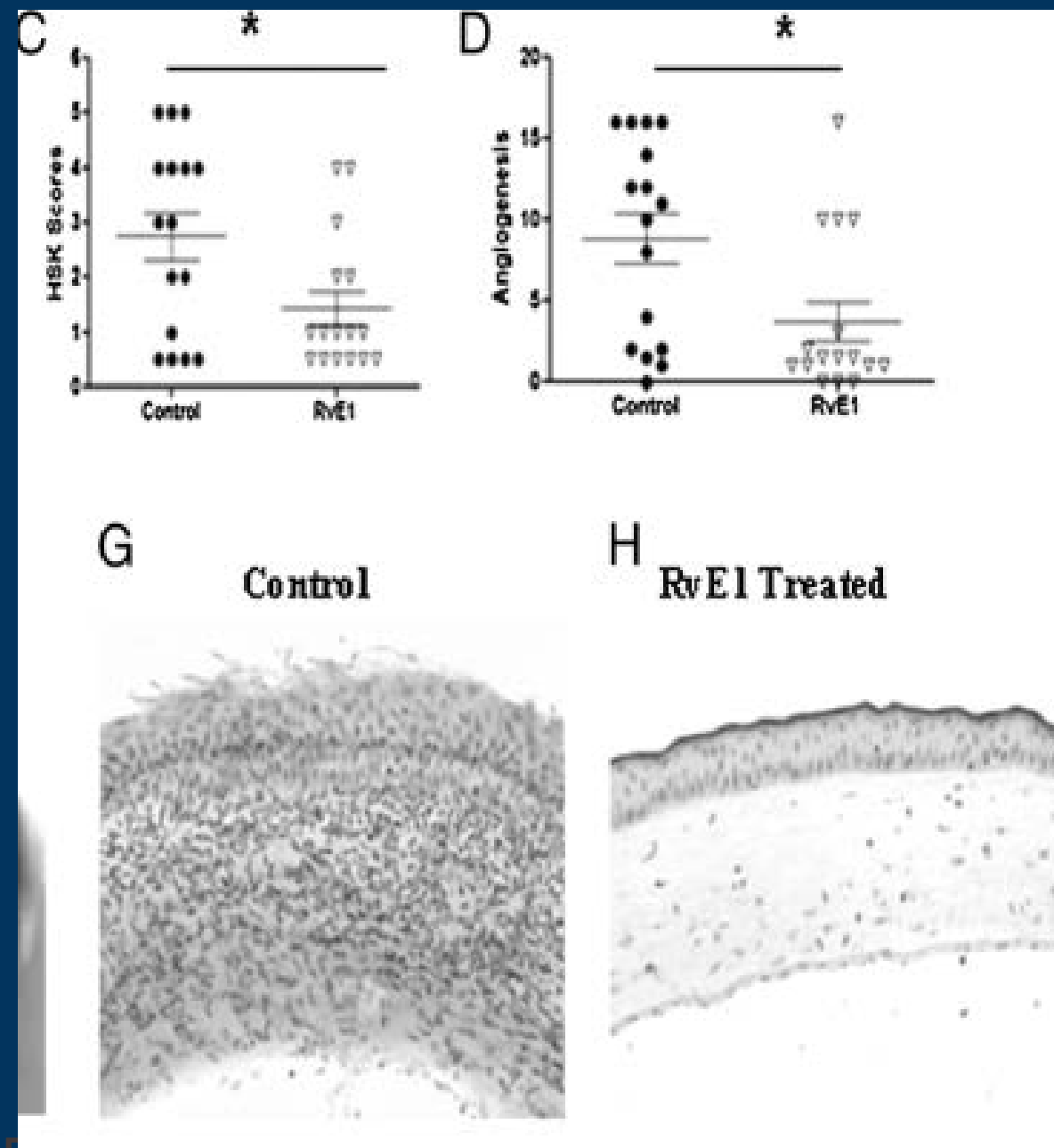
Several Resolvins lower mortality in viral illness



Baillie JK et al NEJM 2013

Controlling Herpes Simplex Virus-Induced Ocular Inflammatory Lesions with the Lipid-Derived Mediator Resolvin E1

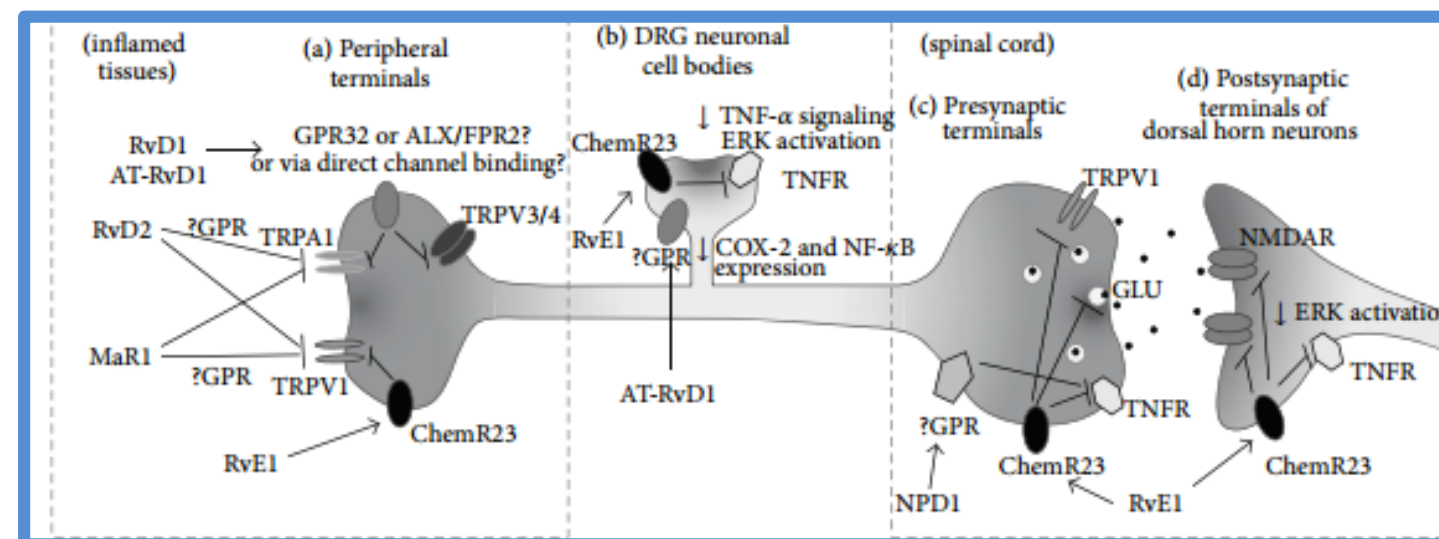
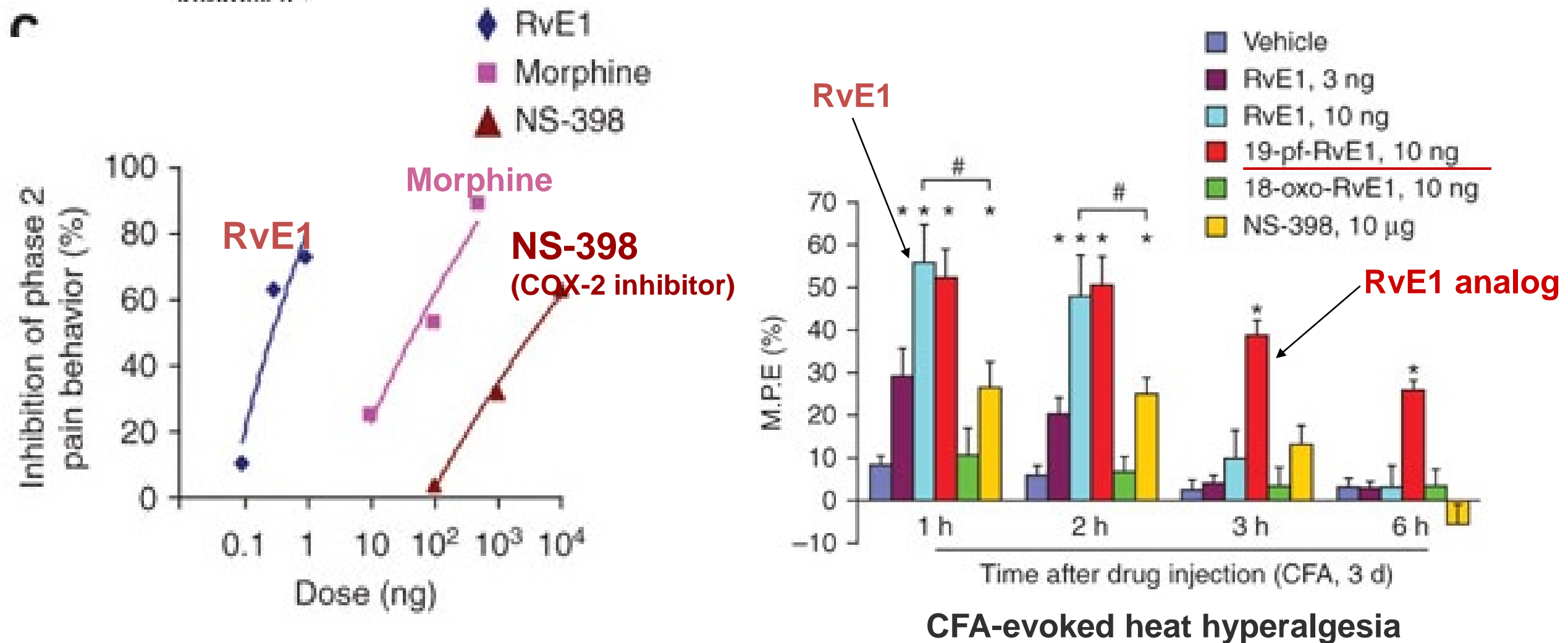
Naveen K. Rajasagi,* Pradeep B. J. Reddy,* Amol Suryawanshi,* Sachin Mulik,* Per Gjorstrup,[†] and Barry T. Rouse*



RvE1 500 ng/eye, twice daily from day 0 until day 10

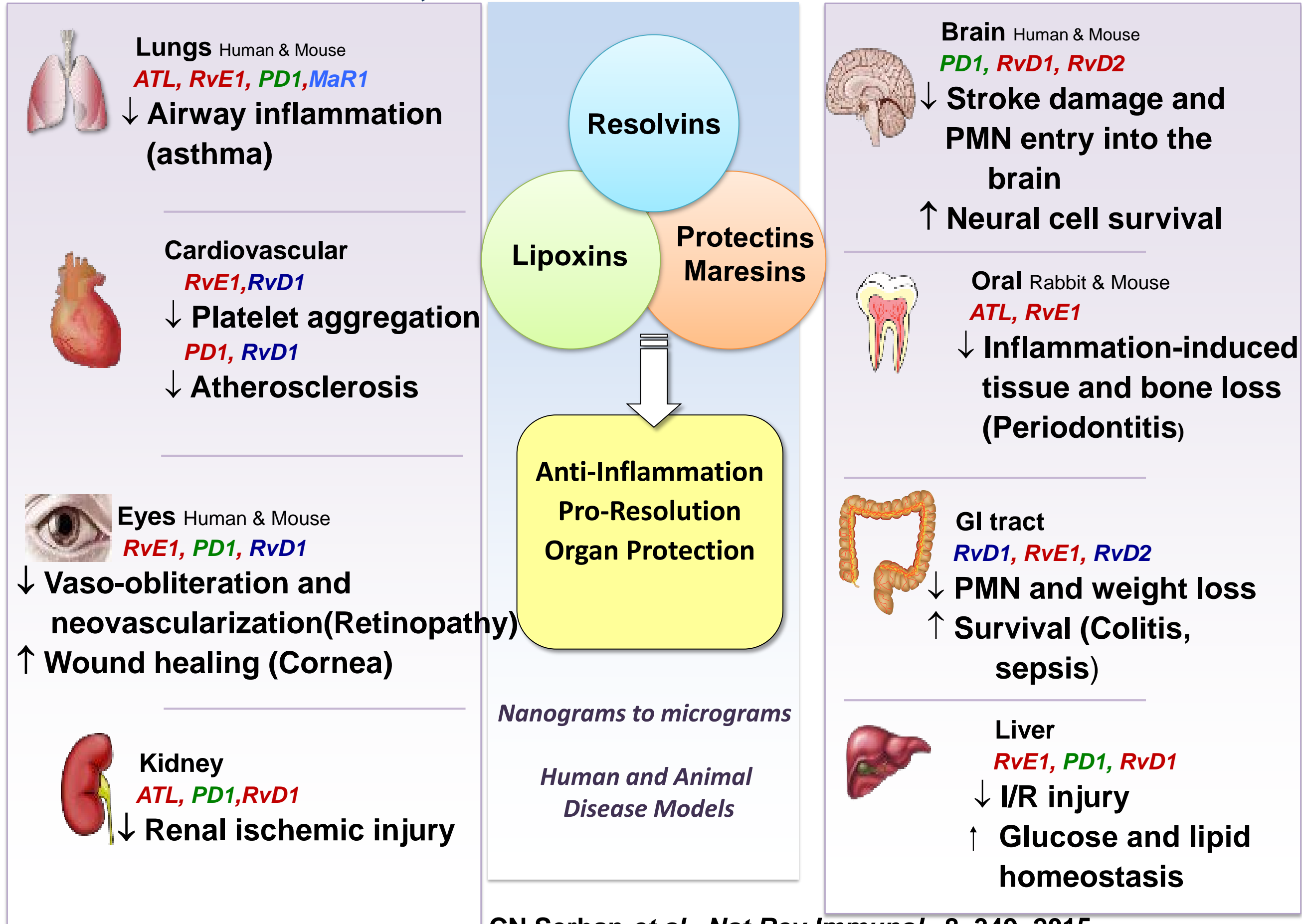
Resolvins RvE1 and RvD1 attenuate inflammatory pain via central and peripheral actions

Zhen-Zhong Xu^{1,3}, Ling Zhang^{1,3}, Tong Liu¹, Jong Yeon Park¹, Temugin Berta¹, Rong Yang², Charles N Serhan^{2,3} & Rui-Rong Ji^{1,3}

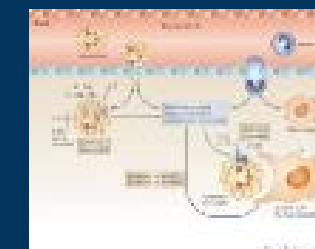


Pain resolution ?

SPM : Resolvins, Protectins and Maresins in Disease



Resolvins, Lipoxins, Protectins, Maresins (SPM's)



- Endogenous mediators generated from ω -3 PUFA's that promote the active resolution of inflammation
- Each SPM is a unique structure possessing precise stereochemistry that is essential for its biological activity
- SPM's exert pro-resolving actions in physiologic (picomolar-nanomolar) dose ranges and have multiple cellular targets, including:
 - neutrophils, macrophages, dendritic cells,
 - vascular smooth muscle cells, and endothelial
- Primary mechanism of action of SPMs is to promote non-inflammatory efferocytosis (apoptotic cell removal)

SPM = Specialized pro-resolving mediators

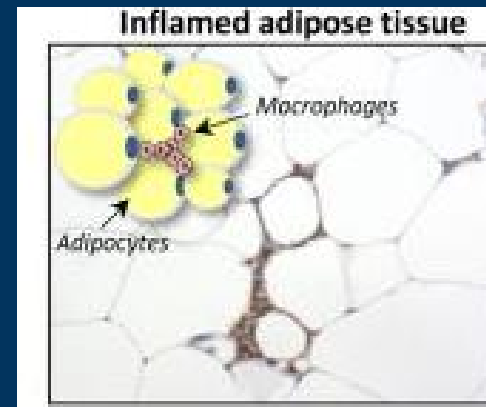
- Zhang MJ et al Ann Rev Nutr 2012
- Serhan C Nature 2014

What current data is available to support clinical use ?

Acute Inflammation

- **Sepsis**
 - Spite et al. Nature, 2009
- **Infections**
 - **Bacterial**
 - Chiang N et al Nature 2012
 - **Virus**
 - Baille J et NEJM 2013
 - **Other**
- **Stroke**
 - Marcheselli et al JBC 2003
- **Trauma**
 - Orr SK et al Critical Care Med 2015
- **Surgery**
- **Acute pain**
 - Xu Z et al Nature Med 2010
 - Lim JY et al Biomed Res 2015

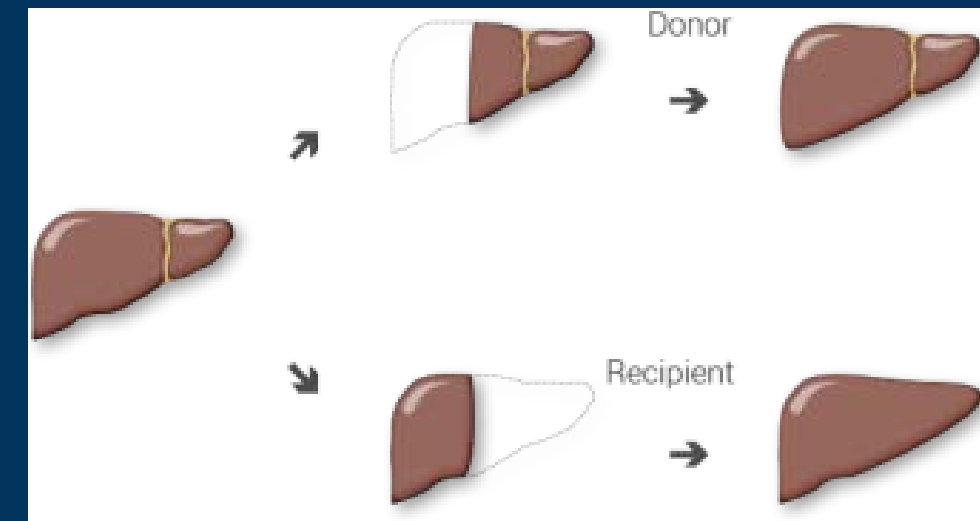
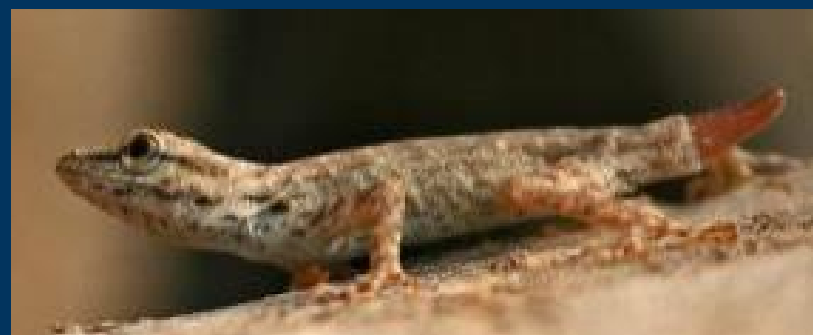
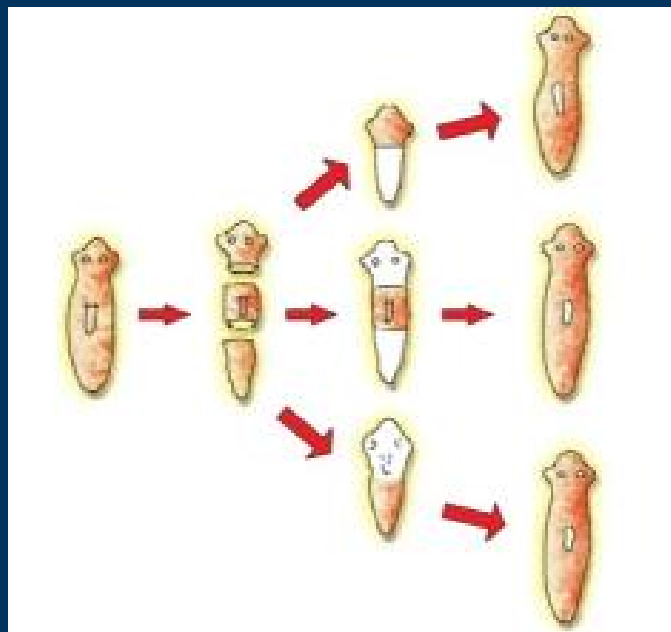
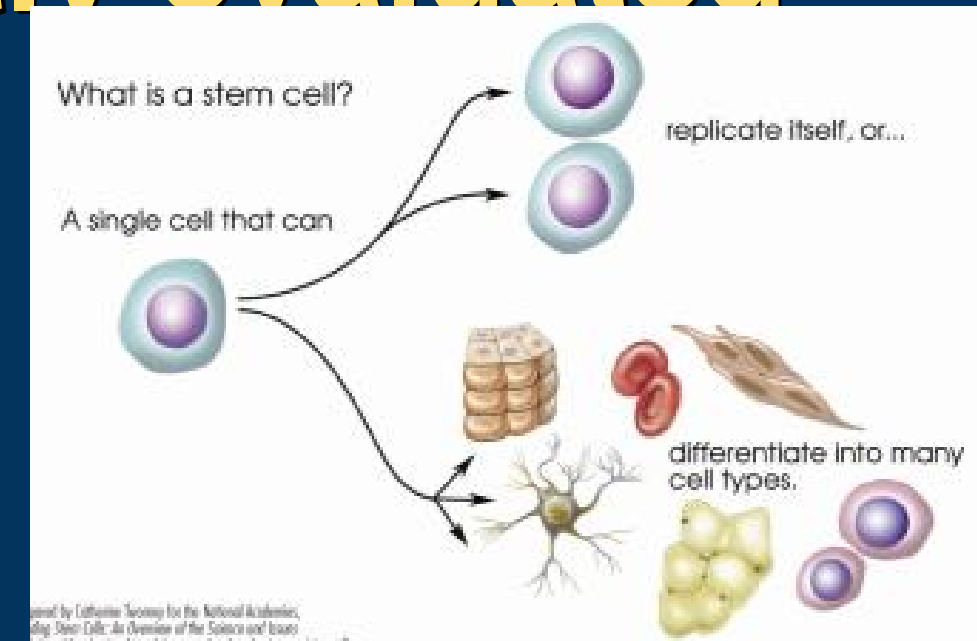
Chronic



- **Asthma**
 - Levy et al. Nature Med. 2002
- **Atherosclerosis**
- **Retinal angiogenesis**
 - Behl T et al Prostaglandins Lipid Med 2016
- **Obesity**
 - Claria et al. J. Immunology, 2012
- **Metabolic syndrome**
 - Barden AE et al Am J Clin Nutr 2015
- **Alzheimer's Disease**
 - Wang X Alzheimers Dementia 2015
- **Periodontitis**
 - Cianci E et al Stem Cells Transplantation 2016
- **Rheumatologic disorders**
 - Headland SE et al Seminar Immunology 2015
- **IBD**
 - Corminboeuf O et al J Med Chem 2015

Other areas for SPM's recently evaluated

- **Stem cells**
 - Das UN et al Nutrition 2011
 - Cianci E et al Stem Cells Trans Med 2016
- **Tissue regeneration**
 - Schlegel M et al Hepatology 2015



Conclusions

Resolution is an *active* process

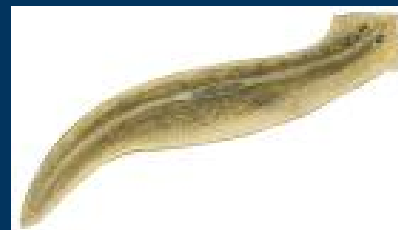
Anti-inflammation is not equivalent to Pro-resolution

•

SPM's

Lipid compounds Isolated in many human tissue during inflammation

- 1) Chemically synthesized in lab and in vivo
- 2) Injected into humans at physiologic doses
- 3) Inflammation resolves faster – mimics natural healing
- 4) Prevents transition to chronic inflammation
- 5) Increases bacterial and viral killing, decreases need antibiotics
- 6) In some tissues stimulates “regeneration”



Summary and Conclusion



- Current “fish oil” literature remains a bit confusing
- Where can the routine use be supported:
 - Preventing or resolving chronic inflammation
 - Surgical ICU setting:
 - Favorable modulation of inflammatory response shows consistent decrease in LOS, ICU days
 - » TBI, hepatic steatosis, trauma, major surgery
- SPM physiology offer some explanation for the current confusion in the “clinical science” of fish oils
- Where can SPM’s be expected to show benefit :
 - Limitless potential

