“Preventing Collateral Damage” Clinical Relevance of SPM’s

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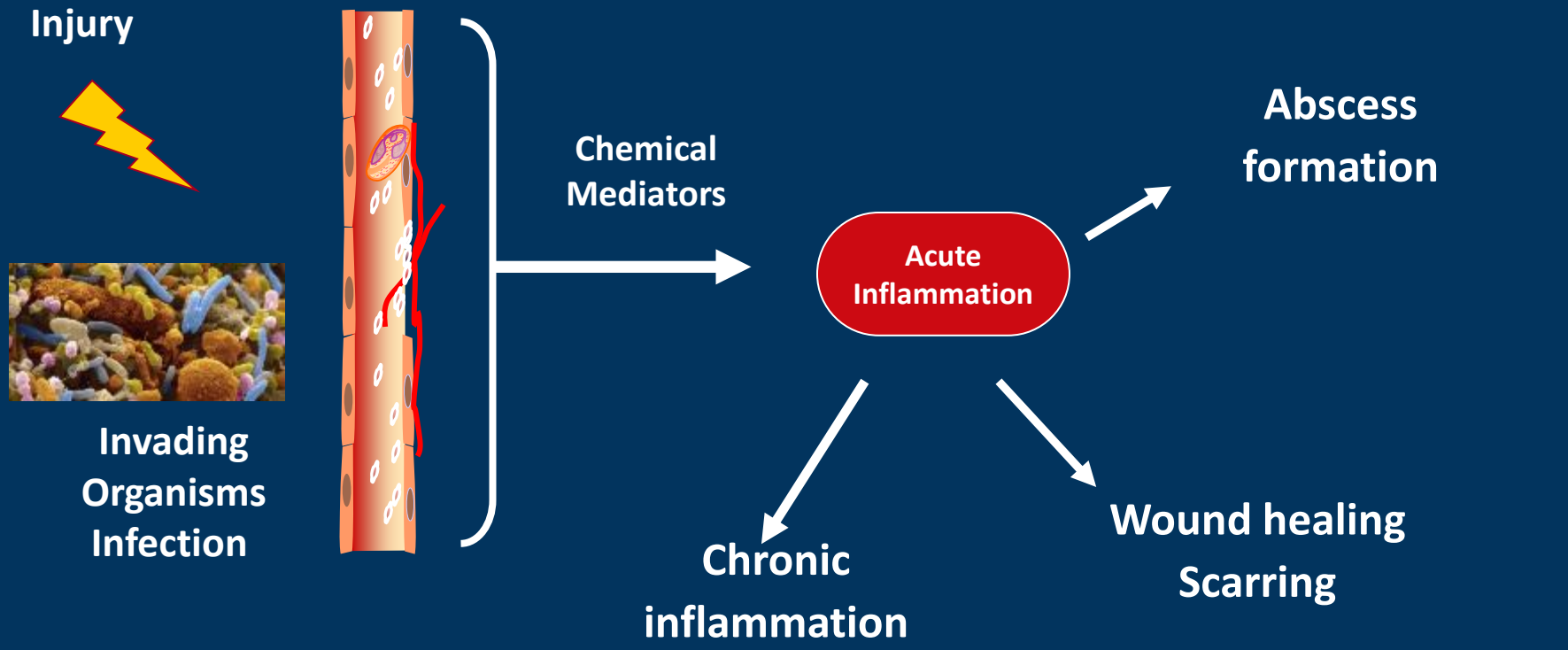
Acute and Chronic Inflammation

We have been lost in trying to prevent inflammation

we forgot resolution inflammation

Acute or Chronic Inflammation



Modified from;CN Serhan, *Am J Pathology* 2010

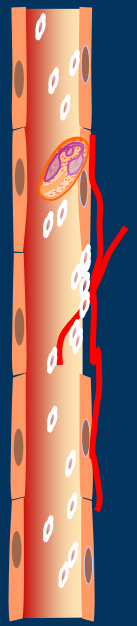
Acute, Chronic, or Resolution of Inflammation

Previously considered passive process ??

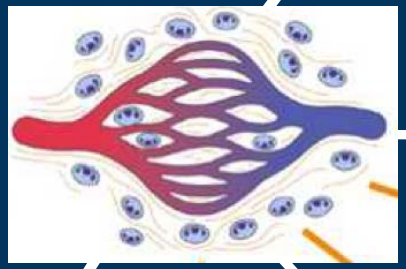
Injury

Resolution

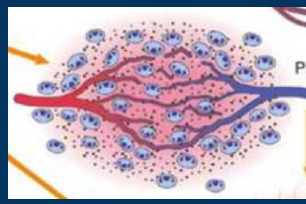
Invading Organisms Infection



Chemical Mediators



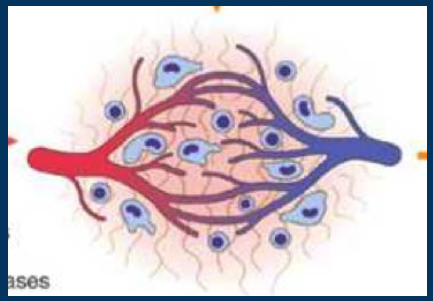
Abscess formation



Chronic inflammation

Periodontal disease
Rheumatoid arthritis
Cirrhosis
Valvular heart disease
Atherosclerosis
Etc etc etc

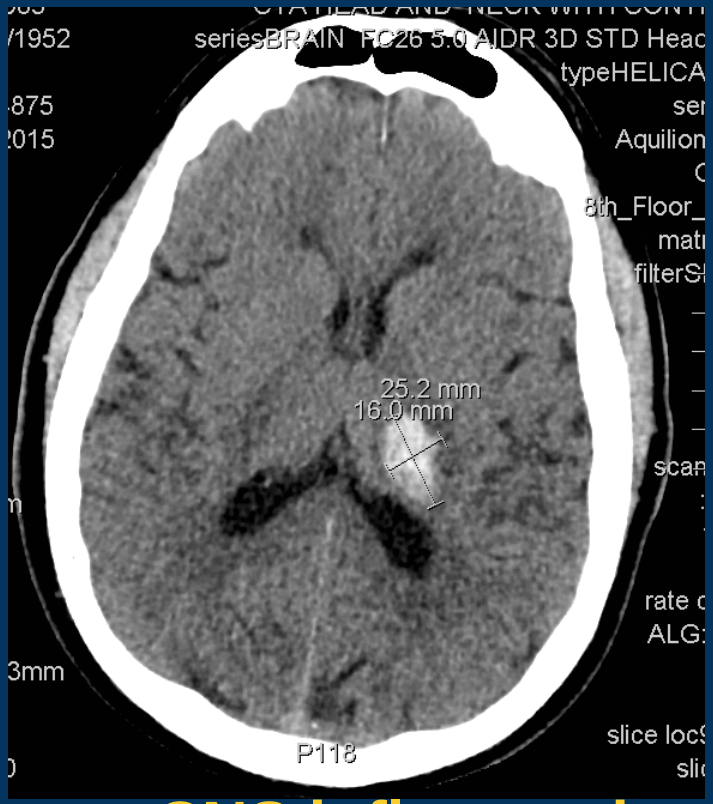
Wound healing Scarring

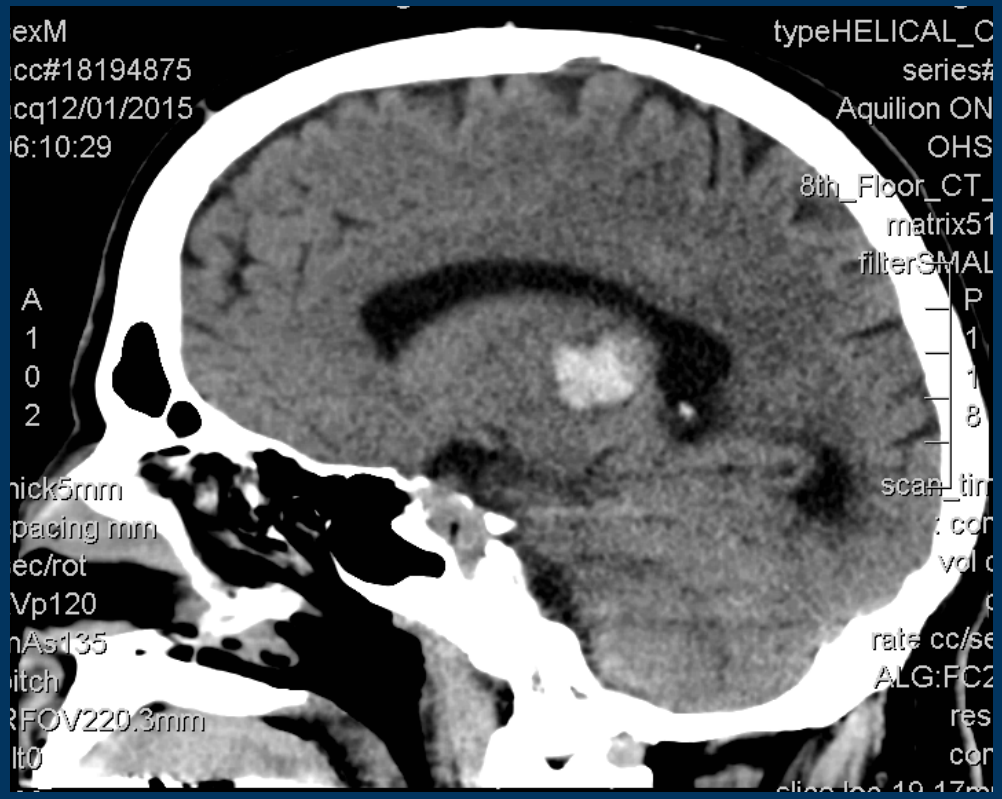


Modified from;CN Serhan, *Am J Pathology* 2010

Case study

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

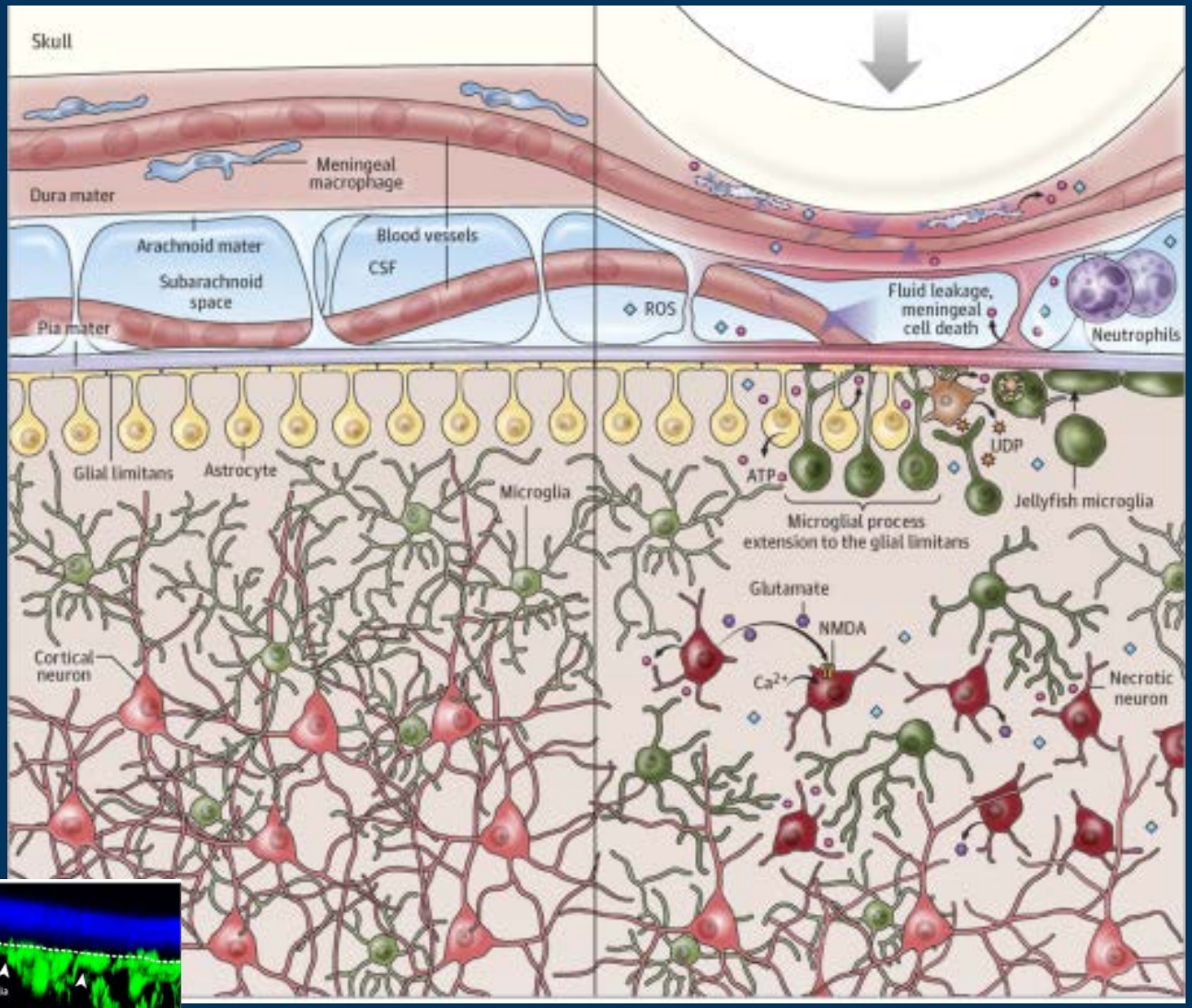


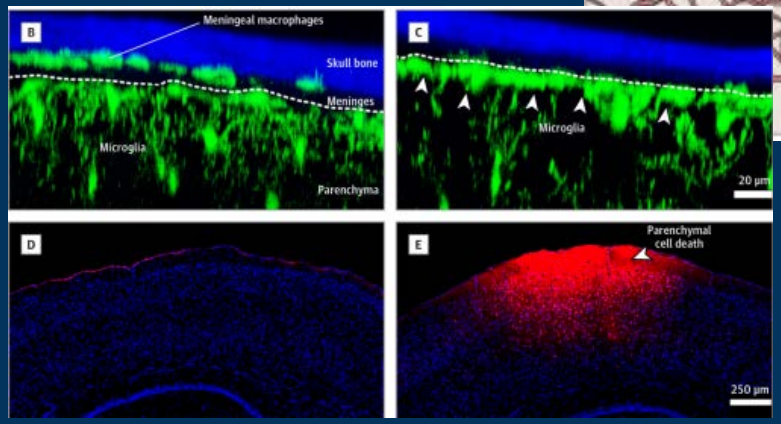


CNS inflammation following bleed is significant.

Now What ?

Inflamed Brain

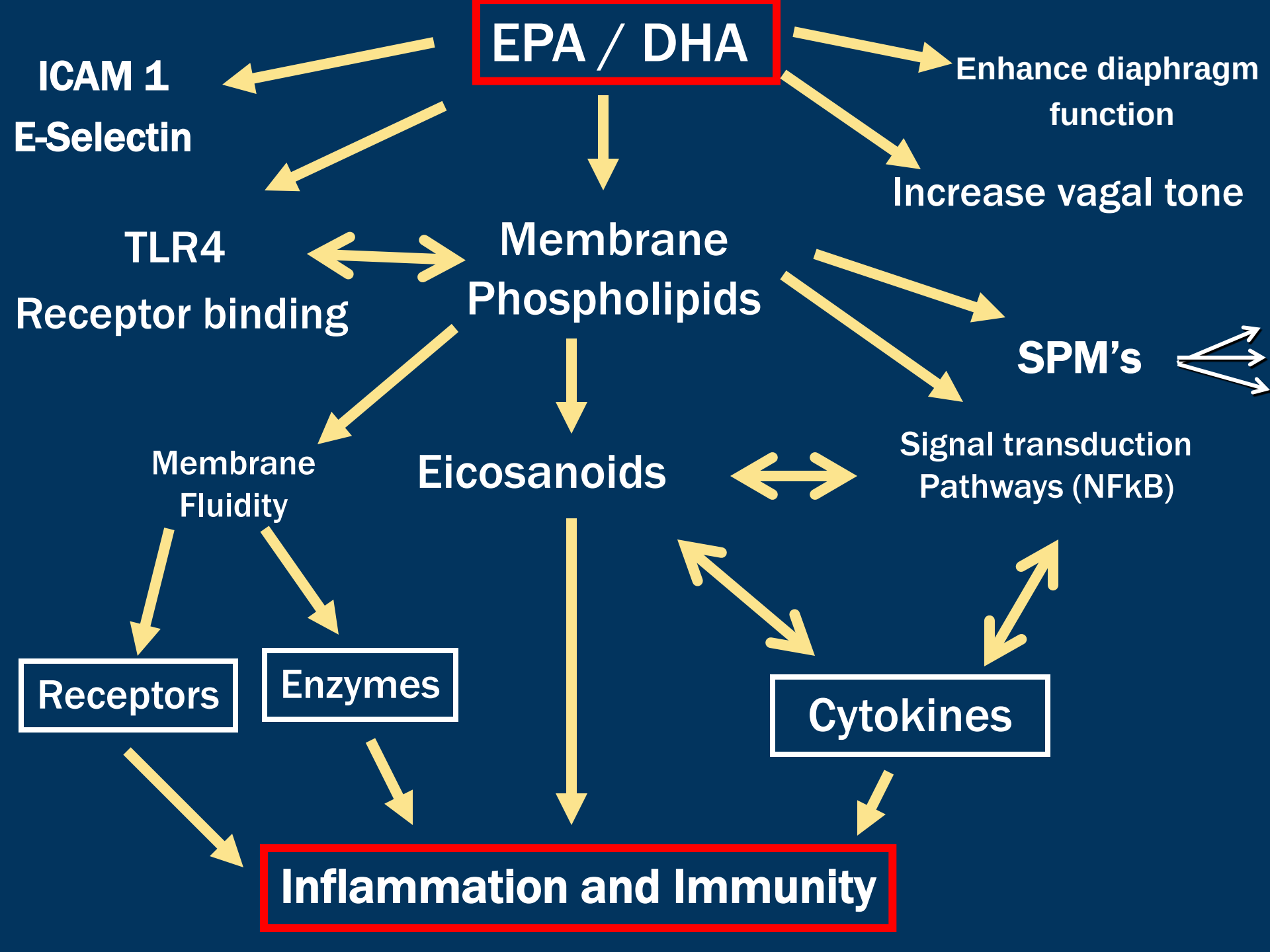




***JAMA –Neurology* 2015**
Inflammation and Neuroprotection

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
- Gaseous mediators
  - NO, CO, H_2S
  - 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


EPA / DHA
ICAM 1
E-Selectin
Enhance diaphragm function
Increase vagal tone
TLR4
Receptor binding
Membrane Phospholipids
SPM's
Membrane Fluidity
Eicosanoids
Signal transduction Pathways (NFkB)
Receptors
Enzymes
Cytokines
Inflammation and Immunity

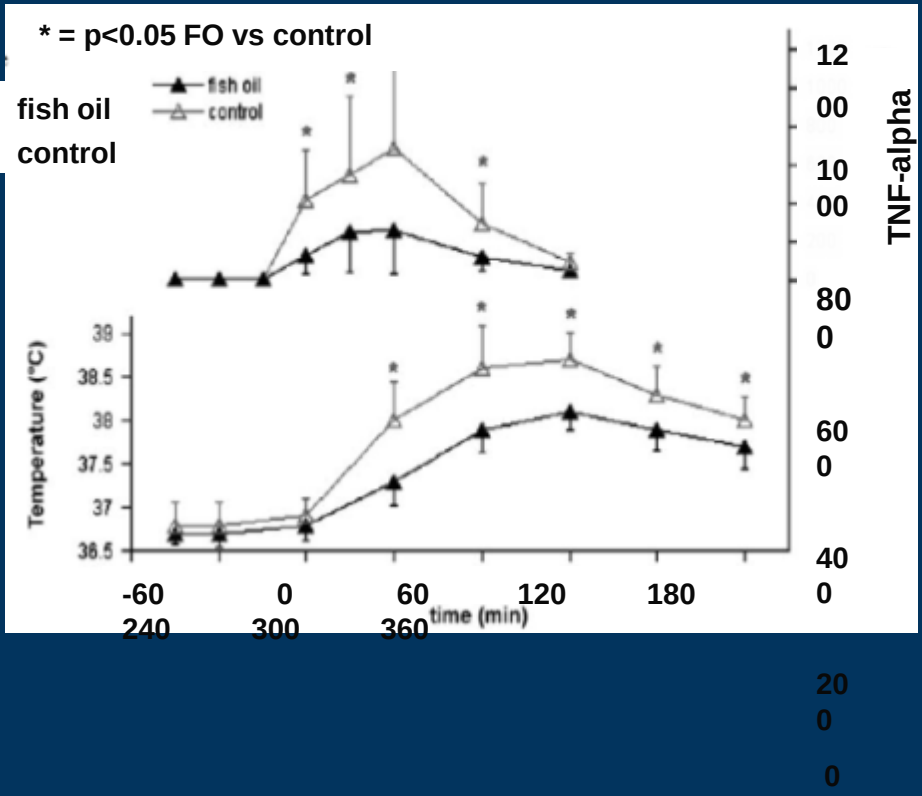
Reported benefits of EPA and DHA in clinical settings

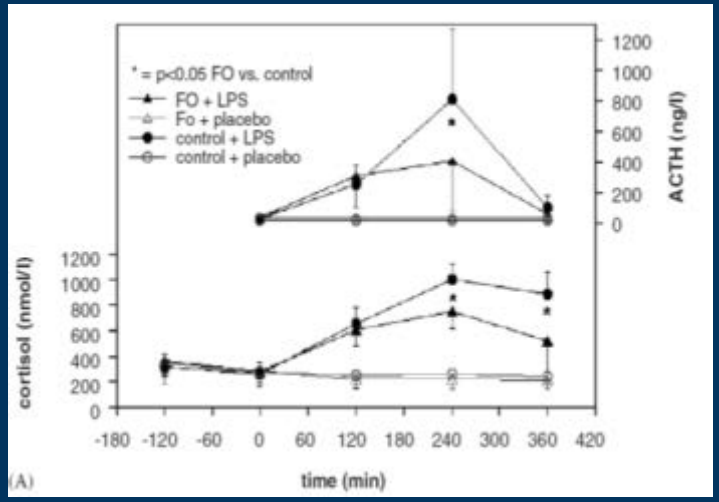
- Cardiovascular Ds
- Cardiac Arrhythmias
- Rheumatoid Arthritis
- Psoriasis
- IBD
- Renal Transplant
- Multiple Sclerosis
- Glucose tolerance
- Lupus
- ARDS
- Cystic Fibrosis
- Psychiatry
  - Depression, suicide
- etc etc etc ……

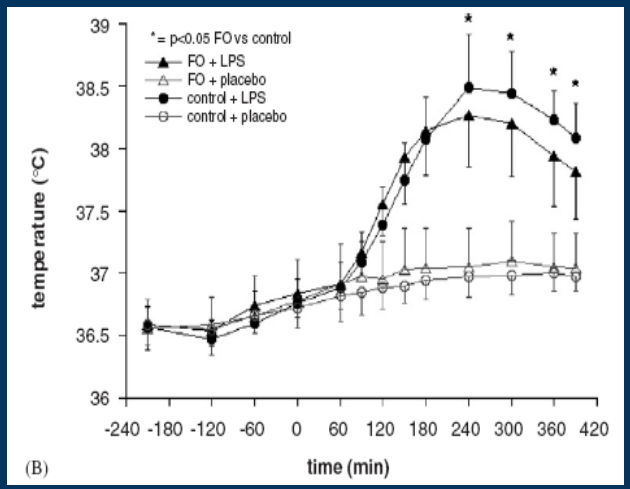
In excess of >4000 clinical trials showing benefits of fish oil or omega 3 fatty acids in clinical medicine !!!

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 trial[1–3]

Am J Clin Nutr 2013

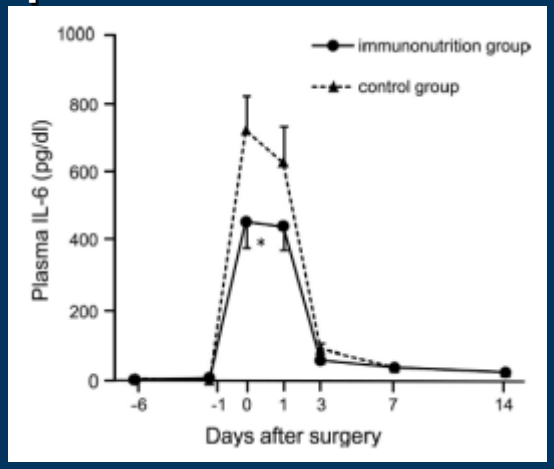
- **PRBCT Evaluation influence of FO infusion in immediate peri-operative period in CABG**
  - **N=28 equal groups**
  - **Three 2 hour infusion with/in 12 pre-op period**
  - **Results: FO showed;**
    - **Pilot study not powered for clinical outcome**
      - **No change in mortality, clinical outcome, 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 E_2 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**

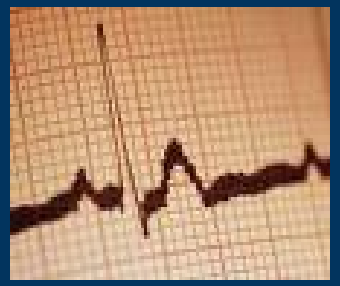


Aida T et al *Surgery* 2014

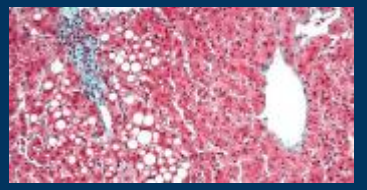
Not all the data is positive or consistent !
Fish Oils use in the ICU / Trauma:
Clinical Outcome Dependent on Several Factors:

- **ARDS / ALI (variable)**
  - Dependent upon;
    - Route of feeding (EN v PN)
    - Bolus versus continuous
    - Background nutrition

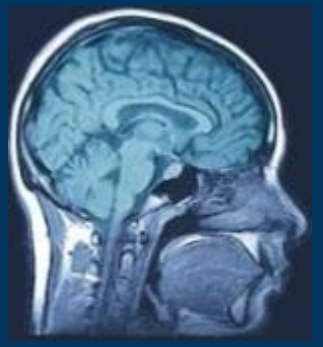
- **Cardiac rhythm stabilization(variable)**
  - Dependent upon
    - Timing of delivery
    - Background cardiac status

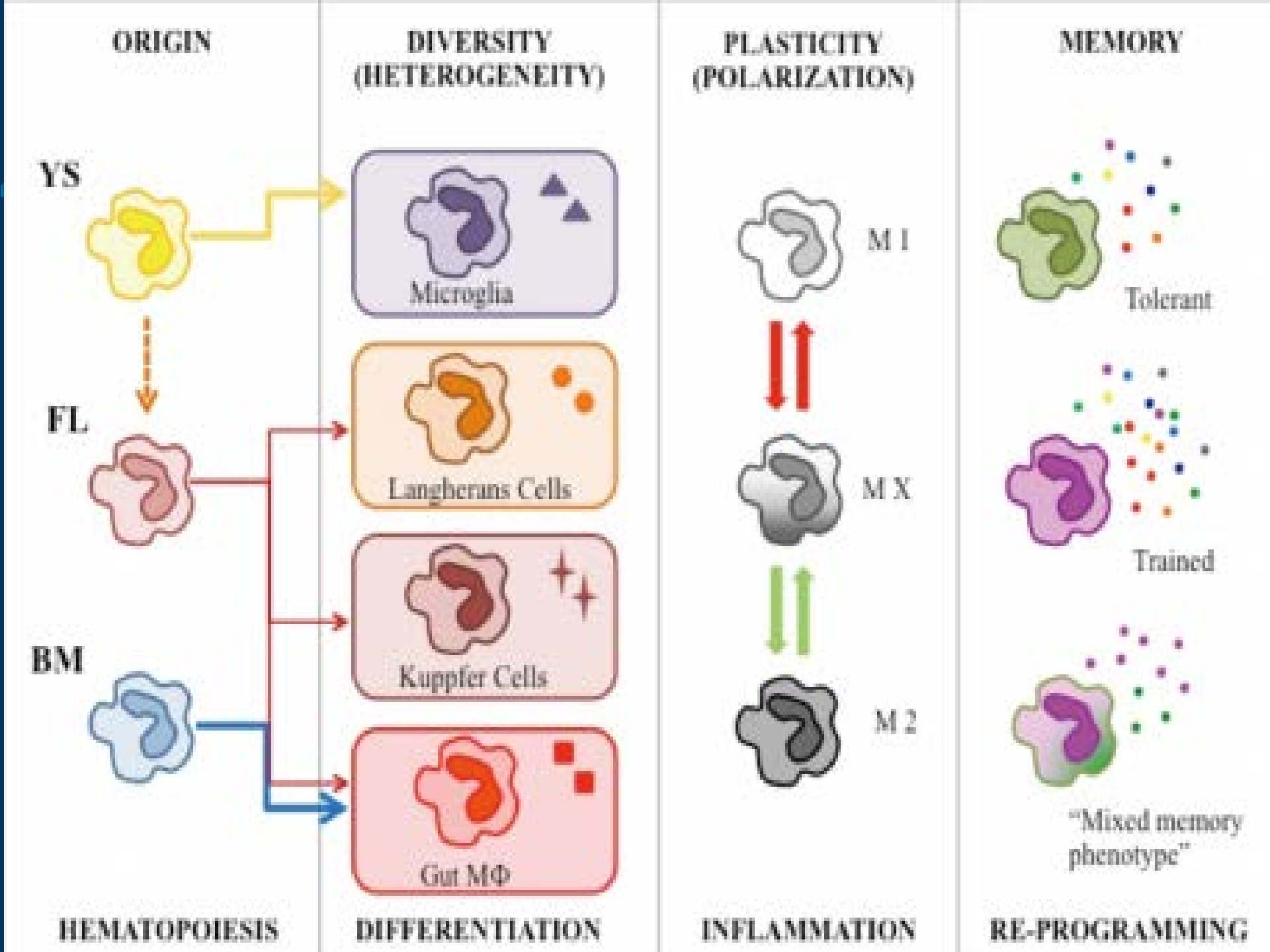


- **Prevention of hepatic steatosis**
  - Anytime



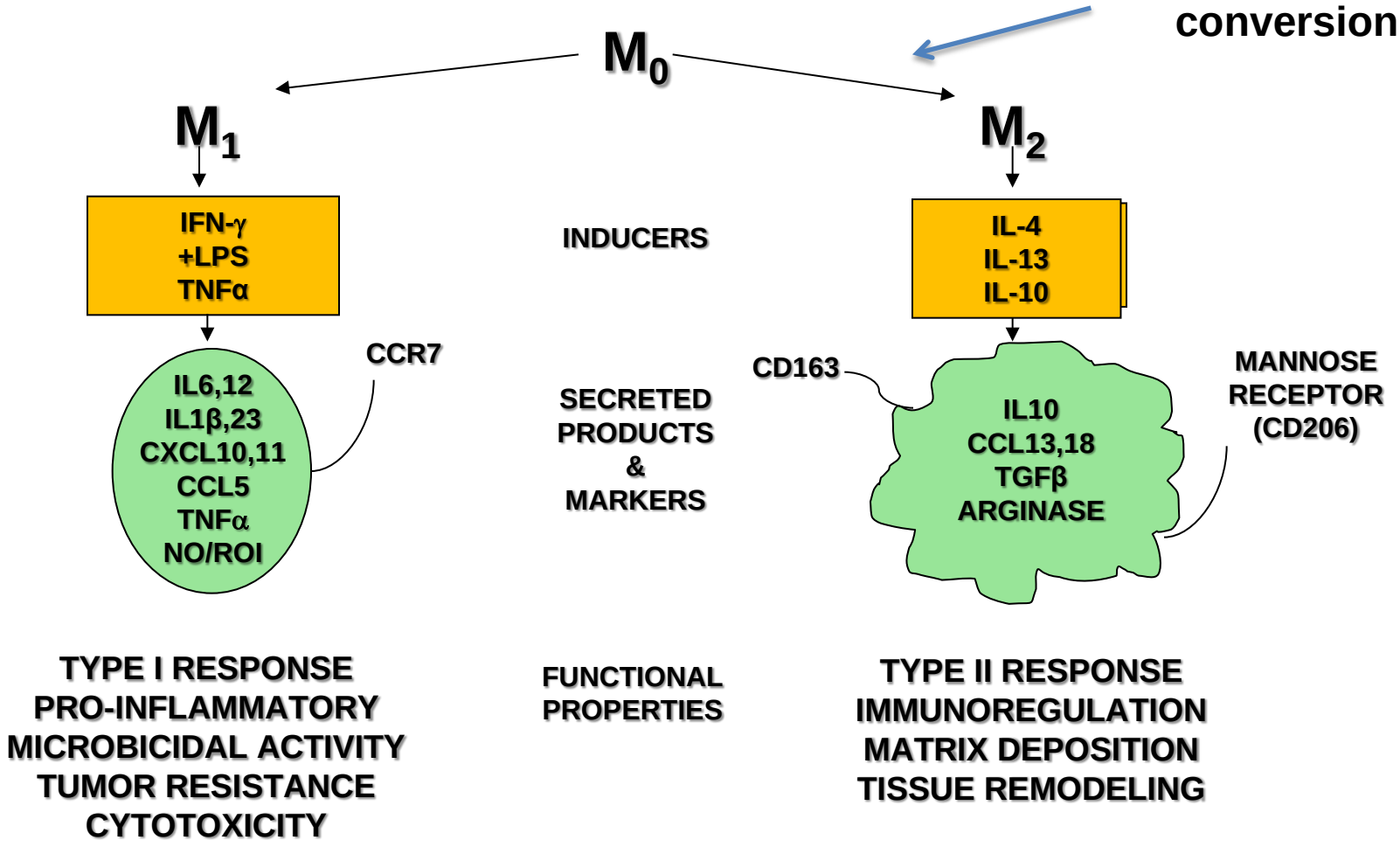
- **Early recovery after traumatic brain injury**
  - Well developed in animal studies
  - As early as possible following injury
  - Dependent on timing of injury



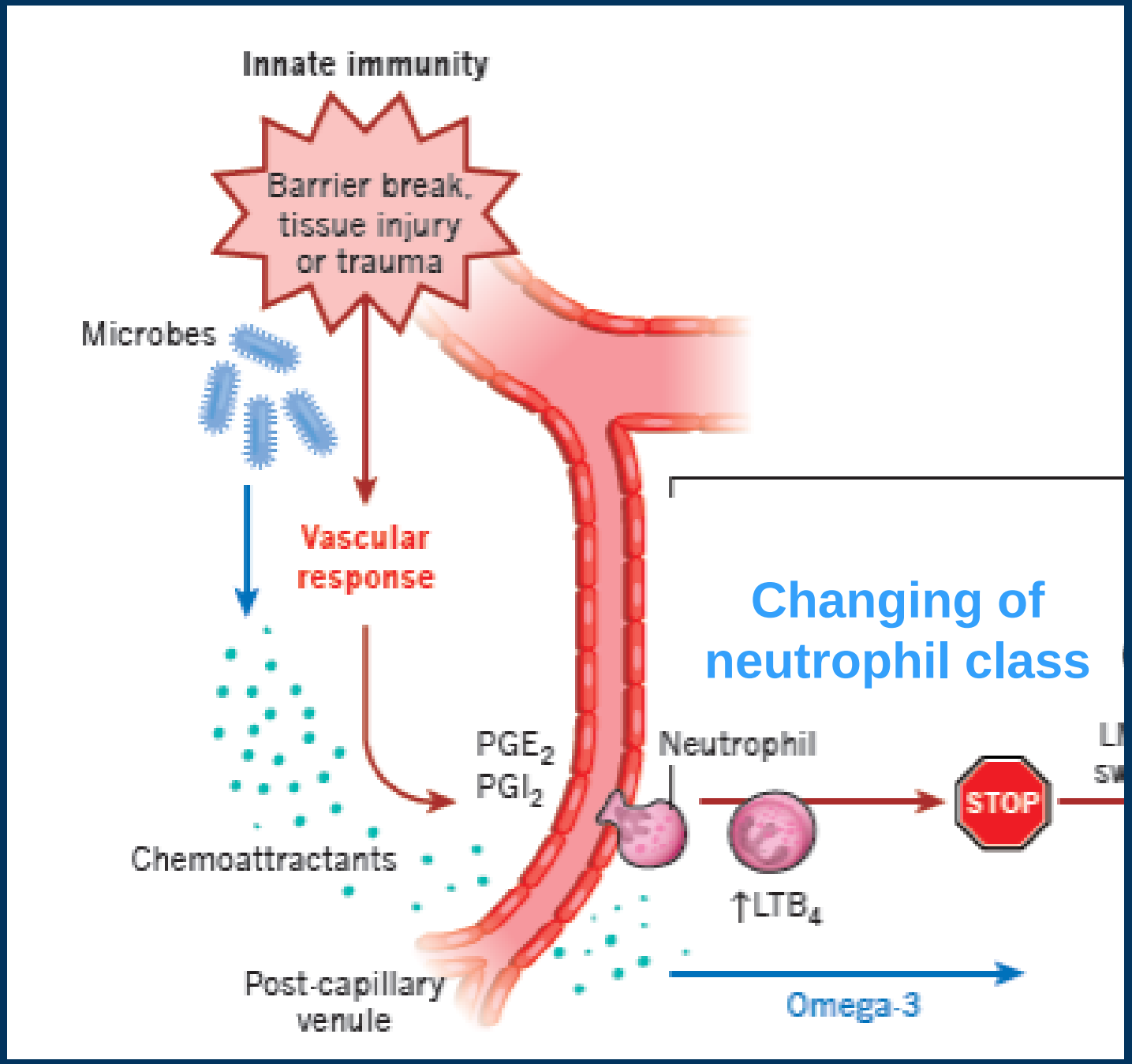

ORIGIN
DIVERSITY (HETEROGENEITY)
PLASTICITY (POLARIZATION)
MEMORY
YS
FL
BM
Microglia
Langherans Cells
Kuppfer Cells
Gut MΦ
M1
M X
M2
Tolerant
Trained
"Mixed memory phenotype"
HEMATOPOIESIS
DIFFERENTIATION
INFLAMMATION
RE-PROGRAMMING

Macrophage Heterogeneity

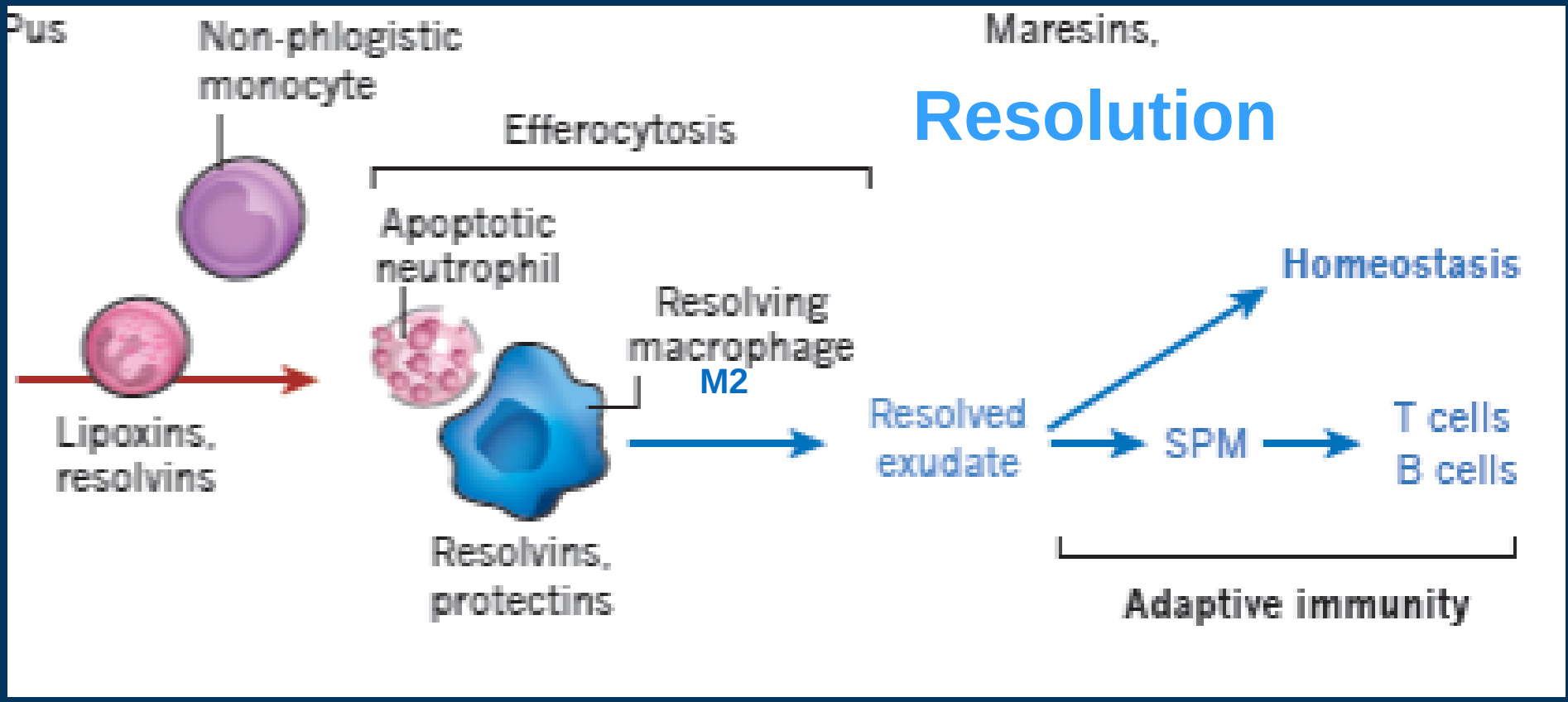
(a cell with "split personality")



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



Dalli J, Serhan C et al *Nature* 2014



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


Charlie Serhan

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

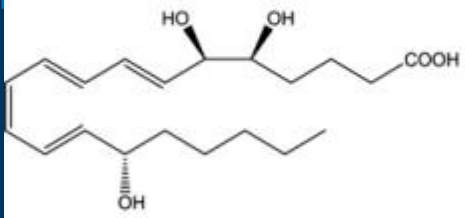
– Actively stimulate cardinal signs of resolution, namely;

- Cessation of leukocytic infiltration
- Counter regulation of pro-inflammatory mediators
- Stimulate the uptake of apoptotic neutrophils
- Clearance of cellular debris

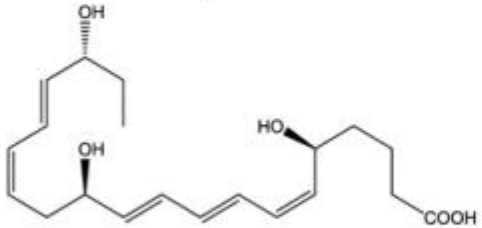
Arachidonic acid (AA)

Eicosapentaenoic acid (EPA)

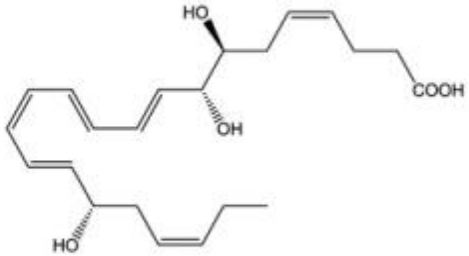
Docosahexaenoic acid (DHA)



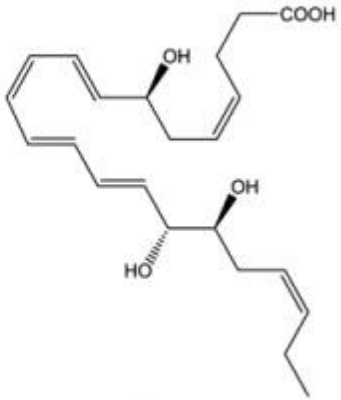
Lipoxin A_4



Resolvin E1



Resolvin D1



Resolvin D2

Monocytes/ Macrophages

Neutrophils (PMN)

Endothelial cells

Dendritic cells

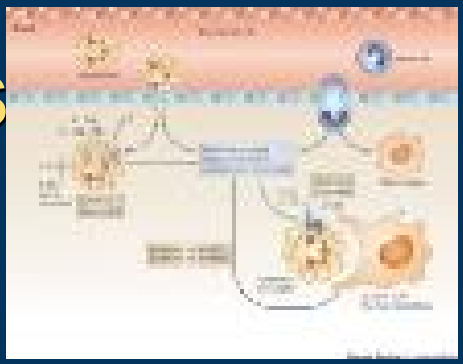
- ↑ Phagocytosis & IL-10 production
- ↓ Pro-inflammatory cytokines

- ↓ Activation, Adhesion & ROS
- ↑ Microbial clearance

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

- ↓ Migration
- ↓ IL-12 production

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*)

Serhan C et al Am J Physiology 2014

SPM : Resolvins, Protectins and Maresins in Disease

Lungs Human & Mouse

ATL, RvE1, PD1,MaR1

↓ Airway inflammation (asthma)

Cardiovascular

RvE1,RvD1

↓ Platelet aggregation

PD1, RvD1

↓ Atherosclerosis

Eyes Human & Mouse

RvE1, PD1, RvD1

↓ Vaso-obliteration and neovascularization(Retinopathy)

↑ Wound healing (Cornea)

Kidney

ATL, PD1,RvD1

↓ Renal ischemic injury

Resolvins

Lipoxins

Protectins Maresins

Anti-Inflammation
Pro-Resolution
Organ Protection

Nanograms to micrograms

Human and Animal Disease Models

Brain Human & Mouse

PD1, RvD1, RvD2

↓ Stroke damage and PMN entry into the brain

↑ Neural cell survival

Oral Rabbit & Mouse

ATL, RvE1

↓ Inflammation-induced tissue and bone loss (Periodontitis)

GI tract

RvD1, RvE1, RvD2

↓ PMN and weight loss

– Survival (Colitis, sepsis)

Liver

RvE1, PD1, RvD1

↓ I/R injury

↑ Glucose and lipid homeostasis

CN Serhan *et al., Nat Rev Immunol 2008;* 8: 349-361

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

Infection regulates pro-resolving mediators that lower antibiotic requirements

Nature 2012

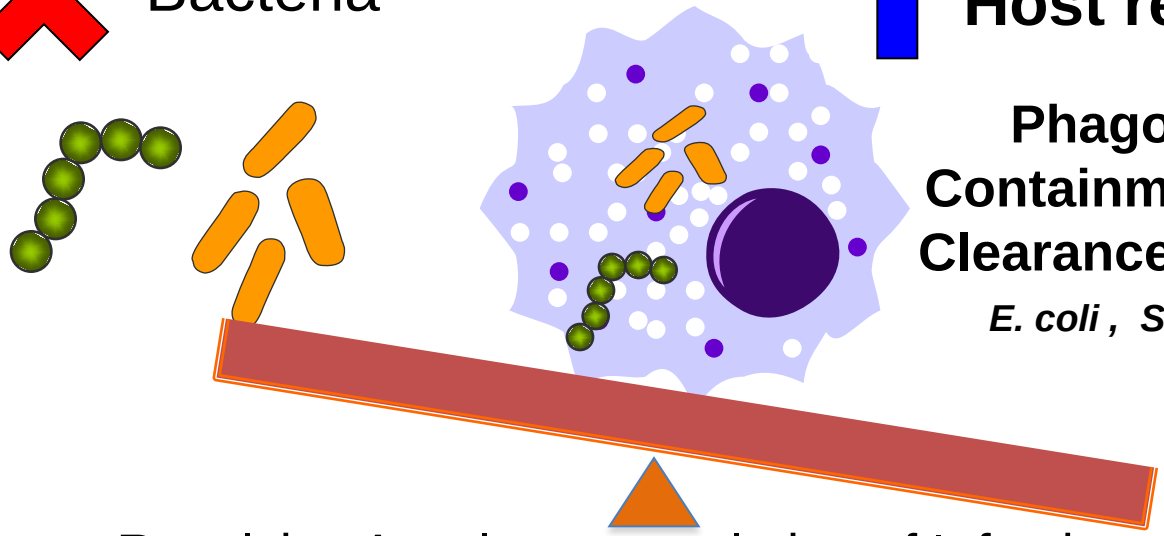
Nan Chiang[1], Gabrielle Fredman[1], Fredrik Bäckhed[2], Sungwhan F. Oh[1], Thad Vickery[1], Birgitta A. Schmidt[1] & Charles N. Serhan[1]

Antibiotics

Bacteria

SPM Resolvins

Host response



Phagocytosis, Containment, Killing, Clearance of Bacteria

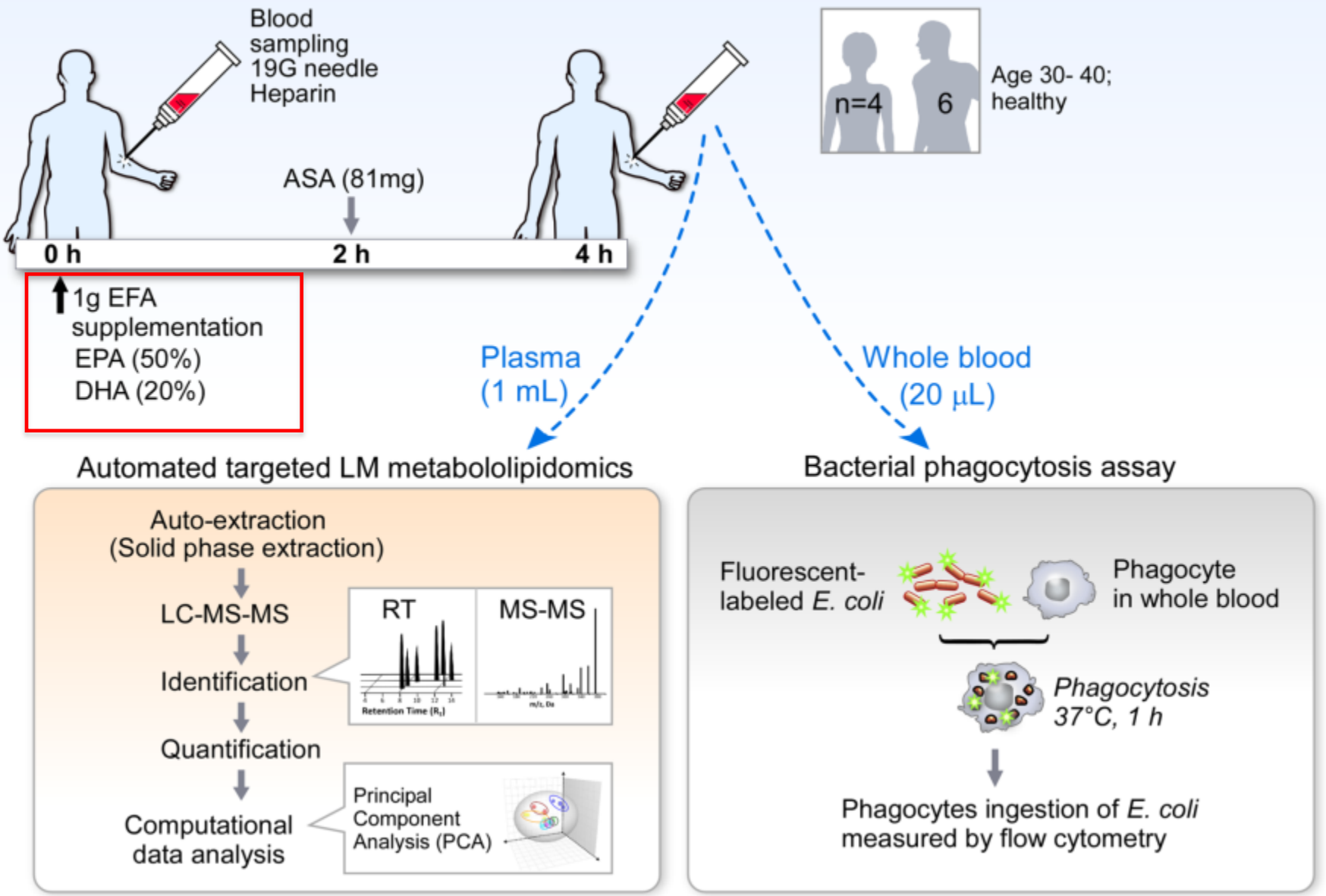
E. coli* , *S. aureus skin

Resolvins Accelerate resolution of Infections

Enhance bacterial killing , reduce inflammation

Treating the host SPM *lowers* the required antibiotic doses

Demonstration : Human SPM Production & Assessment of Function



Colas *et al Am J Physiol Cell Physio* 2014

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, 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

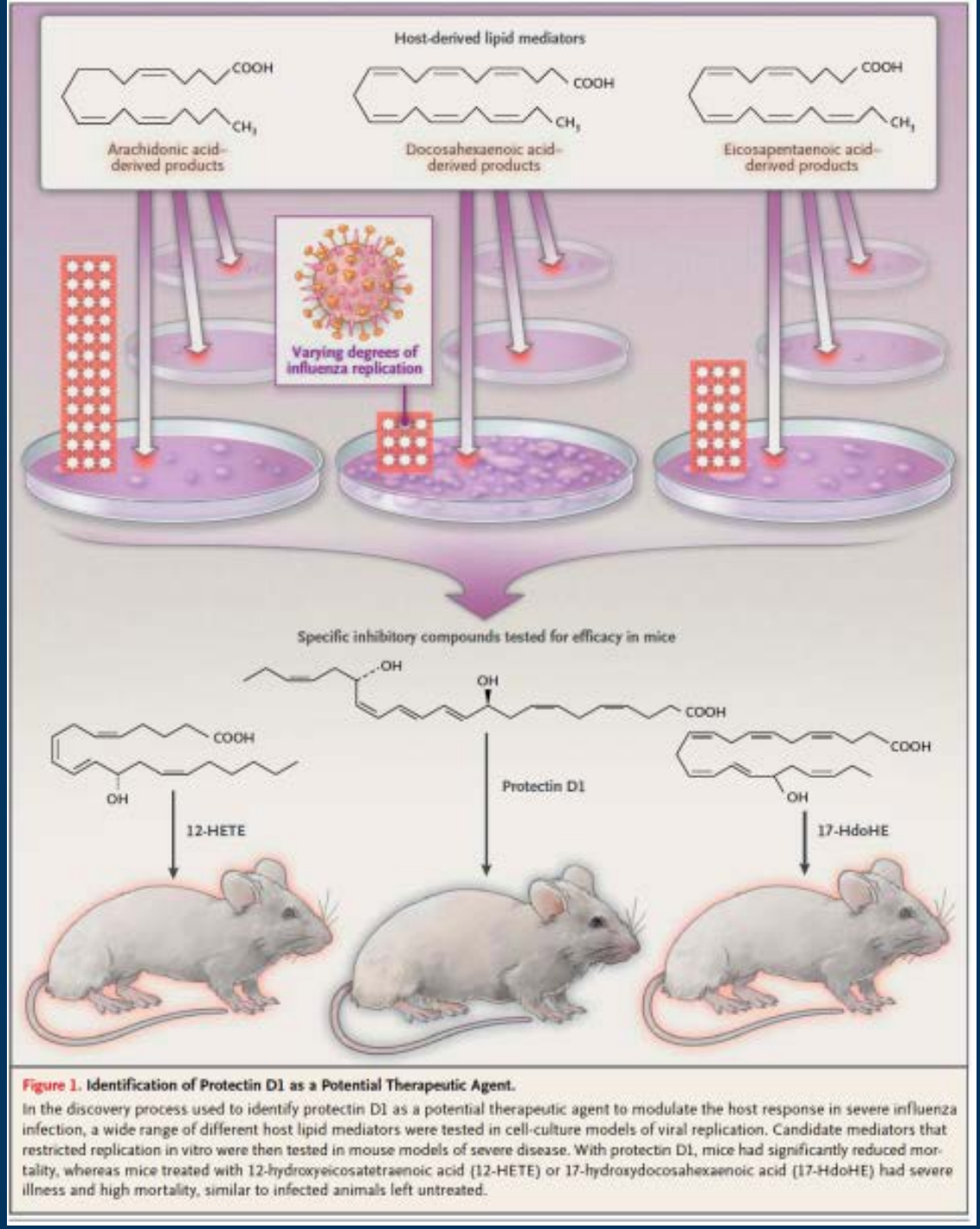


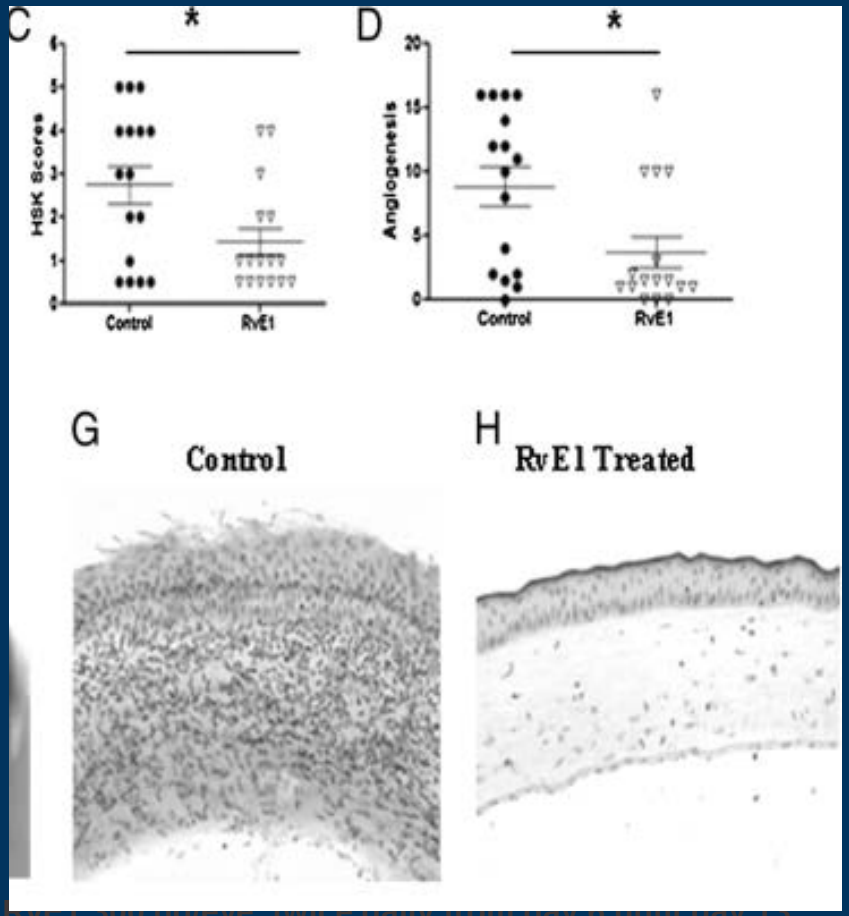
Figure 1. Identification of Protectin D1 as a Potential Therapeutic Agent.

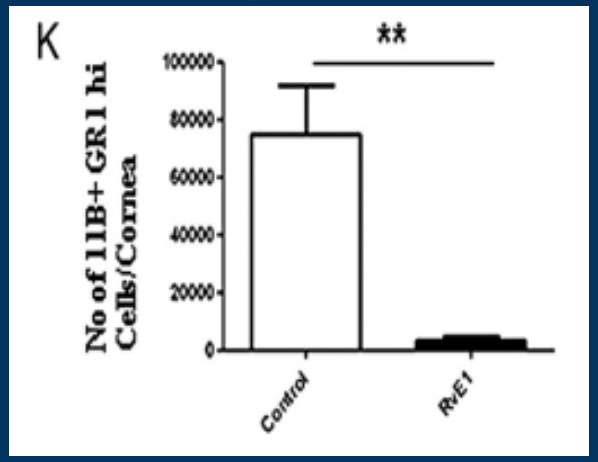
In the discovery process used to identify protectin D1 as a potential therapeutic agent to modulate the host response in severe influenza infection, a wide range of different host lipid mediators were tested in cell-culture models of viral replication. Candidate mediators that restricted replication in vitro were then tested in mouse models of severe disease. With protectin D1, mice had significantly reduced mortality, whereas mice treated with 12-hydroxyeicosatetraenoic acid (12-HETE) or 17-hydroxydocosahexaenoic acid (17-HdoHE) had severe illness and high mortality, similar to infected animals left untreated.

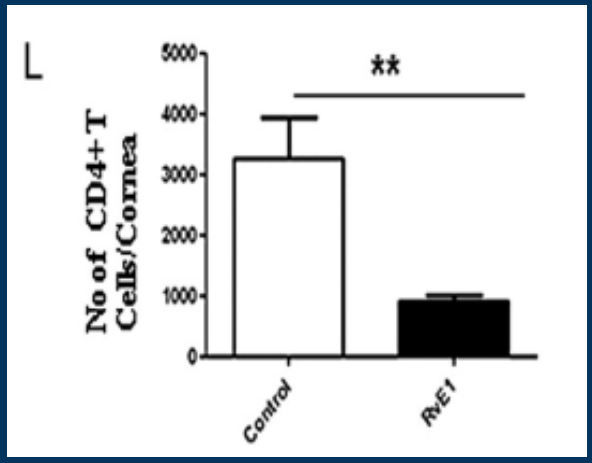
Baillie JK et al *NEJM* 2013

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*





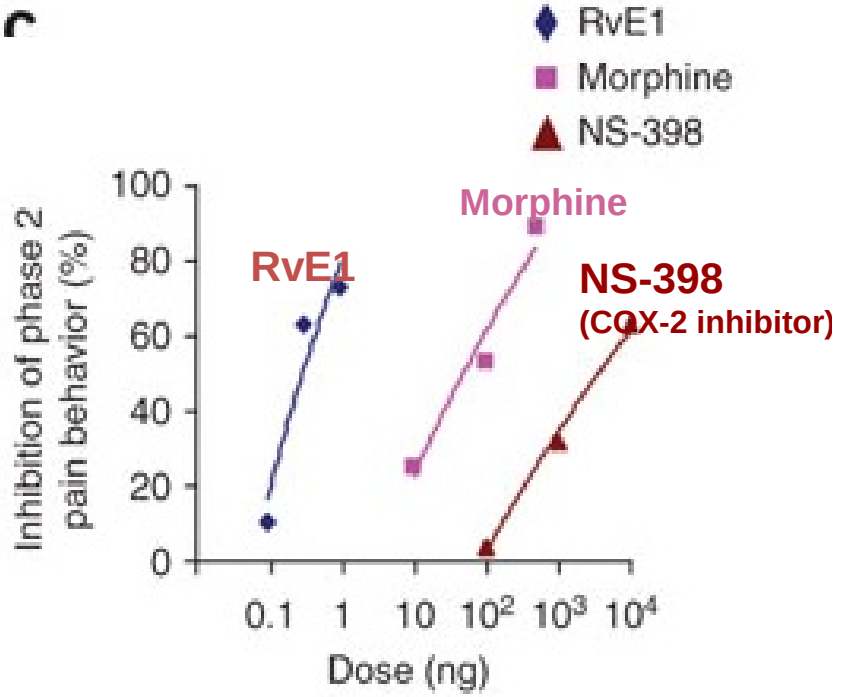


RvE1 300 ng/eye, twice daily from day 8 until day 13

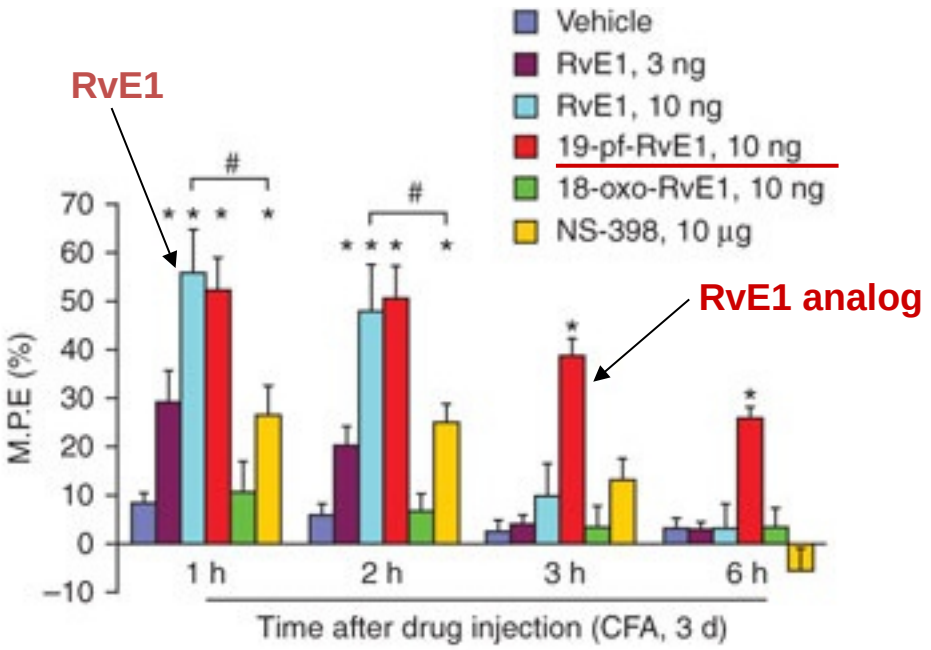
Rajasagi NK *J Immunology* 2011;186:1735

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

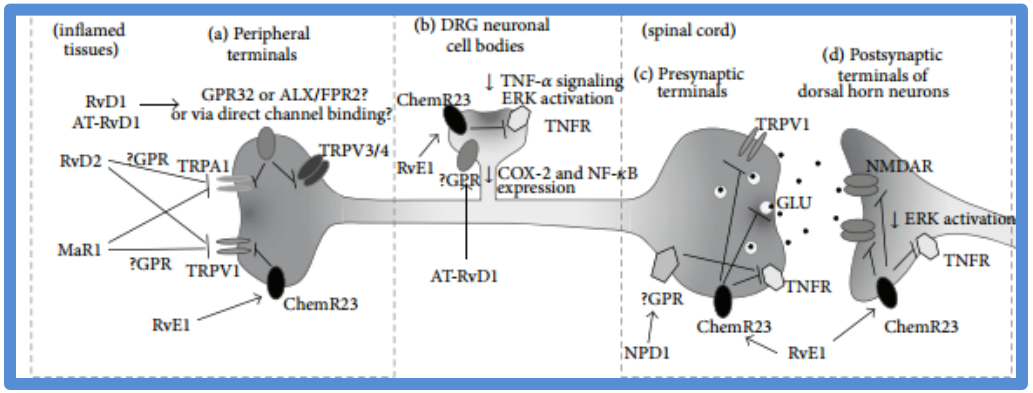
Zhen-Zhong Xu[1,3], Ling Zhang[1,3], Tong Liu[1], Jong Yeon Park[1], Temugin Berta[1], Rong Yang[2], Charles N Serhan[2,3] & Ru-Rong Ji[1,3]



Formalin-induced Spontaneous Pain

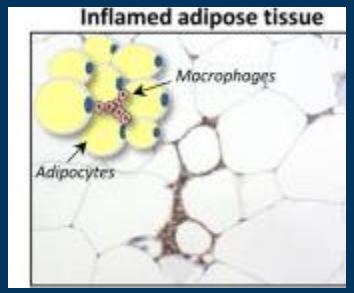


CFA-evoked heat hyperalgesia



Pain resolution ?

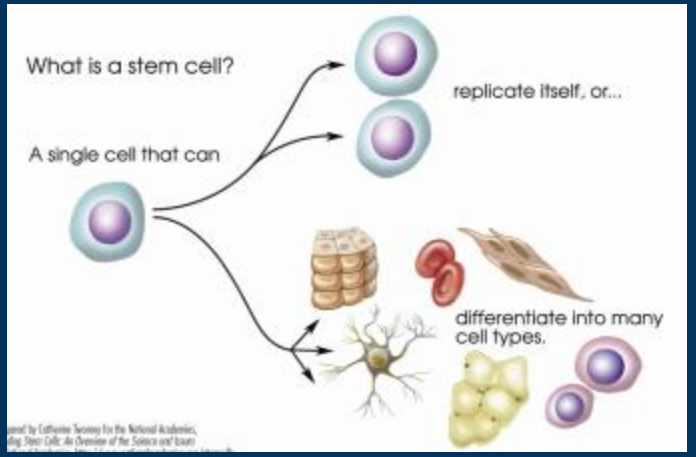
Chronic



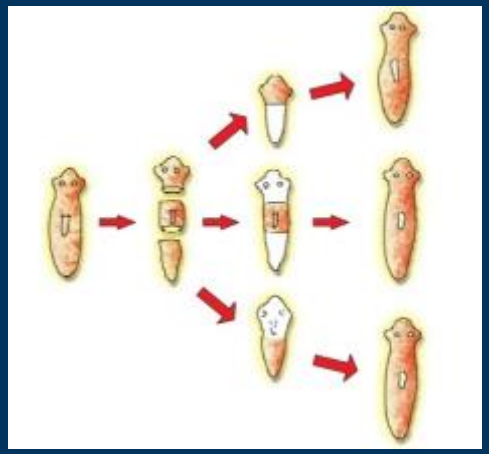
- Asthma
  - Levy et al. *Nature Med* 2002
- Atherosclerosis
- Retinal angiogenesis
  - Behl T et al *Prostaglandins Lipid Med* 2016
- Obesity
  - Claria et al. *J. Immunology* 2012
- Metabolic syndrome
  - Barden AE et al *Am J Clin Nutr* 2015
- Alzheimer's Disease
  - Wang X *Alzheimers Dementia* 2015
- 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

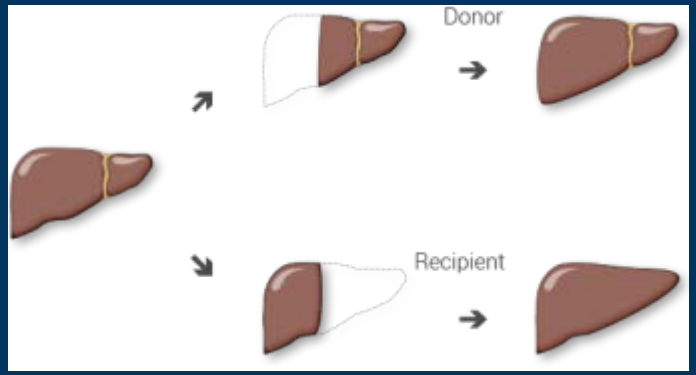
Other areas for SPM's recently evaluated

- **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"**

Serhan CN, Dalli J et al *Immunology* 2015

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







Sum…on

- Current "…bit confusing
- Where ca…ed:
  - Preve…mation
  - Surg…
    - Fa…response shows co…
- SPM phys…some of the current c…nce" of fish oils
- Where ca…v benefit :
  - Limitless potential