Disclosures for Charles N. Serhan

Harvard Medical School requires the following disclosures to the audience:

Research Support/P.I.	**NIH : NIGMS, NIDCR, NIDDK, BayerHeathCare NIH Center Grant**
Employee	**No relevant conflicts of interest to declare**
Consultant	**No relevant conflicts of interest to declare**
Major Stockholder	**No relevant conflicts of interest to declare**
Speakers Bureau	**No relevant conflicts of interest to declare**
Scientific Advisory Boards	**Solutex GC, Inflammation Research Foundation Nocendra, Corbus Pharma, Thetis, Jupiter Therap, Institute Pasteur**

Institut Pasteur

Nov 3rd, 2021 Today'sTitle:

Resolving Inflammation Stimulates Tissue Regeneration via Novel Mediators

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

Board on Health Sciences Policy
Forum on Regenerative Medicine

Today's Outline Presentation;

- *What immune factors and pathways*
- *play a role in regeneration ?*

Endogenous Control Mechanisms In Resolution of Inflammation:

Role of Pro-Resolving Lipid Mediators

Protective

Acute inflammatory response

Resolvins, SPMs, microparticles

Resolution

SPMs

Homeostasis

Stem cells

Failed resolution

Chronic inflammation

Novel chemical mediators

Resolvins
SPMs
cys-SPMs

Tissue regeneration

amplification

Collateral tissue damage

Previous science perspective

- Inflammation faded out by itself
- Blocking inflammation was the goal

Current perspective

- Inflammation resolution is an active process required for homeostasis
- Resolution is coordinated by specialized pro-resolving mediators

Novel Mediators for Regenerative Medicine

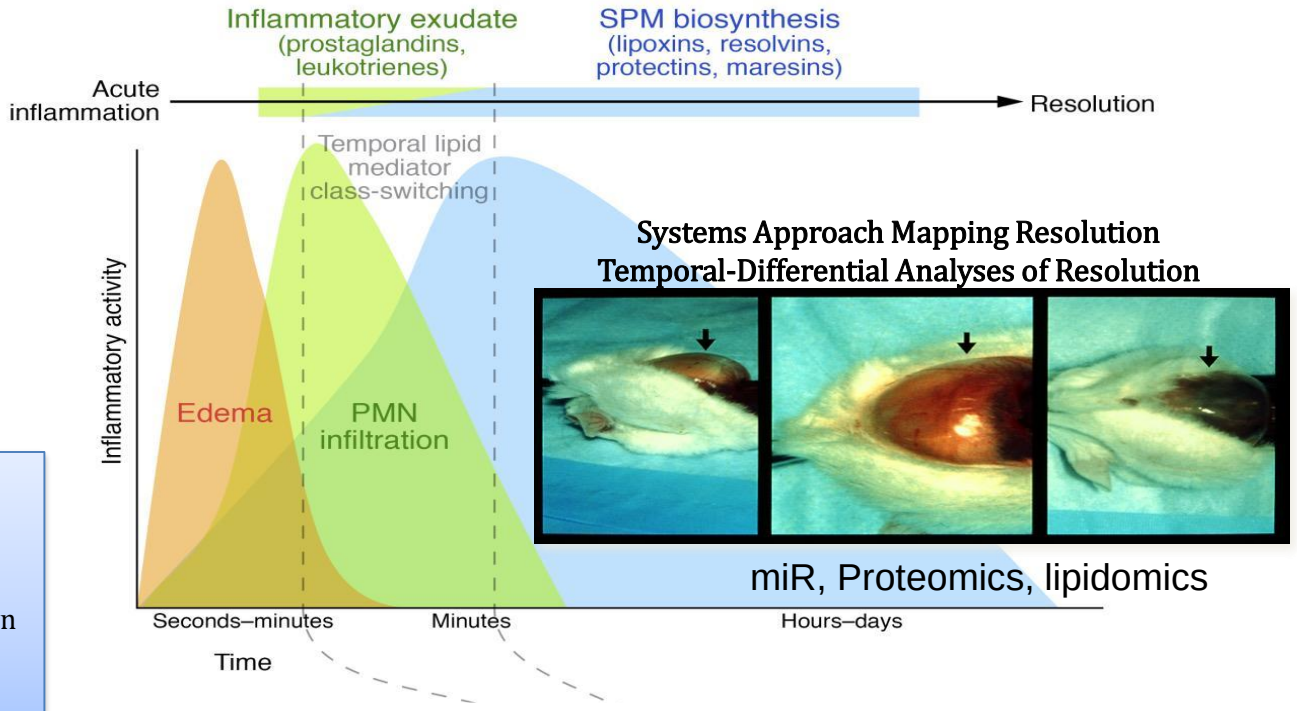
Acute inflammatory response and its Ideal outcome:

Complete Resolution
SPM superfamily
Lipid Mediators

Cessation of inflammation without suppuration.
The return to normal

Decomposition; absorption or breaking down of the products of inflammation.

Taber's Medical Dictionary

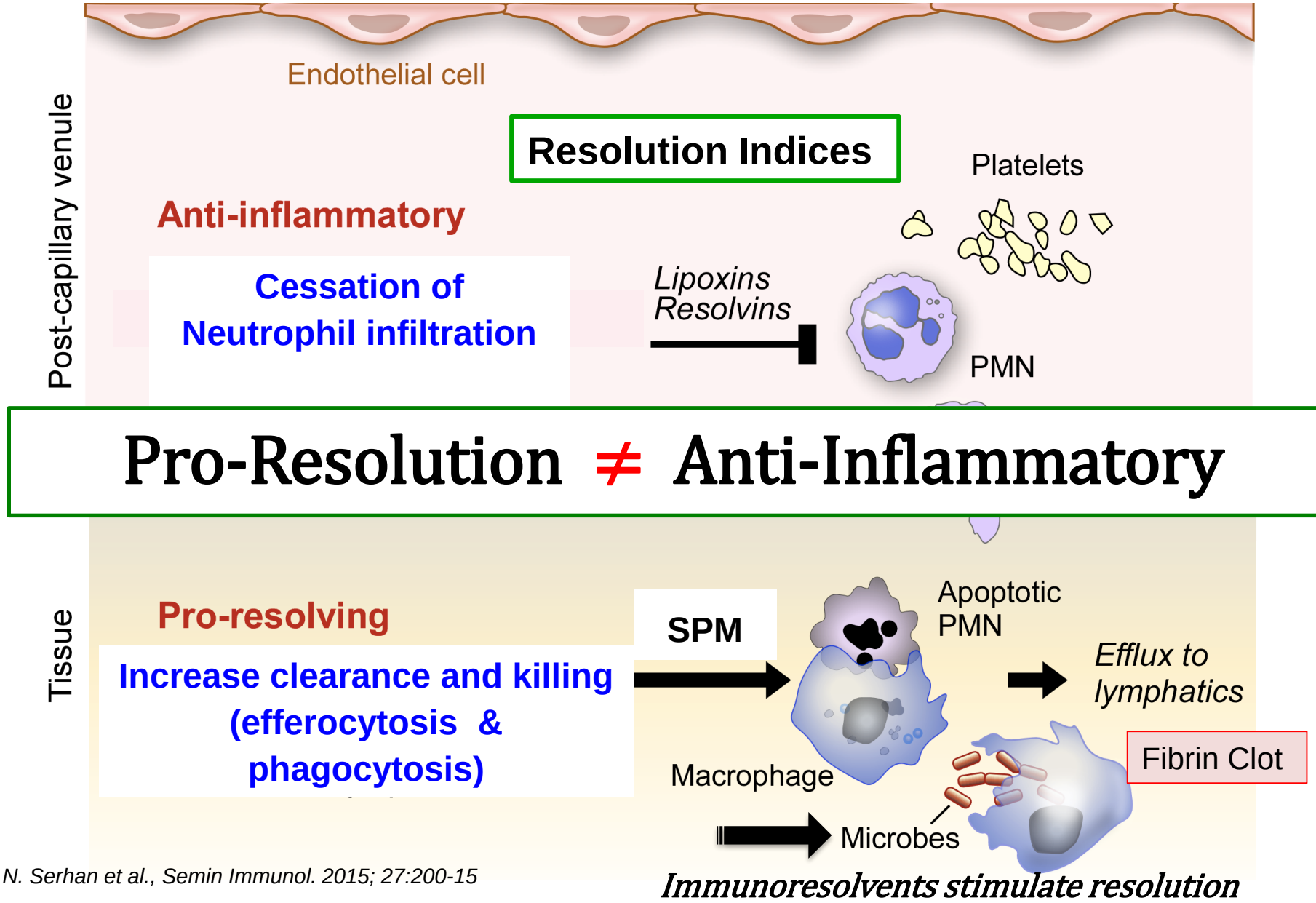


SPM
Specialized Pro-Resolving Mediators functions

CN Serhan et al 2018

JCI The Journal of Clinical Investigation

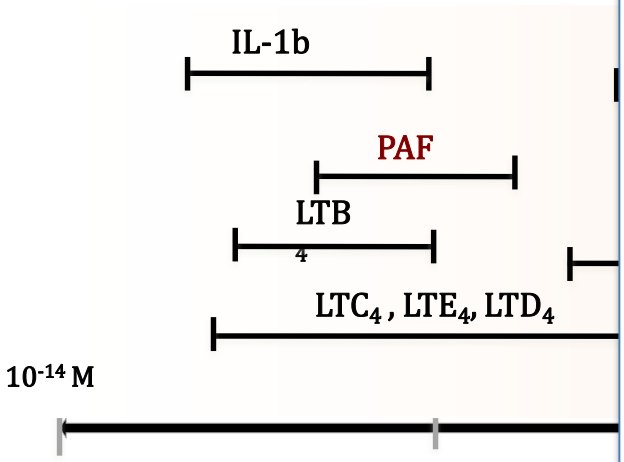
Structure-Functional Elucidation of Novel Resolution Phase Mediators



C.N. Serhan et al., Semin Immunol. 2015; 27:200-15

Chemical Mediators

Lipid



Protectins PD1

Maresin R1 regeneration & pa

Resolvins E series D series

Lipox

SPM
Pro-Resolving Mediators

Science
AAAS

Inflammation's STOP SIGNALS

Inflammation doesn't just peter out. The body actively shuts it down, using signals that researchers hope to transform into therapies *By* **Mitch Leslie**

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.

ILLUSTRATIONS: V. ALTOUNIAN/SCIENCE

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

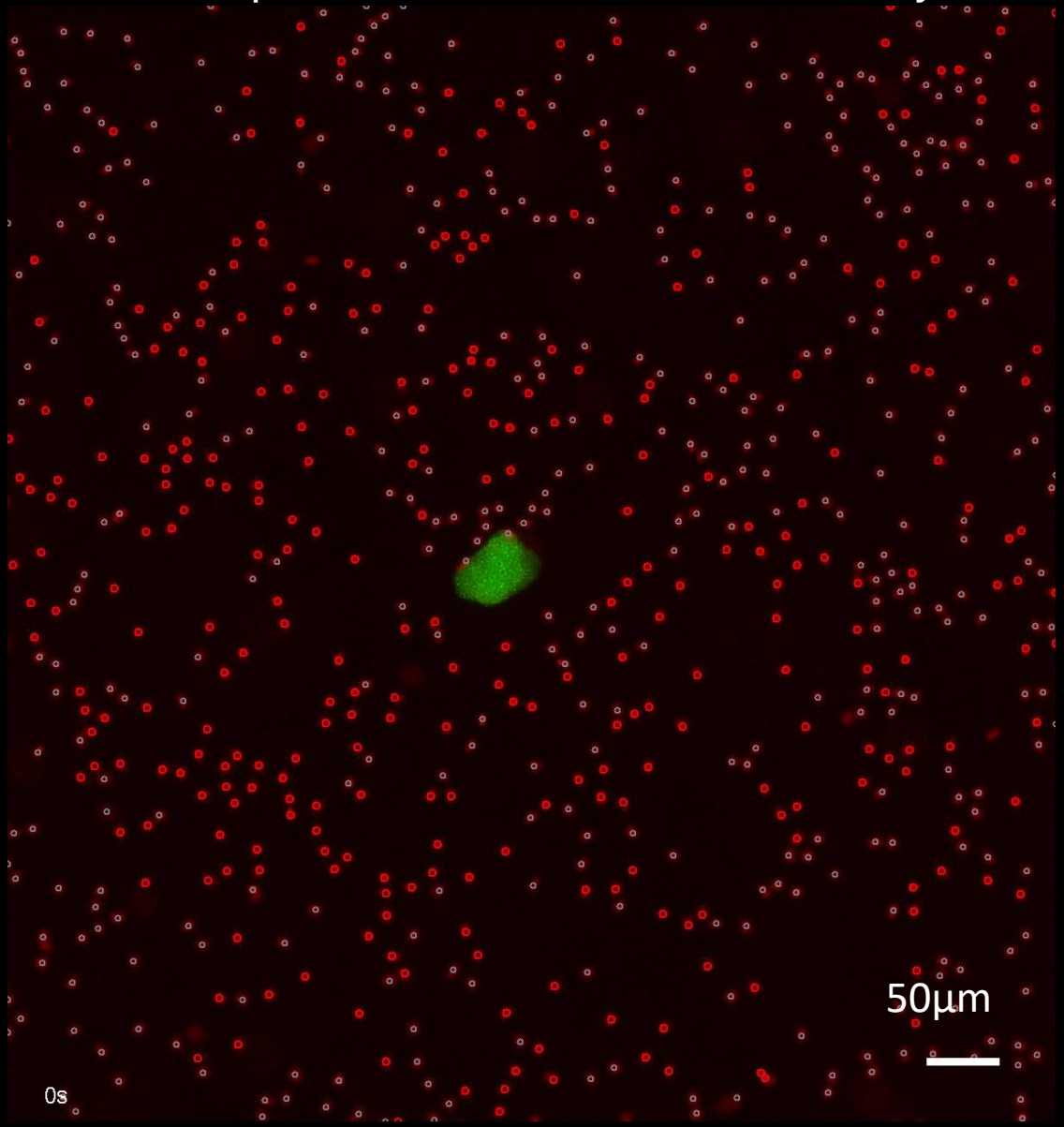
Annexin A1
A protein released by dying neutrophils, its functions include preventing other neutrophils from entering the injured site.

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

Agonists of Resolution

Human Neutrophil Swarming

Experimental and Simulation Overlay



Reategui et al

Experimental:

- Human neutrophils (red)
- Zymosan target (green)

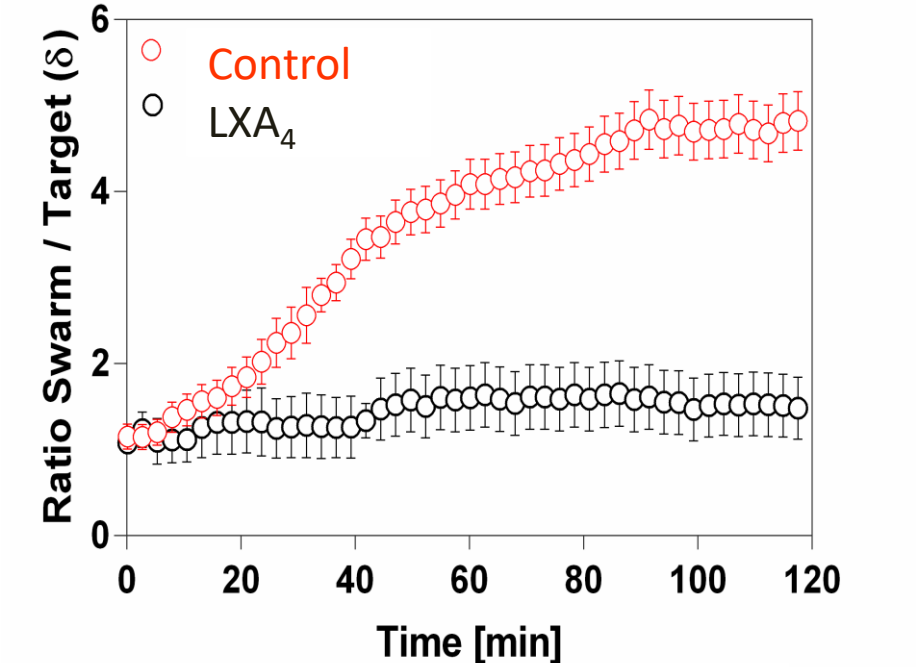
Simulation overlay

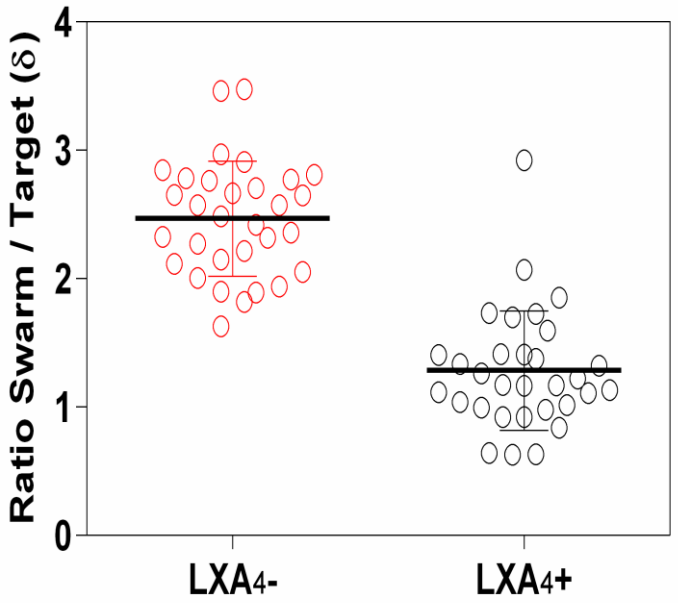
- LTB4 gradient (blue)
- Moving neutrophils (red)
- Chemotaxing neutrophils (green circles)

*Hundreds of Peptide Mediators

1st responders PMN Swam like sharks

Validation of STOP Signals with Human Neutrophils





nature biomedical engineering
ARTICLES
PUBLISHED: 30 JUNE 2017 | VOLUME: 1 | ARTICLE NUMBER: 0094

Microscale arrays for the profiling of start and stop signals coordinating human-neutrophil swarming

Eduardo Reátegui[1,2,3], Fatemeh Jalali[1], Aimal H. Khankhel[1,2], Elisabeth Wong[1], Hansang Cho[1,3], Jarone Lee[3,4], Charles N. Serhan[3,5], Jesmond Dalli[3,5], Hunter Elliott[3,6] and Daniel Irimia[1,3,7*]

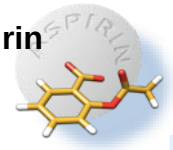
SPM stop human PMN swarms

Direct Evidence

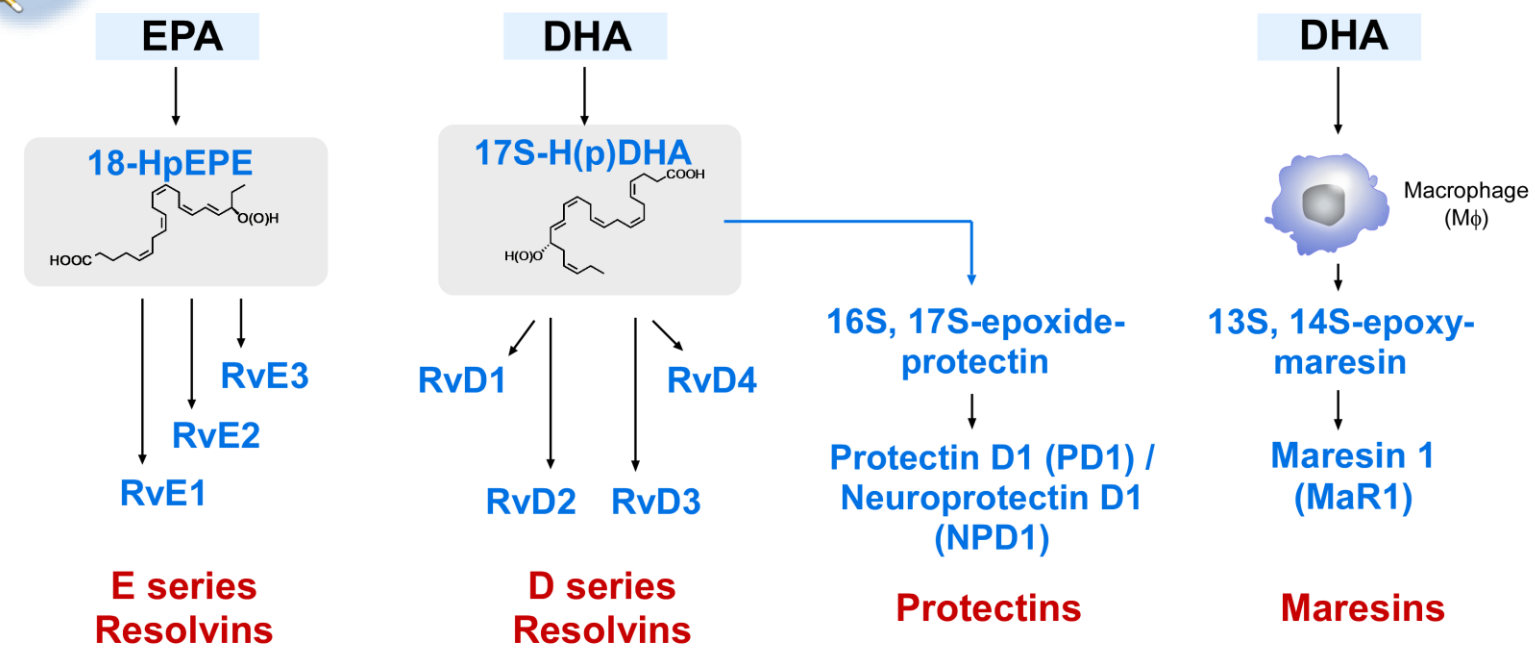
Bioengineer tool to assess immune status ?

Specialized Pro-Resolving Mediators :SPMs

Aspirin



Network Resolution Metabolome: LC-MS-MS based profiling



Complete stereochemistry & biosynthesis established for each pathway

Pro-Resolving Functions

- Reduce pro-inflammatory cytokines and their counter-regulation , reduce eicosanoid storms
- Enhance PMN clearance and bacterial killing
- Stimulate phagocytosis of apoptotic PMNs (efferocytosis)
- Increase removal of inflammatory debris via lymphatics
- Reduce **Pain**

Shorten R_i resolution interval

Pro-resolving lipid mediators are leads for resolution physiology

Charles N. Serhan[1]

| NATURE | VOL 510 | 5 JUNE 2014

Translational Potential of SPM

confirmed functions : Animal Models

Inflammation

Gut, IBD Brazil
Lung
Joints, **Arthritis** RvD1 RvD3
Periodontitis (Rabbit, minipigs)
Vessel/endothelium
Acute/chronic

RvE1, NPD1,
RvD1, RvD2, RvD3

Infection control

Bacterial sepsis
Bacterial aspiration pneumonia
Viral keratitis

RvE1, D series Rv, PD1

Neural Inflammation / Pain

Stroke
Pain
Epilepsy
Neuronal cell survival

100X more potent than morphine

RvE1, NPD1, RvD1, MaR1

Tissue protection

Myocardium
Kidney
Cornea
Retina
Neovascularization
Lung

RvE1, RvD1, MaR1, NPD1

Tissue repair/wound healing

Cornea, Retina. skin
Promote vessel growth
Anti-Fibrosis
Septic wound

RvE1, NPD1, RvD1, MaR1

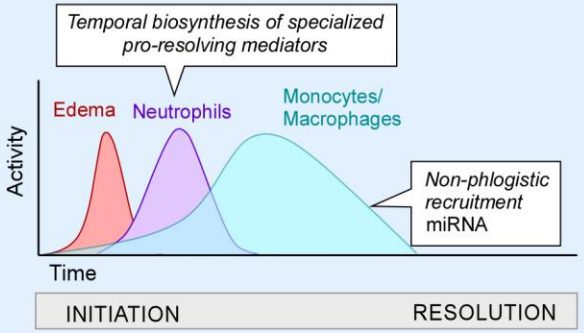
Cancer Models

picomolar to nanomolar quantities
100 -1000X more potent than NSAID

resolvins pubmed.gov

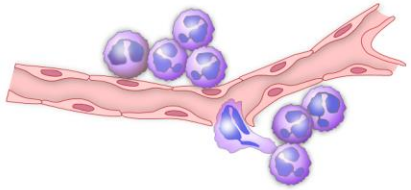
SPM Producing Cell Types

Biomarkers of Resolution Status ?



Apoptotic PMN → SPM

PMN-Endothelial cells



→ Resolvin E1
D series Resolvins

PMN-Epithelial cells
GI, Airway → Lipoxins

GM-CSF PMN → Lipoxins

Microglial cells → D series Resolvins

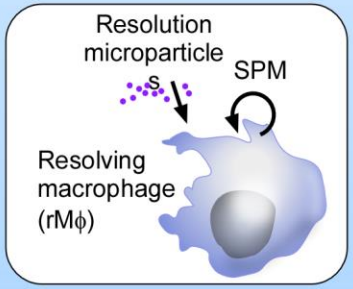
Platelet-PMN → Maresin 1

M2-Macrophages → SPM

Microparticles → 17-HDHA; 14-HDHA

Muscle

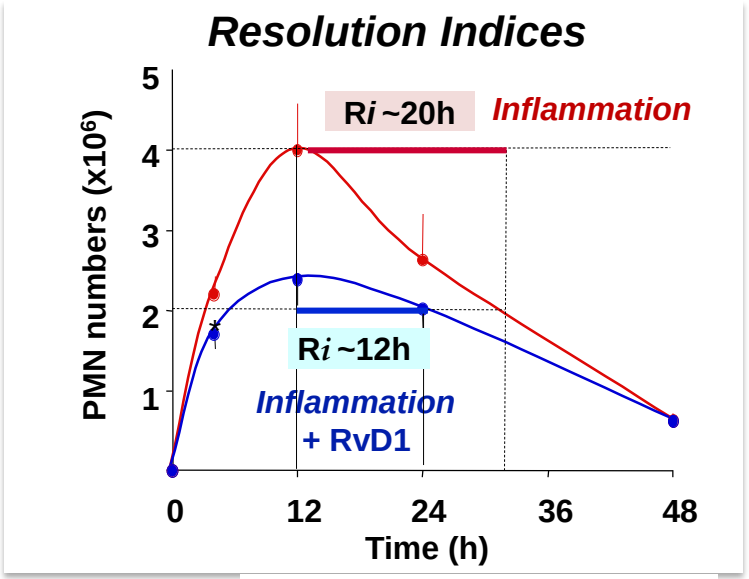
Adipose



Human lung, spleen, marrow, lymph nodes, Brain

How Do SPMs Work? Novel MOA

SPM limit the magnitude and duration and of the acute inflammatory response.



SPM Reduce both EICOSANOID & CYTOKINE STORMS

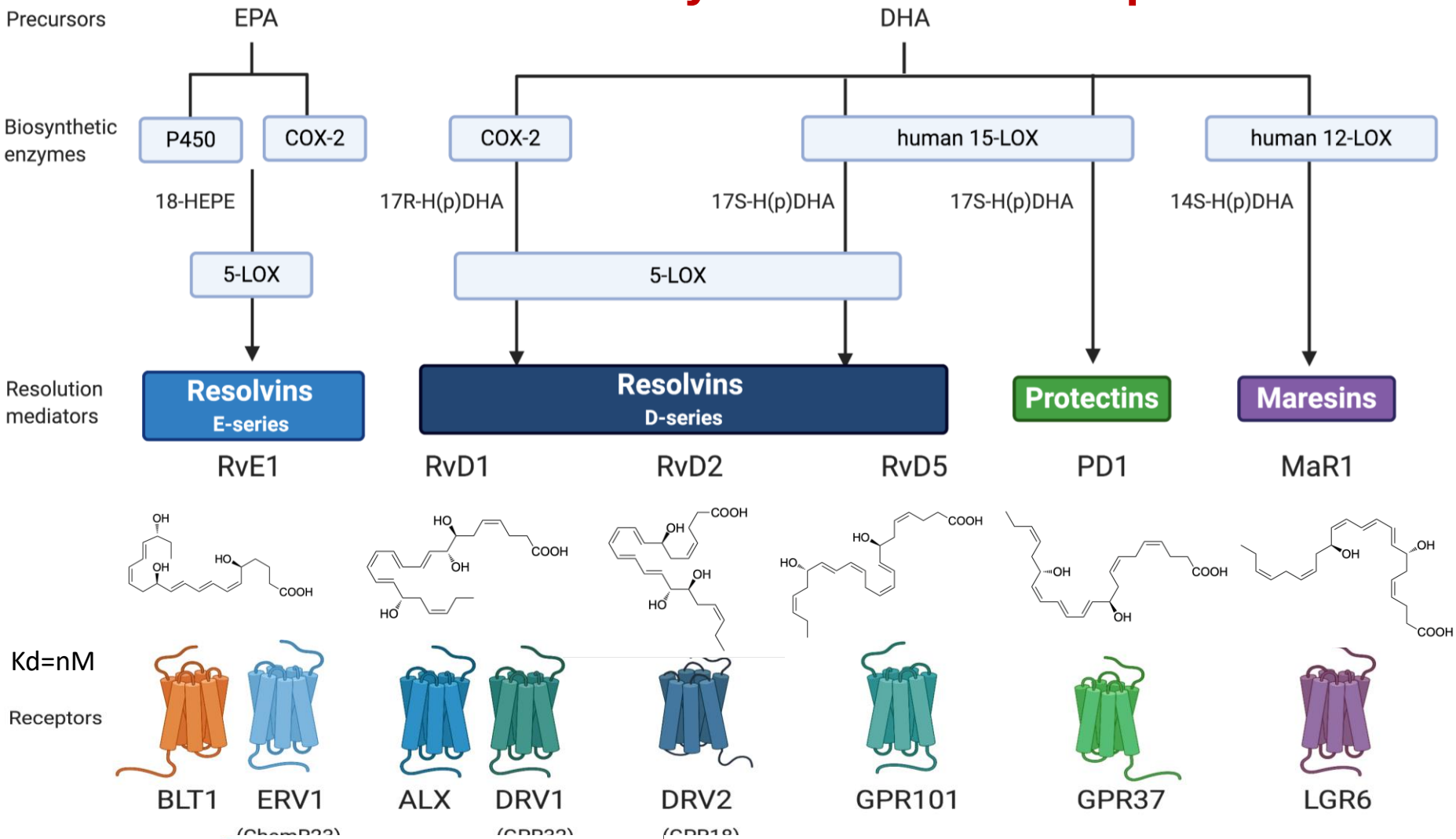
pico to nanogram

- ↓ Prostaglandins (COX-2 expression), Leukotrienes (LTB_4, LTC_4, LTD_4)
- ↓ PAF formation and actions

Chemokines and cytokines

- ↓ TNFα, IL-1β, IL-6, IL-8, IL-12, etc. ↑ IL-10
- ↓ NF-$_k$B activity, Inflammasome NLRP3 ↑A20, SIGIRR
- MicroRNAs , Growth factors (VEGFs)
- ↓ Edema

SPM Network Biosynthesis and Receptors



Cardinal signs of inflammation
Rubor, calor, tumor and dolor

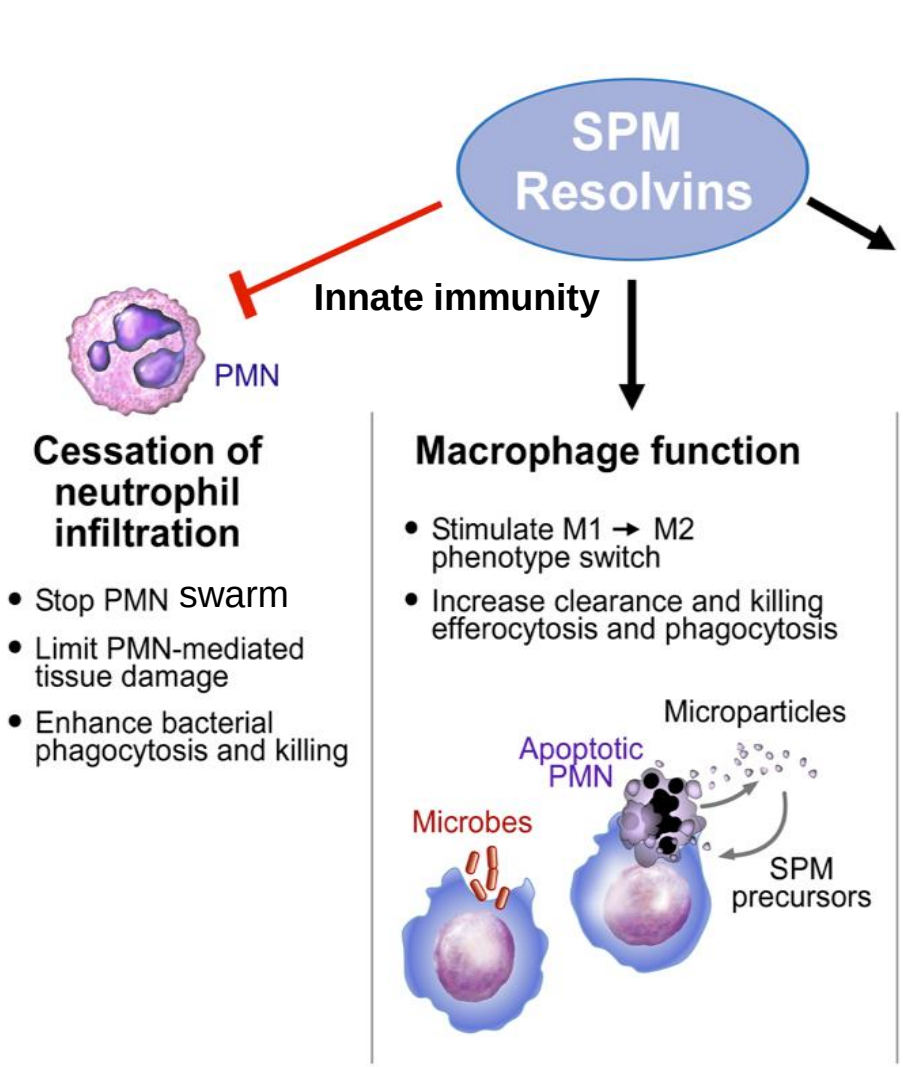
Edema, chemotaxis
Excessive leukocyte infiltration
Pro-inflammatory proteins and "cytokine storms"

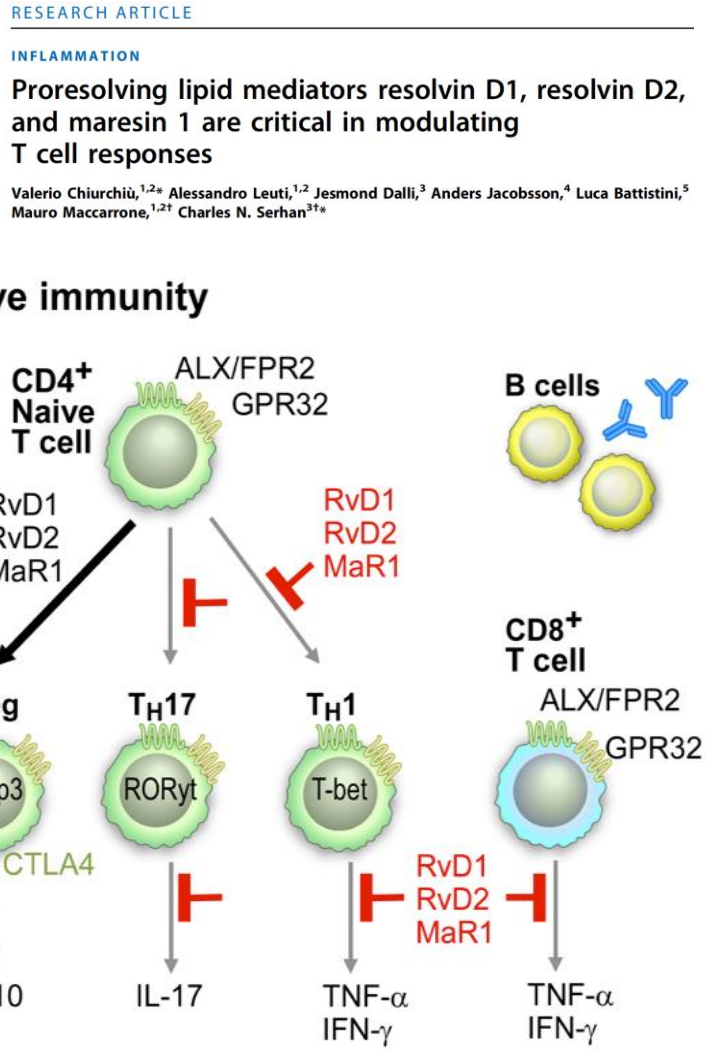
Signs of resolution

PMN clearance from epithelial surface
Phagocytosis of apoptotic PMN
Removal of inflammatory debris
Clearance of bacteria
Wound repair, tissue regeneration

from Molecular Aspects Medicine 2021

Cell Type-Specific Mechanisms and Receptor-Mediated Actions of SPM





Serhan, Chiang and Dalli, Mol Aspects Med. 2018

SPM stimulate Stem Cells

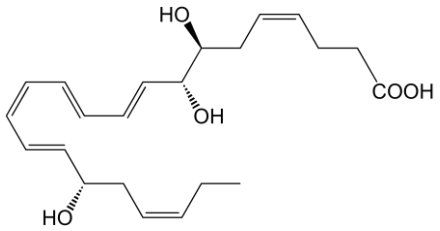
STEM CELLS TRANSLATIONAL MEDICINE

TISSUE-SPECIFIC PROGENITOR AND STEM CELLS

Human Periodontal Stem Cells Release Specialized Proresolving Mediators and Carry Immunomodulatory and Prohealing Properties Regulated by Lipoxins

ELEONORA CIANCI,[a,b,c] ANTONIO RECCHIUTI,[c] ORIANA TRUBIANI,[b,c] FRANCESCA DIOMEDE,[b,c] MARCO MARCHISIO,[a,b] SEBASTIANO MISCIA,[a,b] ROMAIN A. COLAS,[d] JESMOND DALLI,[d] CHARLES N. SERHAN,[d] MARIO ROMANO[b,c]

- ***human periodontal ligament stem cell migration, accelerating wound closure***

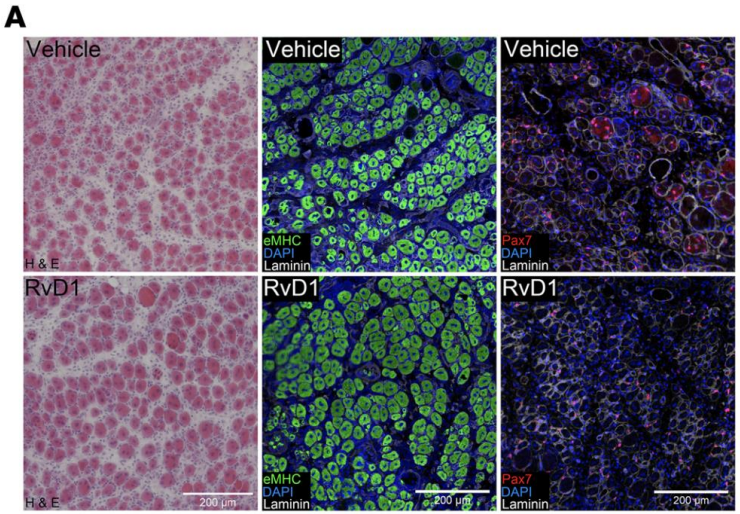


JCI insight

RESEARCH ARTICLE

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

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]



- ***Resolvins enhances myofiber regeneration by modulating muscle stem cells***
- ***neural Stem Cells*** *Wada et al FJ* ***MSC Perrella et al***
- **Resolvin-D2 targets myogenic cells and improves muscle regeneration** in muscular dystrophy.
  Dort et al Nat Commun. 2021 Oct 29;12(1):6264.

Reference information: *JCI Insight*. 2020;5(18):e137713. https://doi.org/10.1172/jci.insight.137713.

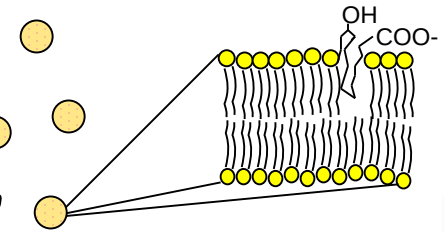
Creating Nano Pro-Resolving Medicines (NPRMs): Mimic Endogenous Resolution Mechanisms

Humanized Nanoparticles : Resolution Mimetics

Control Inflammation

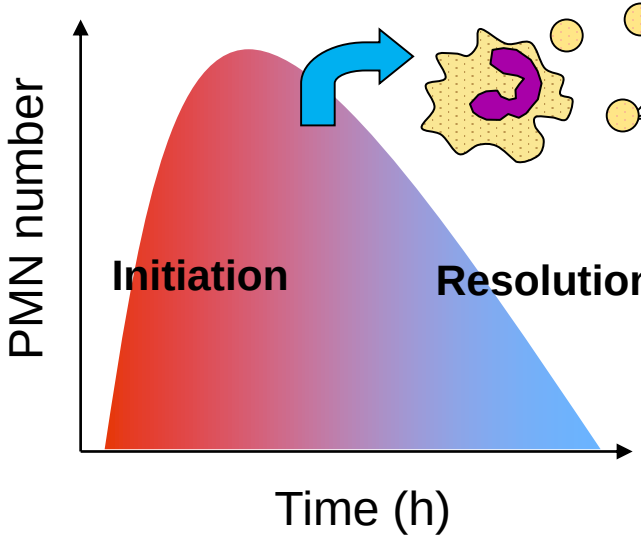
PMN-derived microparticles

resolvin precursors



Human Leukocytes

Acute Inflammation

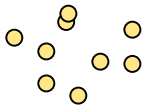


NPRM construction

+ Resolvin D1

+ 1,2-dioleoyl-glycero-3-phospho-L-serine-N (7-nitro-2-1,3-benzoxadiazo-4-yl)

Tracking



Enriched nanoparticles

Anti-Inflammatory Pro-Resolving Nanoparticles

Published April 1, 2011, doi:10.4049/jimmunol.1003865

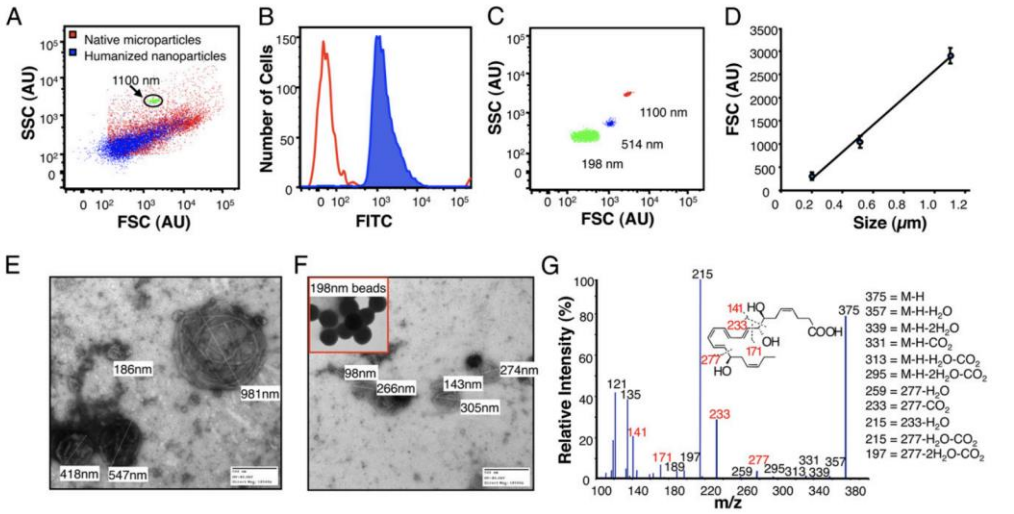
Cutting Edge

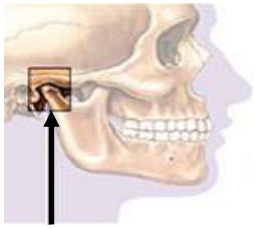
THE JOURNAL OF IMMUNOLOGY

Cutting Edge: Humanized Nano-Proresolving Medicines Mimic Inflammation-Resolution and Enhance Wound Healing

Lucy V. Norling,*,† Matthew Spite,* Rong Yang,* Roderick J. Flower,† Mauro Perretti,† and Charles N. Serhan*

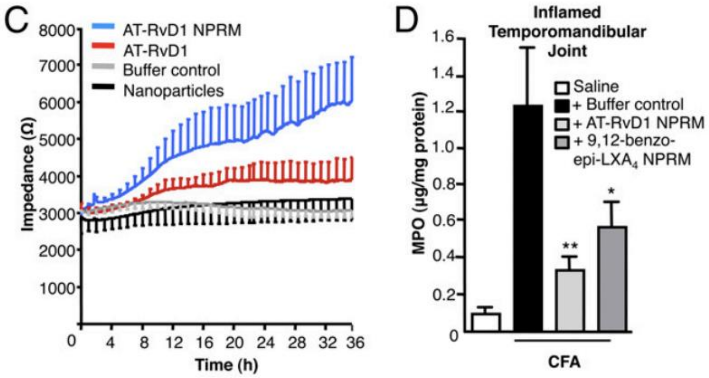
Humanized Nano Pro Resolving Medicines: construction & characterization.





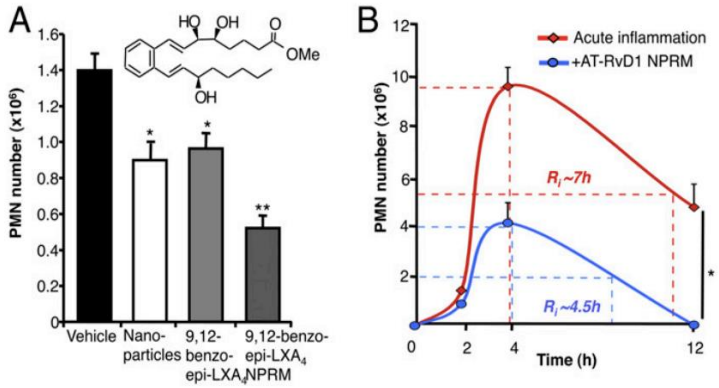
Articular eminence

Temporomandibular joint (TMJ) **Inflammation**



TMJ: temporomandibular disorder

- ***NPRMs limit PMN infiltration to inflammatory sites, enhance wound healing and are protective in TMJ & Age-related delay in Resolution***



THE JOURNAL OF IMMUNOLOGY

This information is current as of September 12, 2014.

Aging Delays Resolution of Acute Inflammation in Mice: Reprogramming the Host Response with Novel Nanoproresolving Medicines

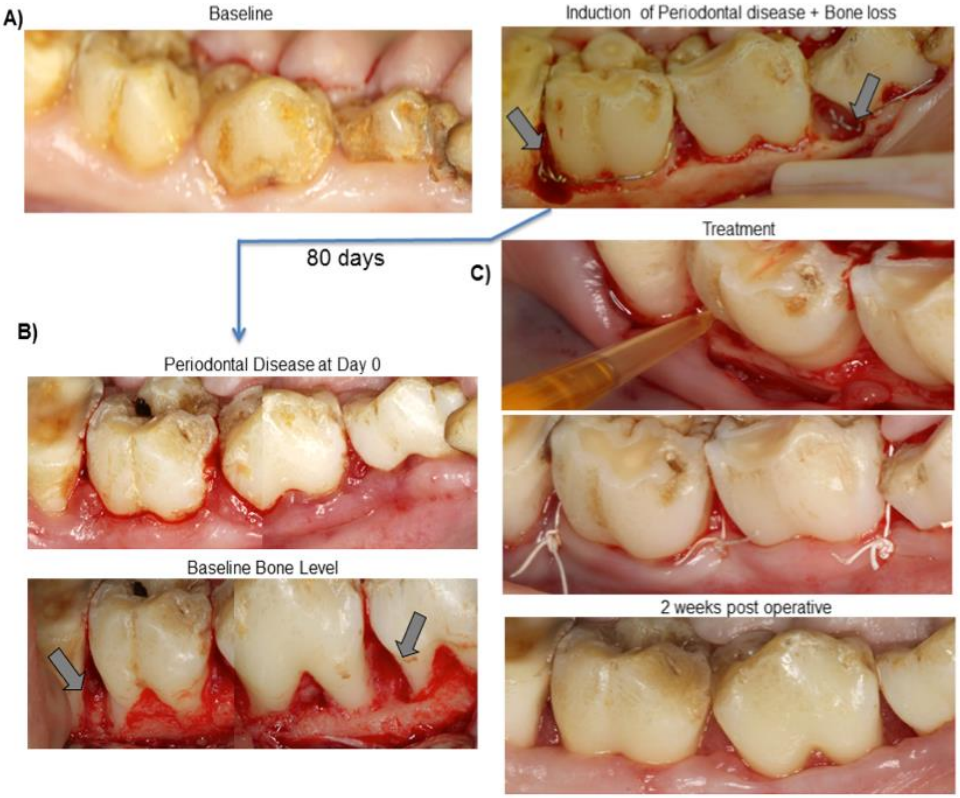
Hildur H. Arnardottir, Jesmond Dalli, Romain A. Colas, Masakazu Shinohara and Charles N. Serhan

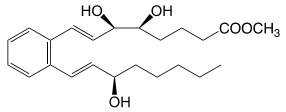
Proresolving Nanomedicines Activate Bone Regeneration in Periodontitis

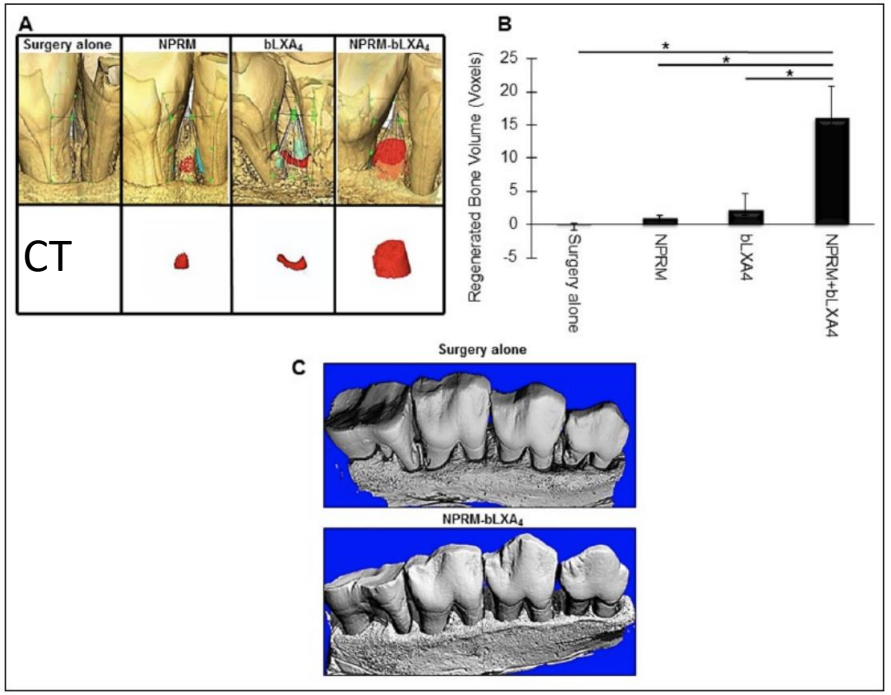
Journal of Dental Research
2015, Vol. 94(1) 148–156

DOI: 10.1177/0022034514557331
jdr.sagepub.com

T.E. Van Dyke[1*], H. Hasturk[1*], A. Kantarci[1], M.O. Freire[1], D. Nguyen[1], J. Dalli[2], and C.N. Serhan[2]







Mini-Pig Model of Periodontal Disease Regeneration

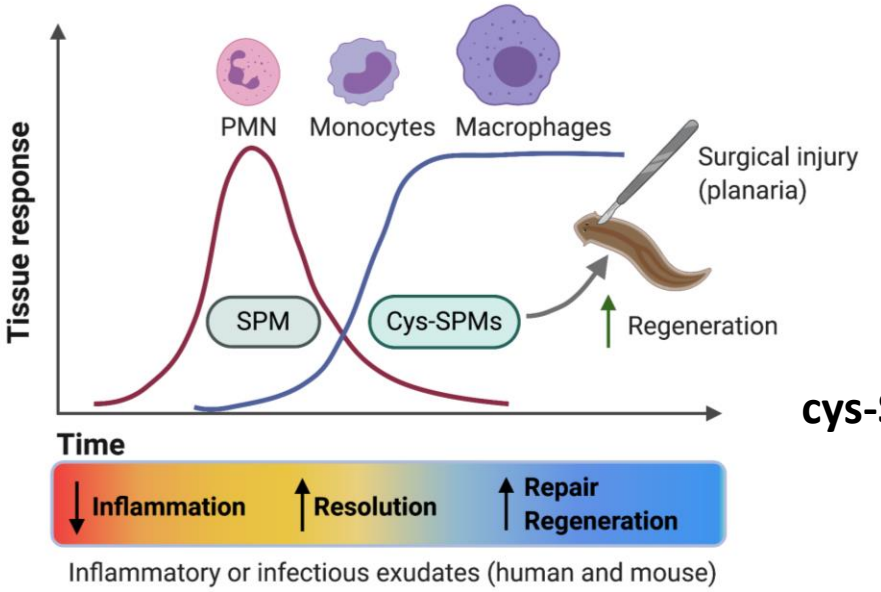
Biosynthesis and actions of novel cys-SPMs in planaria head regeneration

Identification of 14-series sulfido-conjugated mediators that promote resolution of infection and organ protection

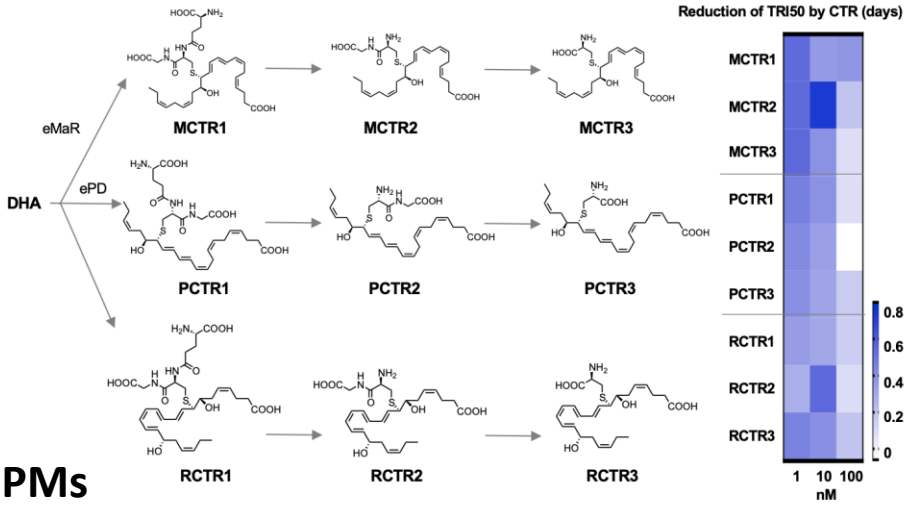
Jesmond Dalli, Nan Chiang, and Charles N. Serhan[1]

Identification and Complete Stereochemical Assignments of the New Resolvin Conjugates in Tissue Regeneration in Human Tissues that Stimulate Proresolving Phagocyte Functions and Tissue Regeneration

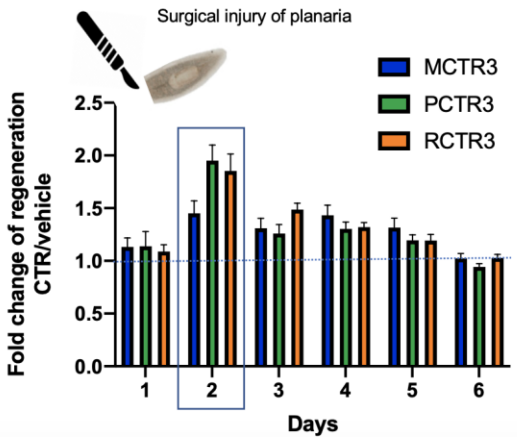
Xavier de la Rosa,* Paul C. Norris,* Nan Chiang,* Ana R. Rodriguez,† Bernd W. Spur,† and Charles N. Serhan*



cys-SPMs



Conserved molecular targets for pro-regenerative environment ?



Cysteinyl-specialized proresolving mediators link resolution of infectious inflammation and tissue regeneration via TRAF3 activation

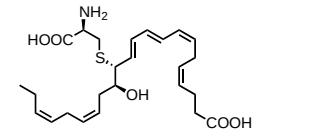
Nan Chiang[a], Xavier de la Rosa[a], Stephania Libreros[a], Hui Pan[b], Jonathan M. Dreyfuss[b], and Charles N. Serhan[a,1]

PNAS Proceedings of the National Academy of Sciences of the United States of America

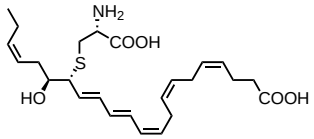
PNAS 2021 Vol. 118 No. 10 e2013374118
https://doi.org/10.1073/pnas.2013374118

Cysteinyl-SPMs activate resolution-regeneration pathways and effectors

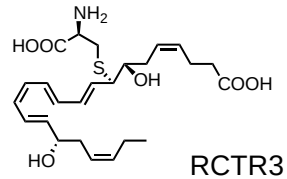
Cysteinyl-SPM → Planarian regeneration → Planarian RNA sequencing & bioinformatics → Mouse in vivo → Human translation Macrophages



MCTR3



PCTR3



RCTR3

Surgical injury

Head regeneration

MCTR3 PCTR3 RCTR3

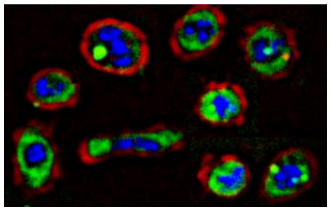
$NF_{\kappa}B$ and epigenetic related pathways & TRAF3

https://www.ncbi.nlm.nih.gov/Structure/pdb/1FLL

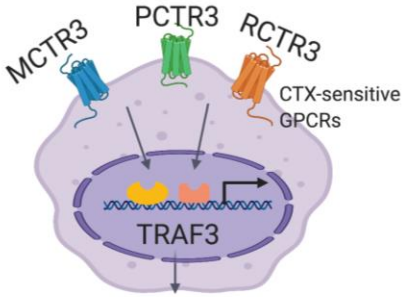
E. coli infection

In vivo TRAF3 silencing

IL-10
Phagocytosis
Cys-SPM actions



Macrophages (red) phagocytosis of *E. coli* (green)



IL-10

Phagocytosis

CETRI Center for Experimental Therapeutics and Reperfusion Injury
CNSerhanlab

Summary

Endogenous Resolvins Specialized Pro-Resolving Mediators (SPM) and cys-SPM: Functions

- **Active Resolution Programs of Inflammation**

***via* cell surface GPCRs**

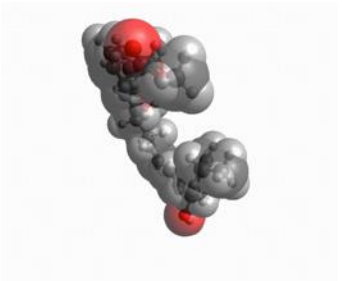
- **Intrinsic Controllers of Infection**

lower the doses required for antibiotic treatment:

SPM *are not* immunosuppressive

- **Stimulate Tissue Regeneration**

Stereospecific pico to nanomolar



Resolution Phase Mimetics Potential Regenerative Therapies ?

From C.N. Serhan FASEB J 2017

Acknowledgements

CETRI
Center for Experimental Therapeutics and Reperfusion Injury

Thank you !

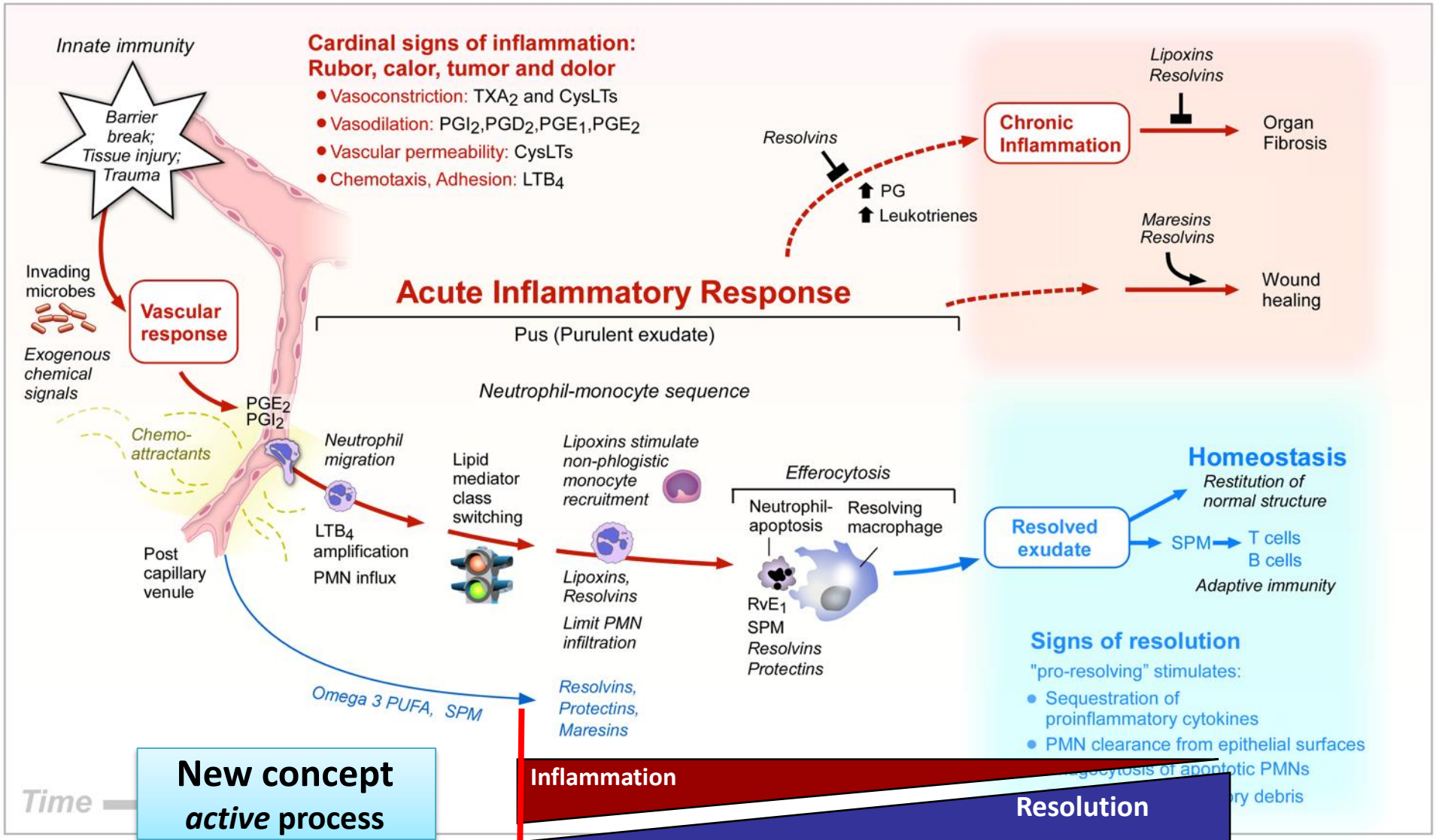
National Institutes of Health
Program Project Grant P01GM095467

National Institute of General Medical Sciences

NIDCR National Institute of Dental and Craniofacial Research

P50-DE016191
CN Serhan, PI/PD

Resolution of Inflammation is an Active Process With Novel Mediators & Control Mechanisms

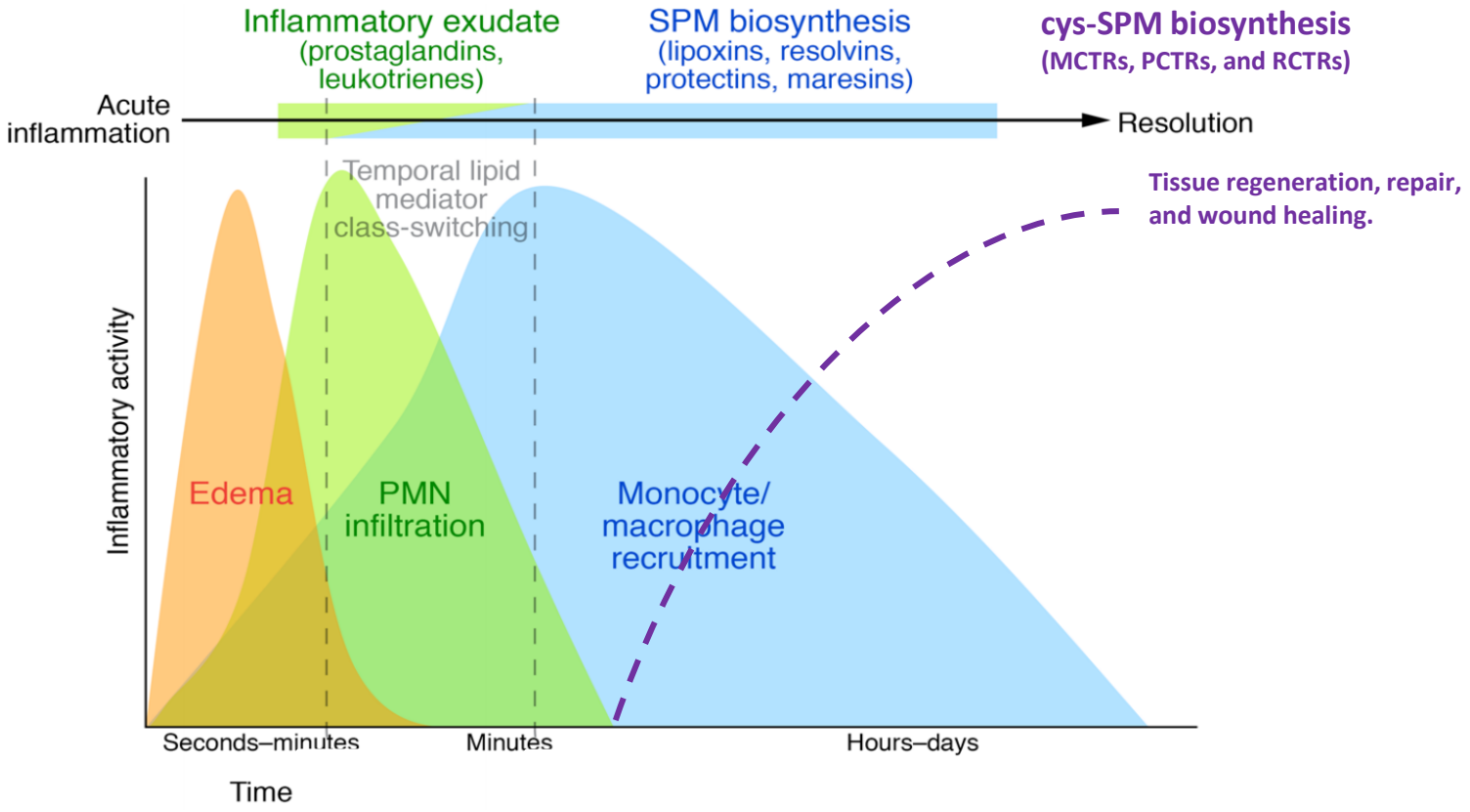


CN Serhan Nature vol 510 June 2014 ; FJ 2017

nature

Summary

The Acute Inflammatory Response and Lipid Mediator Biosynthesis

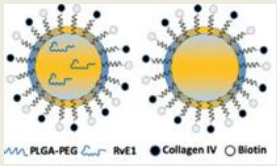


Adapted from: Serhan & Levy *JCI* 2018.

CETRI Center for Experimental Therapeutics and Reperfusion Injury

Resolvin Scaffold Systems Promote Regeneration

- ***Perivascular delivery of RvD1 gel or wrap reduce neointimal hyperplasia within rabbit vein grafts***



Perivascular delivery of resolvin D1 inhibits neointimal hyperplasia in a rabbit vein graft model

Check for updates

Bian Wu, MD,[a] Evan C. Werlin, MD,[a] Mian Chen, MD,[a] Giorgio Mottola, MD,[a] Anuran Chatterjee, PhD,[a] Kevin D. Lance, PhD,[b] Daniel A. Bernards, PhD,[b] Brian E. Sansbury, PhD,[c] Matthew Spite, PhD,[c] Tejal A. Desai, PhD,[b] *and* Michael S. Conte, MD,[a] *San Francisco, Calif; and Boston, Mass*

RvD1 prepared using Pluronic F127 gel
RvD1 wrap prepared using a thin bilayered poly(lactic-co-glycolic acid) (PLGA) film

- ***Intramucosal injections of nanoparticles containing RvE1 promote intestinal epithelial wound repair***

Resolvin E1 is a pro-repair molecule that promotes intestinal epithelial wound healing

Miguel Quiros[a,1], Darius Feier[a], Dorothee Birkl[a], Rachit Agarwal[b], Dennis W. Zhou[b], Andrés J. García[b], Charles A. Parkos[a], and Asma Nusrat[a,1]

Hydrogels , PEGs

Biomaterials 268 (2021) 120475

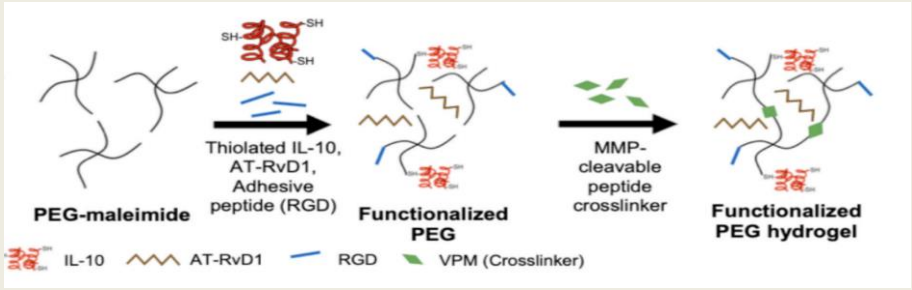
Contents lists available at ScienceDirect

Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials

Dual delivery of IL-10 and AT-RvD1 from PEG hydrogels polarize immune cells towards pro-regenerative phenotypes

Mary Caitlin P. Sok[a,c,1], Nusaiba Baker[a,c,1], Claire McClain[a], Hong Seo Lim[a], Thomas Turner[a], Lauren Hymel[a], Molly Ogle[a], Claire Olingy[a], Joshua I. Palacios[a], José R. Garcia[a], Krithik Srithar[a], Andrés J. García[b,d], Peng Qiu[a,b], Edward A. Botchwey[a,b,*]

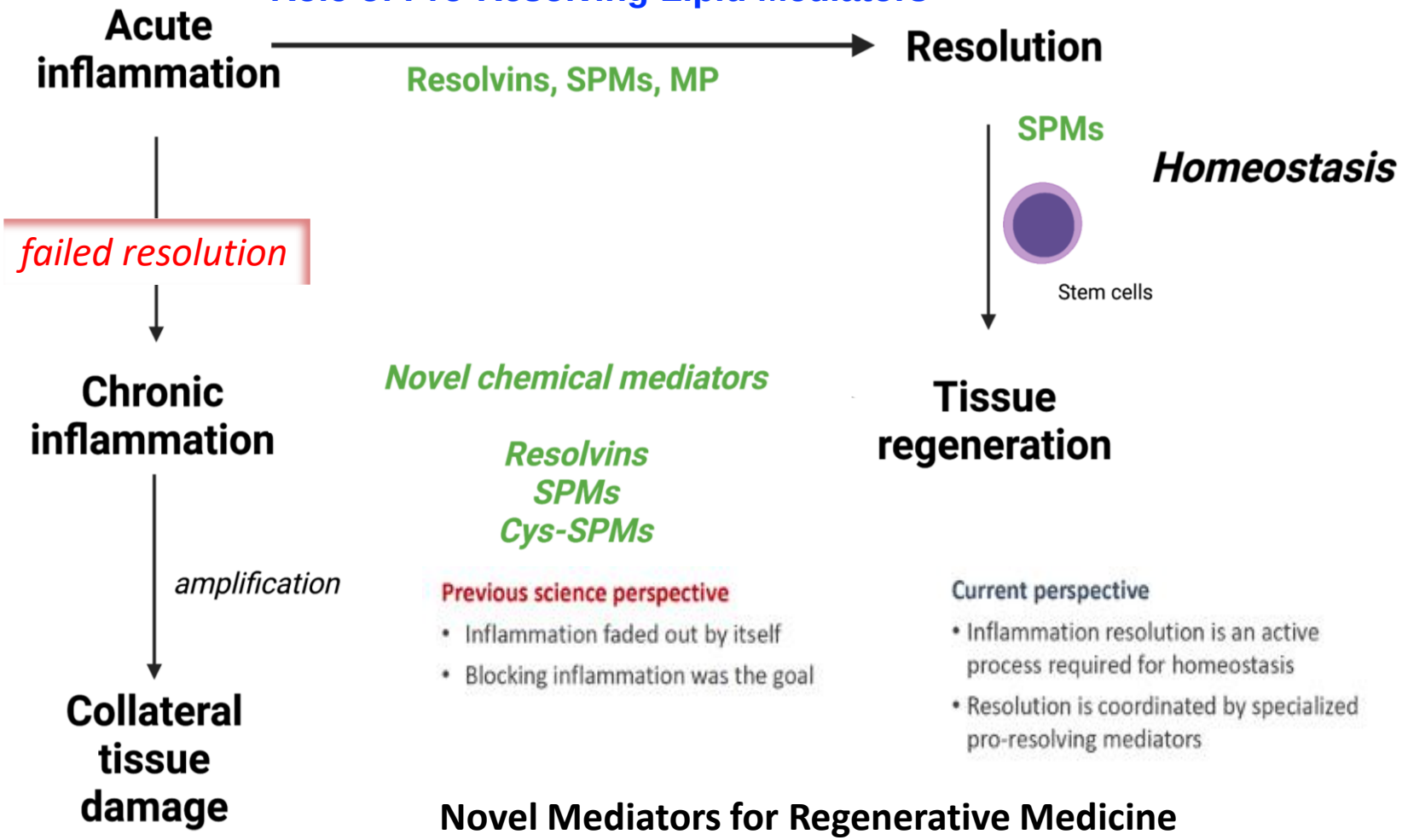


Today's Outline Presentation;

- ***What immune factors and pathways play a role in regeneration ?***

Endogenous Control Mechanisms In Resolution of Inflammation:

Role of Pro-Resolving Lipid Mediators



Novel Mediators for Regenerative Medicine

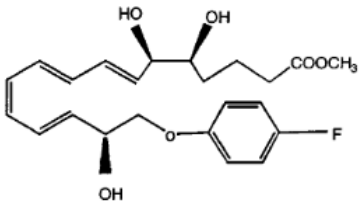
SPM & Analog Mimetics *Lessons from* Transplant Models

RvE1 & LXA_4 – Kidney transplantation
LXA_4 – Cardiac transplantation

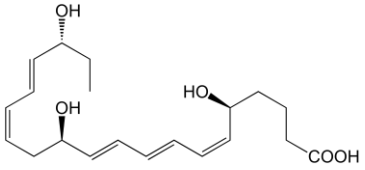
The endogenous pro-resolving mediators lipoxin A_4 and resolvin E1 preserve organ function in allograft rejection

Bruce D. Levy [a,b,*], Qing-yin Zhang [c], Caroline Bonnans [a], Valeria Primo [c], John J. Reilly [a], David L. Perkins [d], Yurong Liang [e], M. Amin Arnaout [c], Boris Nikolic [c], Charles N. Serhan [b,*]

[a] Pulmonary and Critical Care Medicine, Department of Internal Medicine, Brigham and Women's Hospital, Harvard Institutes of Medicine, 77 Avenue Louis Pasteur, Boston, MA 02115, USA
[b] Center for Experimental Therapeutics and Reperfusion Injury, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Institutes of Medicine, 77 Avenue Louis Pasteur, Boston, MA, USA
[c] Division of Nephrology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[d] Department of Medicine, School of Medicine, University of California, San Diego, CA, USA
[e] Hospital & Institute of Hepatobiliary Surgery, Chinese PLA General Hospital, Beijing, China



ATLa (LXA_4 analog)



RvE1

- ↓ Neutrophil accumulation
- ↓ Calcineurin
- ↓ Hepatic tissue injury
- ↓ Serum ALT and AST levels
- ↓ IFNγ

- ↑ IL-10
- ↑ **Survival**

LXA_4 – BMT induced GvHD

The FASEB Journal • Research Communication

A synthetic eicosanoid LX-mimetic unravels host-donor interactions in allogeneic BMT-induced GvHD to reveal an early protective role for host neutrophils

Pallavi R. Devchand,* Birgitta A. Schmidt,* Valeria C. Primo,† Qing-yin Zhang,† M. Amin Arnaout,† Charles N. Serhan,*,[1] and Boris Nikolic†

*Center for Experimental Therapeutics and Reperfusion Injury, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, USA; and †Renal Division, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

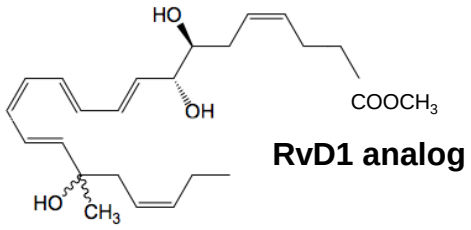
RvD1 – Corneal transplantation

Cornea

The Resolvin D1 Analogue Controls Maturation of Dendritic Cells and Suppresses Alloimmunity in Corneal Transplantation

Jing Hua,[1] Yiping Jin,[1] Yihe Chen,[1] Takenori Inomata,[1] HyunSoo Lee,[1] Sunil K. Chauhan,[1] Nicos A. Petasis,[2] Charles N. Serhan,[3] and Reza Dana[1]

[1]Schepens Eye Research Institute and Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, Massachusetts, United States
[2]Department of Chemistry and Loker Hydrocarbon Research Institute, University of Southern California, Los Angeles, California, United States
[3]Center for Experimental Therapeutics and Reperfusion Injury, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, United States



RvD1 analog

- ↓ DC maturation
- ↓ IFNγ–secreting T cells
- ↓ T-cell infiltration
- ↓ Angiogenesis

- ↑ **Survival**

Loss of Resolution (reduced SPMs) in Humans

Failed Resolution Mechanisms? Aging ?

- Atherosclerosis

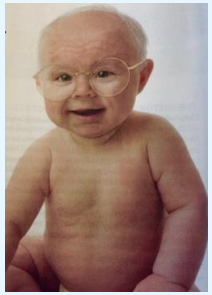
  (*e.g.* SPM to LTB_4 are reduced in plaques)
- Dry eye
- Autoimmunity
- Arthritis (synovial fluid)
- Obese patients (omental adipose tissue)
- Alzheimer's disease (brain and cerebrospinal fluid)
- Smokers
- Periodontal disease

Substrate level

biosynthesis enzymes

SPM-receptor defect

genetic defects



THE JOURNAL OF IMMUNOLOGY

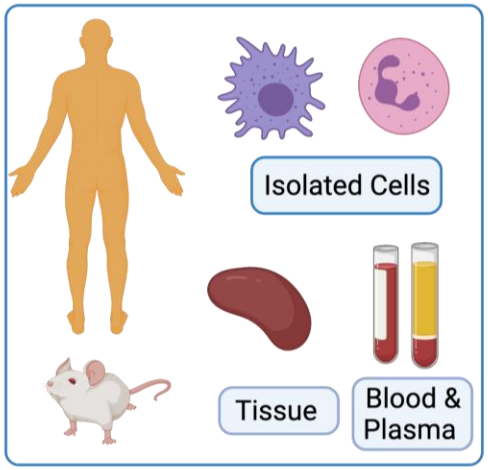
Aging Delays Resolution of Acute Inflammation in Mice: Reprogramming the Host Response with Novel Nanoproresolving Medicines

Hildur H. Arnardottir, Jesmond Dalli, Romain A. Colas, Masakazu Shinohara and Charles N. Serhan

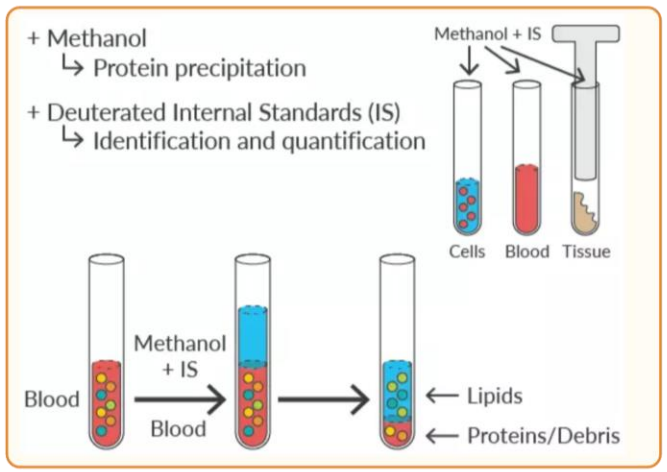
Serhan, *Nature,* 2014
Serhan & Levy, , *JCI,* 2018

Mapping Lipid Mediator in Host Defense Programs using LM-Metabololipidomics

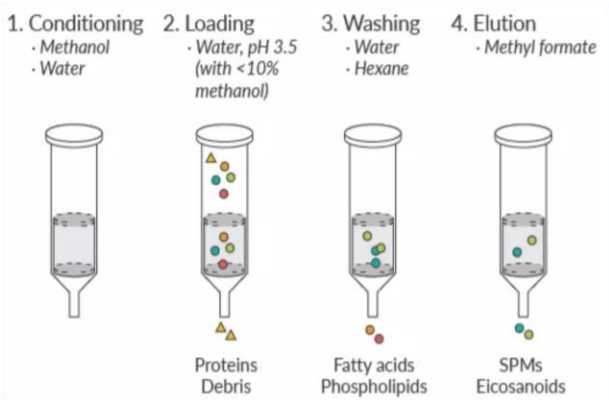
1. Biological Samples



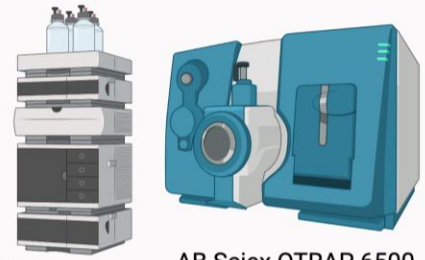
2. Sample Preparation



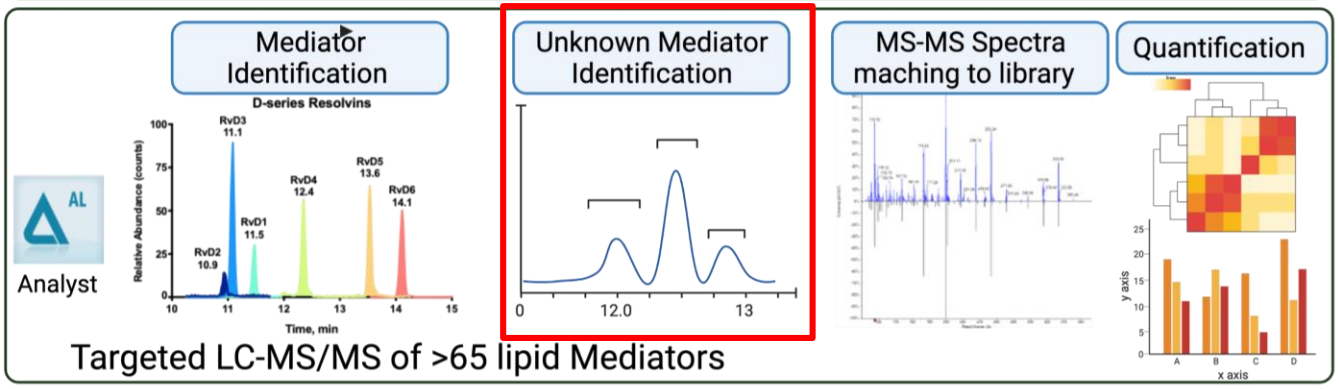
3. Solid-Phase Extraction



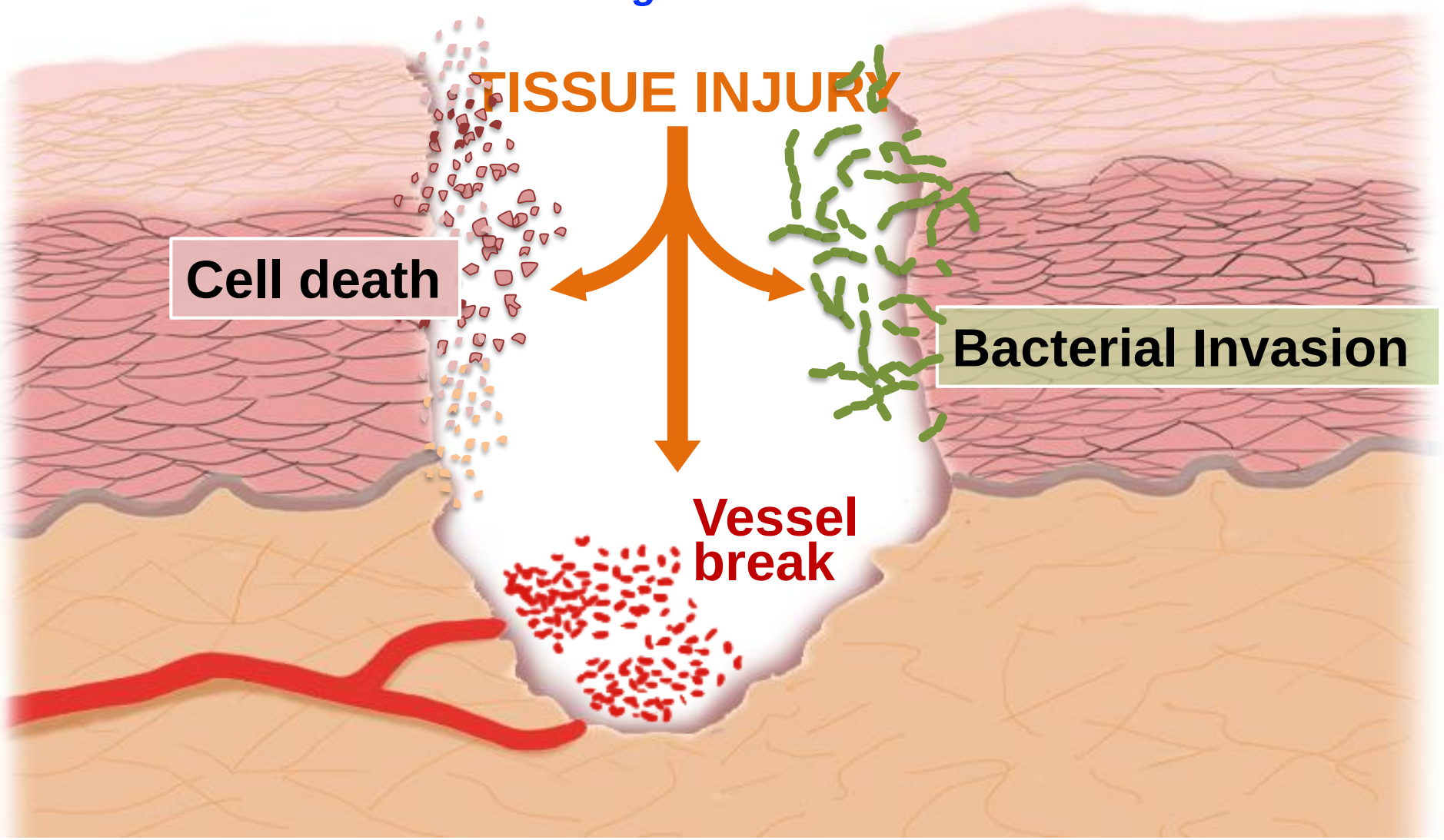
4. Mass Spectrometry



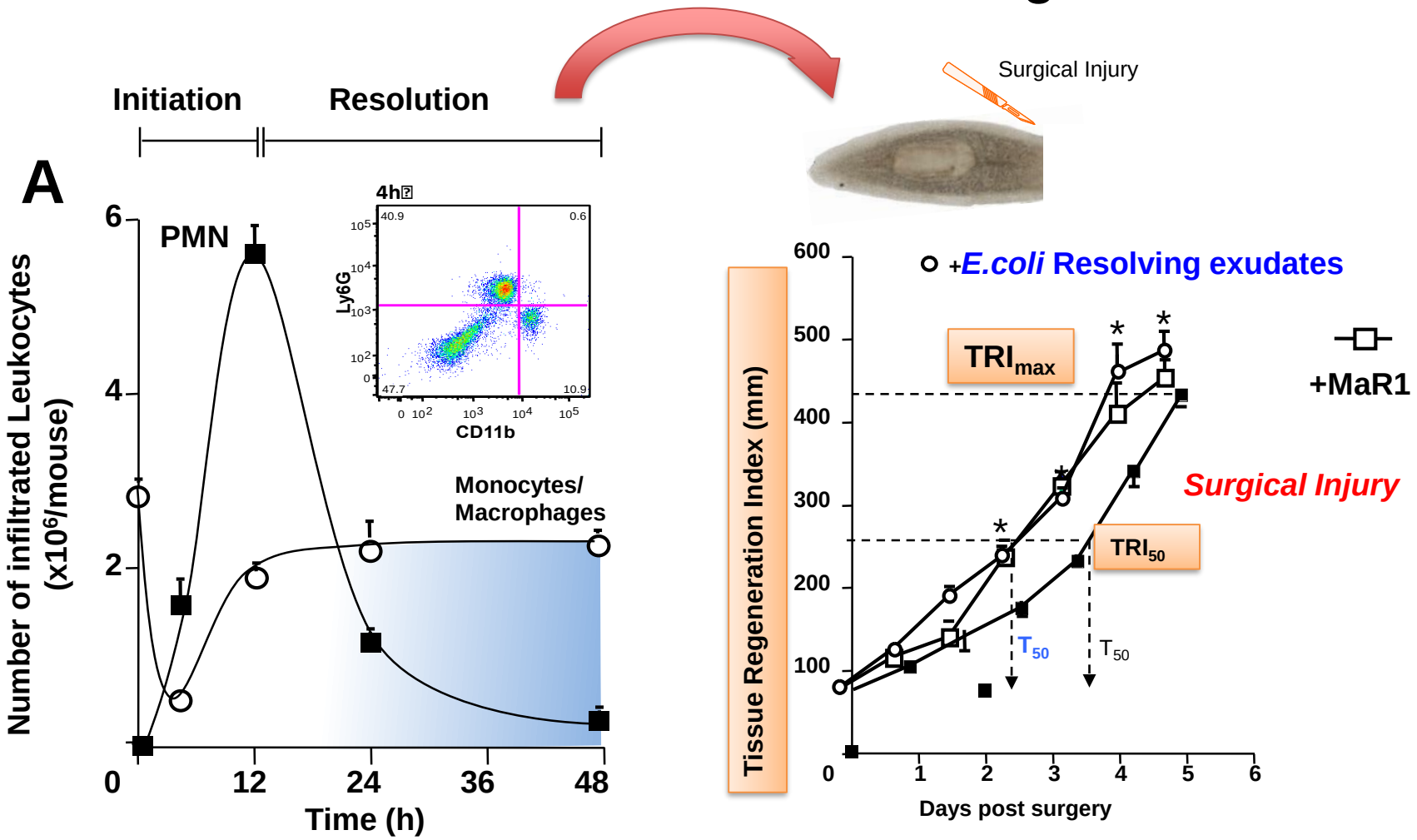
5. Lipid Mediator Identification & Quantification



Are there Novel Mediators in resolving infectious exudates that activate tissue regeneration?



Resolving E. coli Exudates Isolates Contain Novel Molecules that Promote Tissue Regeneration



Surgically injured planaria incubated with SPE-C isolate fraction 2 from E. coli resolving infectious exudates (REs), human milk, maresin 1 (100 nM), or vehicle (surgical injury; water containing 0.01% EtOH).

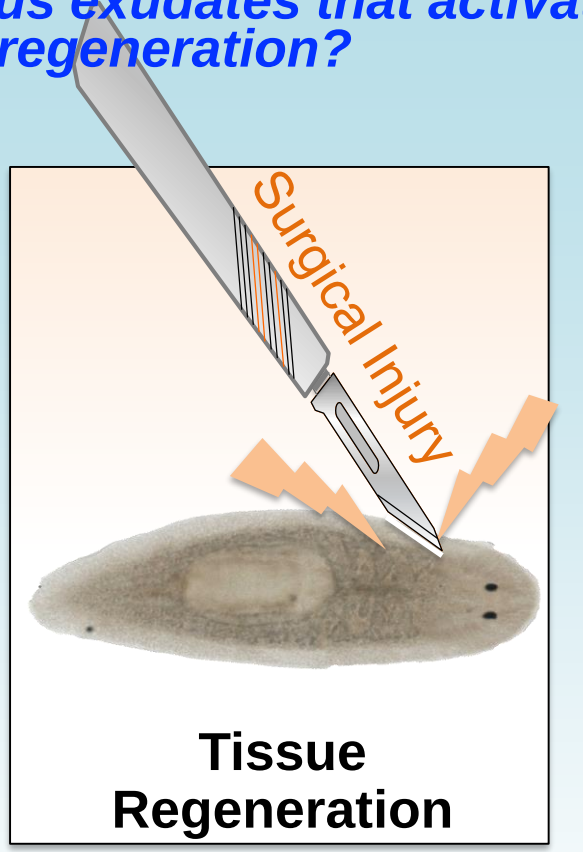
Tissue regeneration indices were determined. T_{50}, time interval corresponding to 50% of maximal tissue regeneration (TRI_{50})=Results are mean ± SEM (n = 9 per group).

Are there Novel Mediators in resolving infectious exudates that activate tissue regeneration?

Hunt for Novel Endogenous Controllers

- ***E. coli* infectious Mouse exudates**
- **Human milk**
- **Human macrophages**

Chemical Mediators



Anti-Inflammatory

Pro-Resolving

MaR1 Directly Activate Regeneration

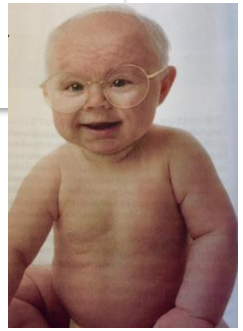
PNAS PLUS

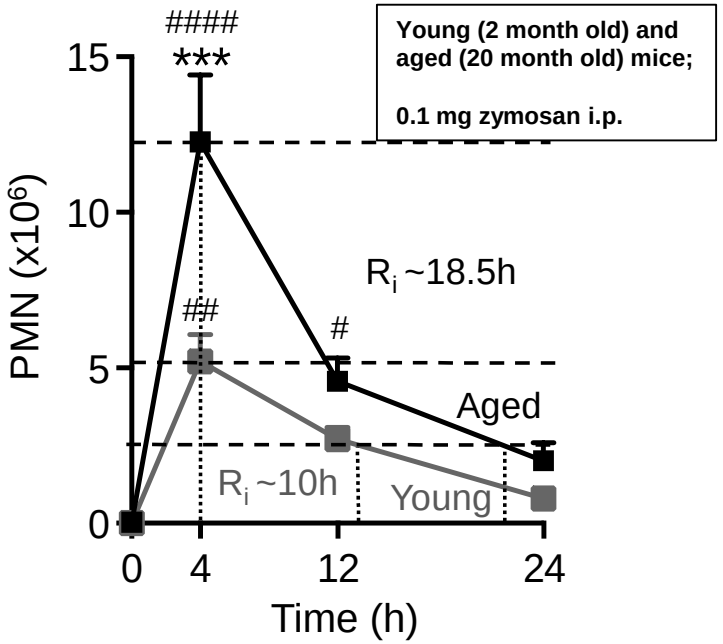
Identification of 14-series sulfido-conjugated mediators that promote resolution of infection and organ protection

Jesmond Dalli, Nan Chiang, and Charles N. Serhan[1]

Center for Experimental Therapeutics and Reperfusion Injury, Department of Anesthesiology, Perioperative and Pain Medicine, Harvard Institutes of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02115

Resolution of Inflammation is Delayed in Aged Mice





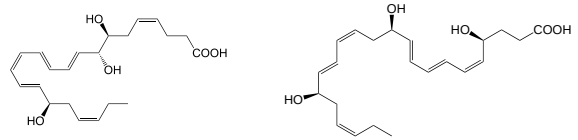
	Young mice peritonitis	Aged mice peritonitis	% increase in aged mice
Ψ_{max} (x10^6)	5.2±0.9	12.3±2.1	**136%**
T_{max} (h)	4.0	4.0	-
T_{50} (h)	~ 14.0	~22.5	**61%**
R_i (h)	~10.0	~18.5	**85%**

THE JOURNAL OF IMMUNOLOGY

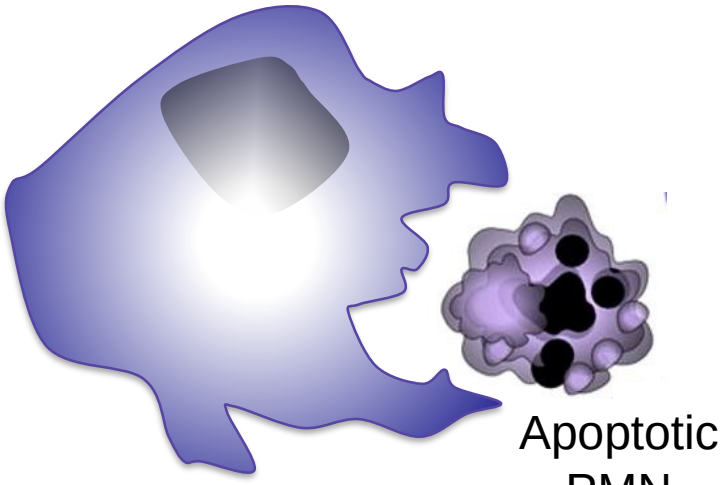
Aging Delays Resolution of Acute Inflammation in Mice: Reprogramming the Host Response with Novel Nanoproresolving Medicines

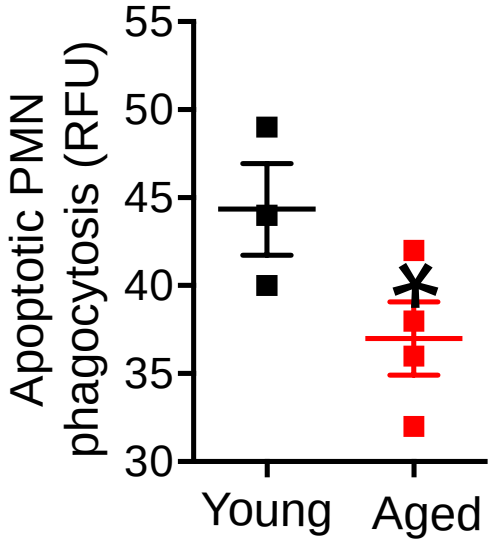
Hildur H. Arnardottir, Jesmond Dalli, Romain A. Colas, Masakazu Shinohara and Charles N. Serhan

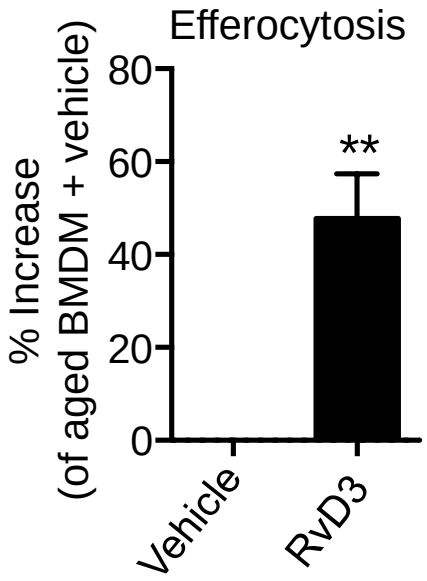
Uptake of Apoptotic PMN is Impaired in Macrophages from Aged Mice: Resolvins & Nano-PR Medicines



Efferocytosis







BMDM from young (2 month old) aged (20 month old) mice

- ***Human Monocyte-derived Resolvin-NanoPRMedicines reduce inflammation and stimulate resolution in aged mice***

The Journal of Immunology

Arnardottir *et al*.

BRIGHAM HEALTH
BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Resolving Inflammation Stimulates Tissue Regeneration via Novel Mediators

Charles N. Serhan, Ph.D., DSc.

Center for Experimental Therapeutics and Reperfusion Injury,
Department Anesthesia, Perioperative and Pain Medicine
Brigham and Women's Hospital and Harvard Medical School

- ***What immune factors and pathways play a role in regeneration ?***

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

Board on Health Sciences Policy
Forum on Regenerative Medicine

CETRI
Center for Experimental Therapeutics and Reperfusion Injury

Journal of Clinical Neuroscience 64 (2019) 227–233

Contents lists available at ScienceDirect

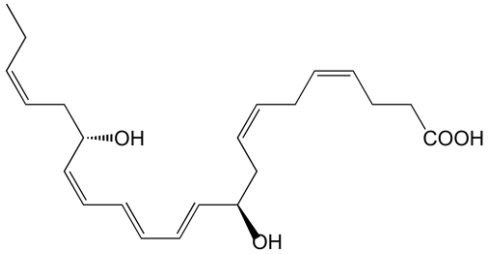
Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

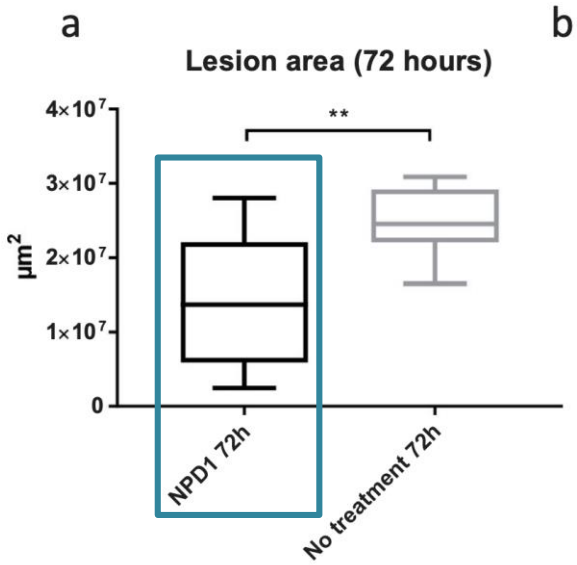
Experimental study

Brain tissue saving effects by single-dose intralesional administration of Neuroprotectin D1 on experimental focal penetrating brain injury in rats

Rand Wilcox Vanden Berg [a], Johan Davidsson [b], Erik Lidin [c], Maria Angéria [c], Mårten Risling [c], Mattias Günther [c,*]



- ***NPD1 decreases the lesion area at bregma***



Photomicrograph of brain slide in dark field illumination showing lesion are marked for quantification.