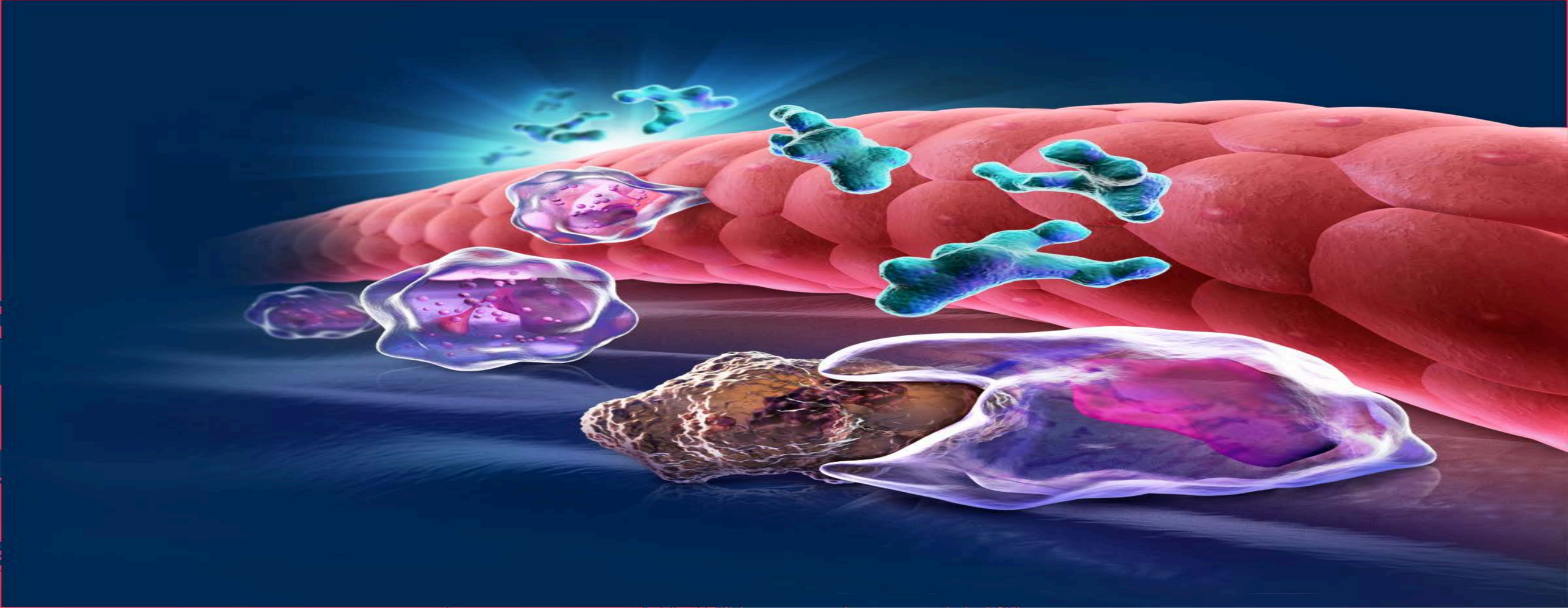


Innovation in Clinical Practice

Role of Specialized Pro-Resolving Mediators (SPMs) in the Resolution of Chronic Inflammation

Jennifer Stagg, ND

Metagenics®

Innovation in Clinical Practice—New News in Patient Care

1. Novel Solution and Pathway to Support Inflammatory Responses

- New Clinical Benefits to Resolve Inflammation
- Fills a Gap in Managing Inflammatory Responses

2. Independent yet Complementary Solutions to Managing Inflammatory Conditions

- Not Blocking, inhibiting or suppressing inflammation
- ‘Resolves’ inflammation to avoid prolongation to to chronic health conditions

3. Proprietary Nutritional Solutions

- Specialized Pro-resolving Mediators
- Standardized Level of Activity

4. Clinical Uses with Superior Improvement in Ability to Resolve Inflammation

- Activates effective resolution response
- Resolution critical component of normal inflammatory response

Inflammation

Young

Optimal Resolution
Low Pro-Inflammatory Status
High Efficiency of Stress Response

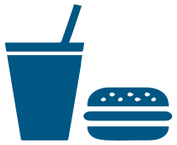
Aged

Inadequate Resolution
High Pro-Inflammatory Status
Low Efficiency of Stress Response

Unresolved inflammation leads to chronic inflammation

Injuries

Infection



Poor Diet

Chronic inflammation

Chronic inflammation is associated with disease pathogenesis

Atherosclerosis

Alzheimer's Disease
Huntington's Disease
Parkinson's Disease

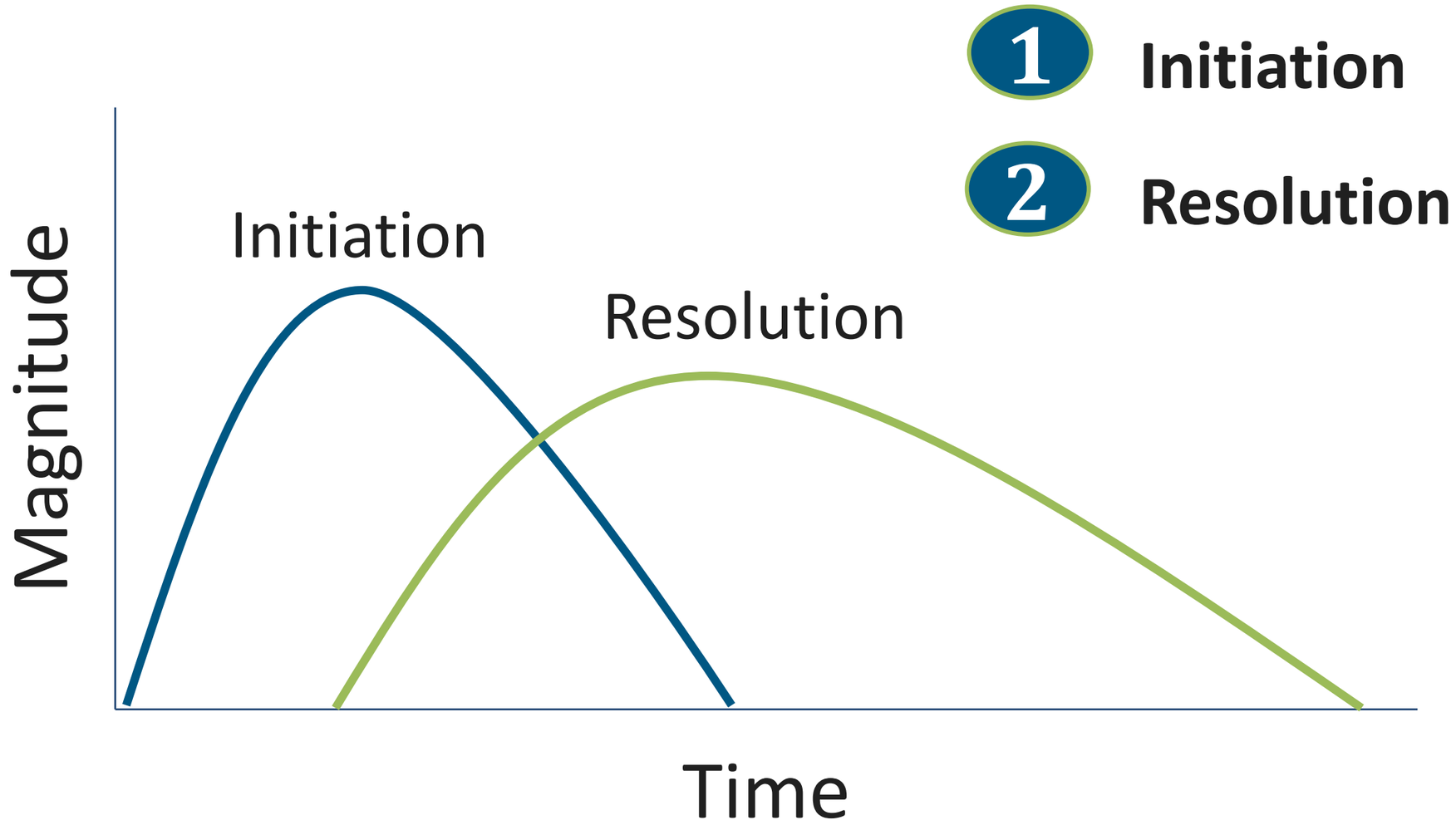
Cancer

Arthritis

Insulin Resistance
Type 2 Diabetes

The Inflammatory Response

Inflammation Has Two Stages

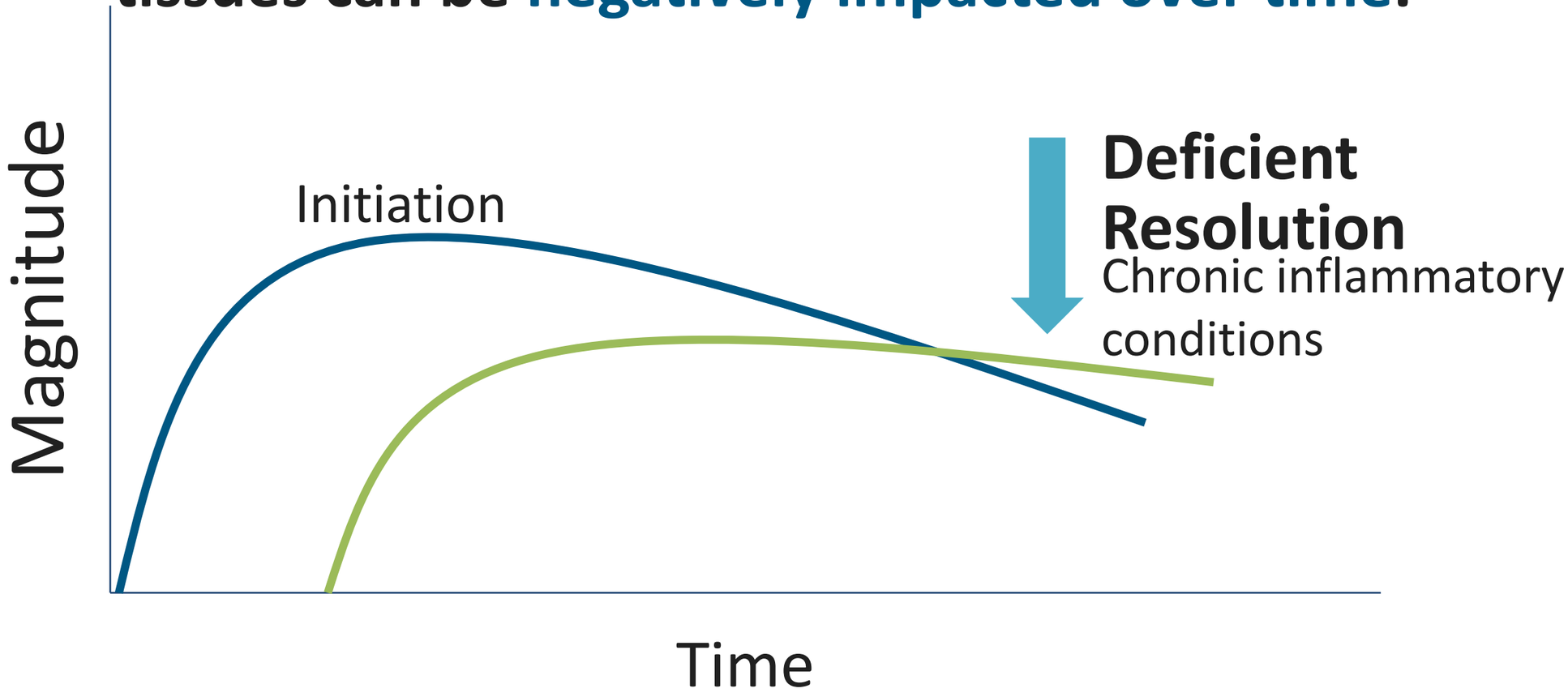


Serhan CN. *Nature*. 2014;510:92-101.

Spite et al. *Cell Metab.* 2014;19:21-36.

Without Resolution, Inflammation Can Become Persistent & Chronic

If the immune response is left unresolved, tissues can be negatively impacted over time.

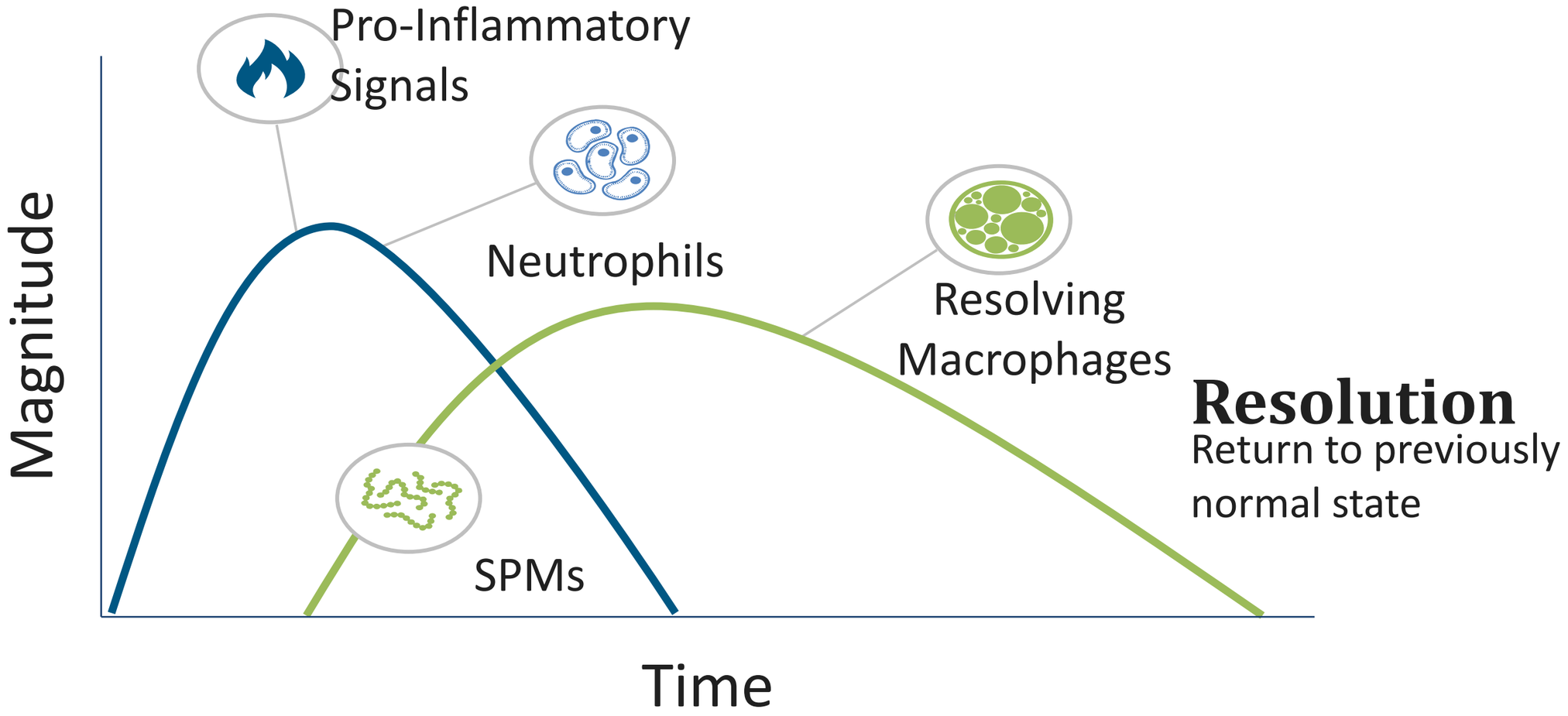


Serhan CN. *Nature*. 2014;510:92-101.

Spite et al. *Cell Metab.* 2014;19:21-36.

Introducing a Novel Nutritional Therapy & Pathway for Addressing Resolution of Inflammation

Process of Inflammation



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

Spite et al. *Cell Metab.* 2014;19:21-36.

Resolution of Inflammation

New thinking to solve an old problem

Previous Science Perspective

Inflammation faded out by itself

Blocking inflammation was the goal

Emerging Science Perspective

Resolution of inflammation is an active process and is necessary for healing. This is now supported by 100s of research publications

Over the last 20 years, Charles Serhan has conducted groundbreaking work focusing on the resolution of inflammation

New science on nutritional components that actively resolve inflammation

Specialized Pro-Resolving Mediators (SPMs)

- EPA and DHA are converted to SPMs that resolve inflammation
  But the conversion is inefficient in the face of inflammation

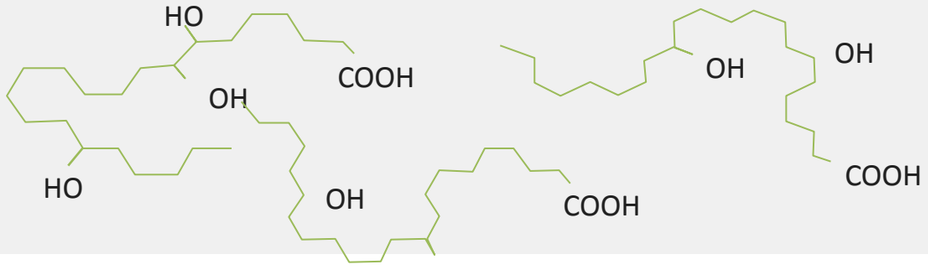
SPMs

EPA → 18-HEPE

DHA → 17-HDHA

Conversion from EPA and DHA is a multi-step process that may be affected by a person's health status

- Maresins
- Resolvins (E-series/D-series)
- Protectins



Different SPMs work together to resolve the immune response and inflammation

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

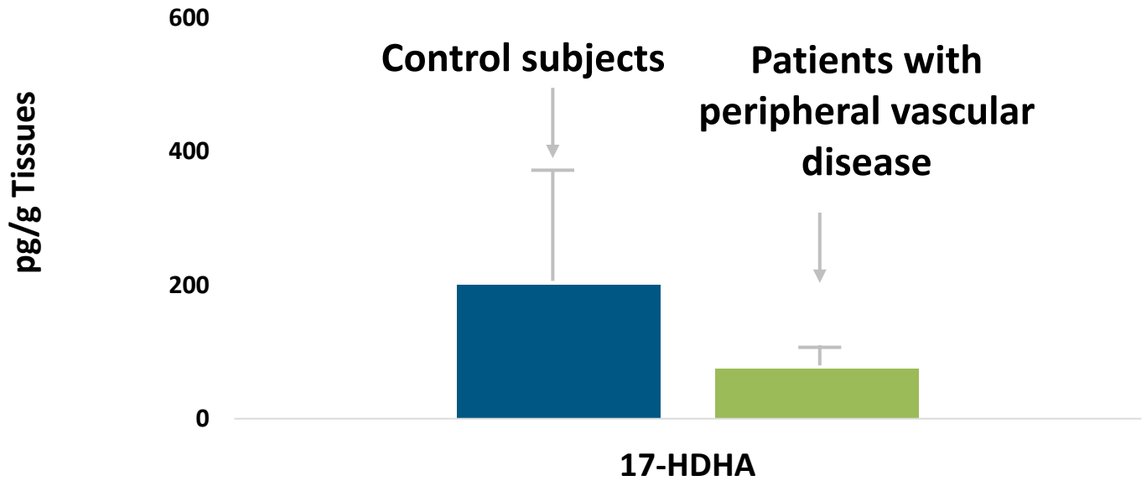
Patients with Peripheral Vascular Disease

Have Reduced Tissue SPM Concentrations

Design: Comparison of tissue SPM concentrations in people with peripheral vascular disease and controls

Key Findings

- ✓ Specific SPMs are reduced in peripheral vascular disease



Claria et al., Am J Physiol Cell Physiol, 2013;304:C1141-9.

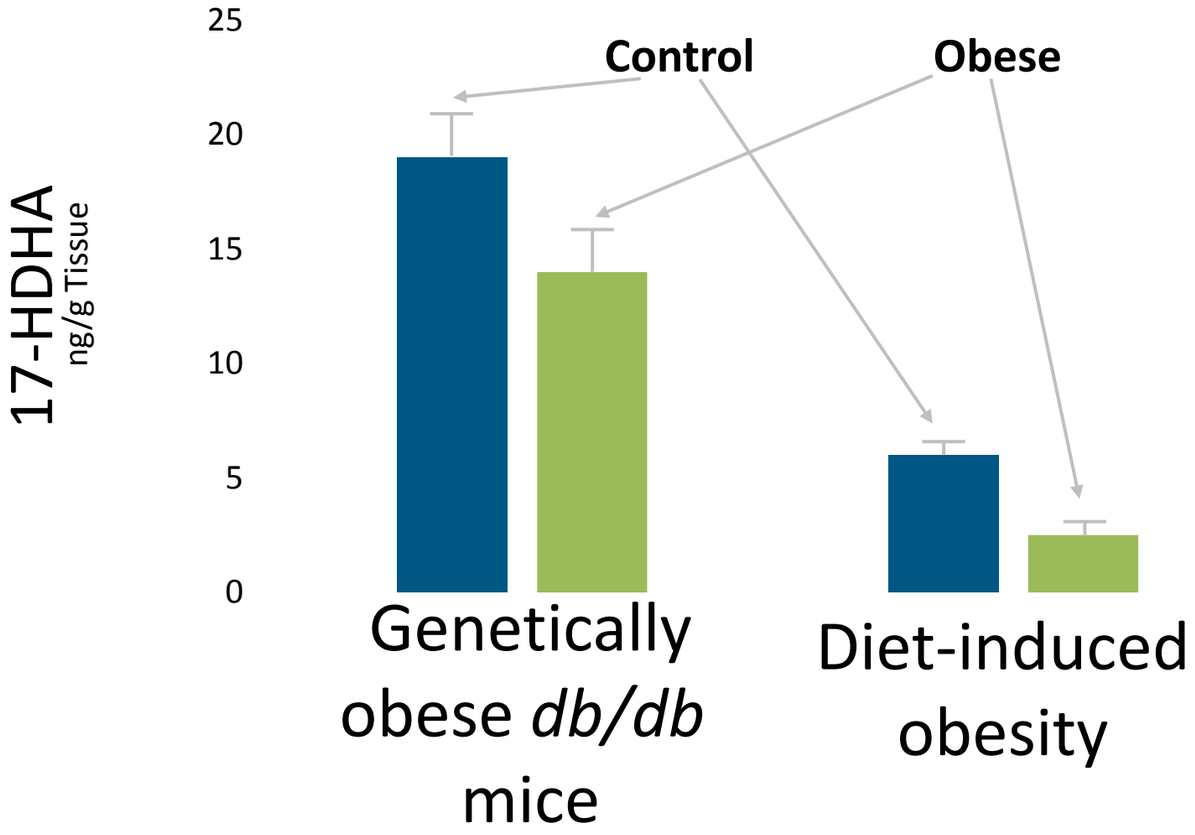
SPMS are Reduced in Obesity States in Animal Model

Design

Model of genetic and diet-induced obesity

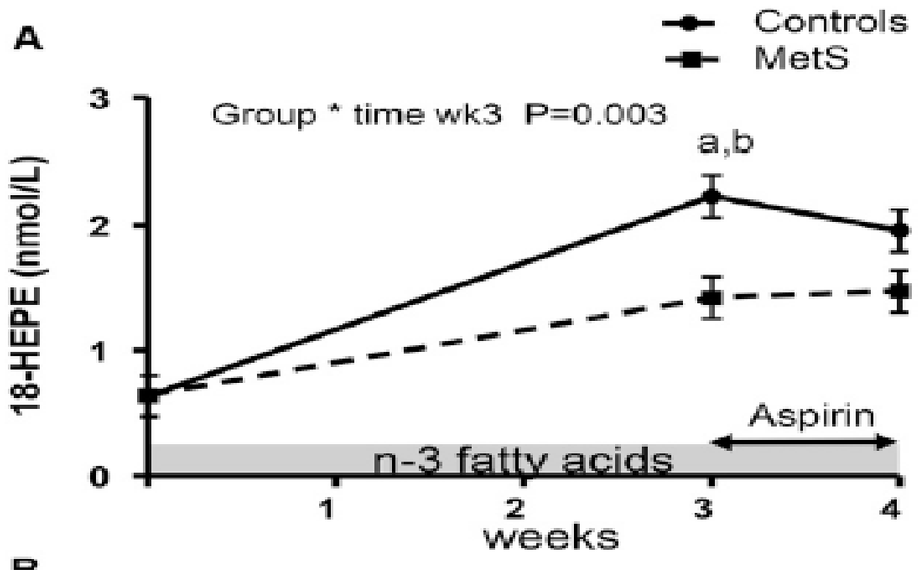
Key Findings

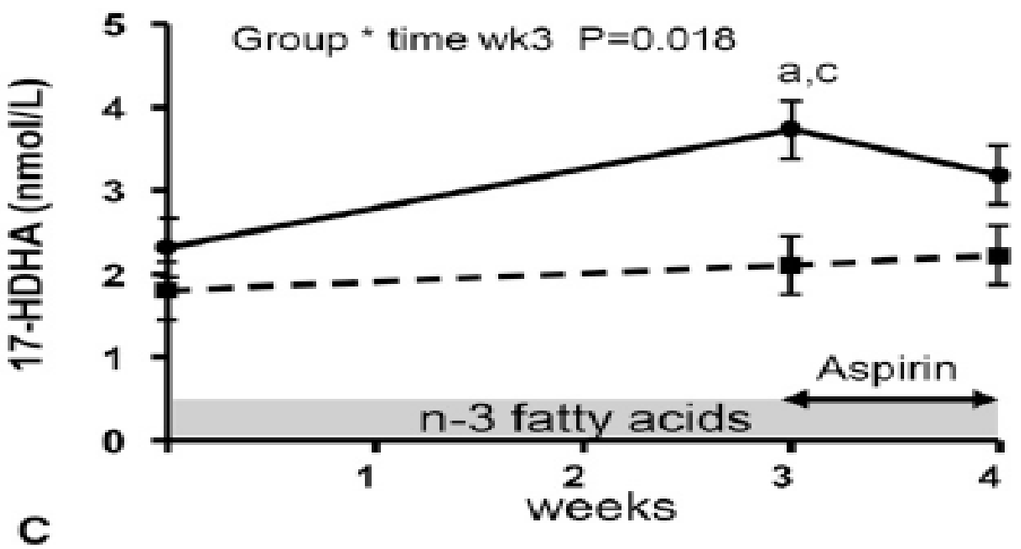
- ✓ SPMs are reduced in tissues of obese mice



Neuhofer et al. *Diabetes* 2013; 62:1945–1956

Appearance of 17-HDHA and 18-HEPE is reduced following fish oil supplementation in Metabolic Syndrome patients compared with healthy controls



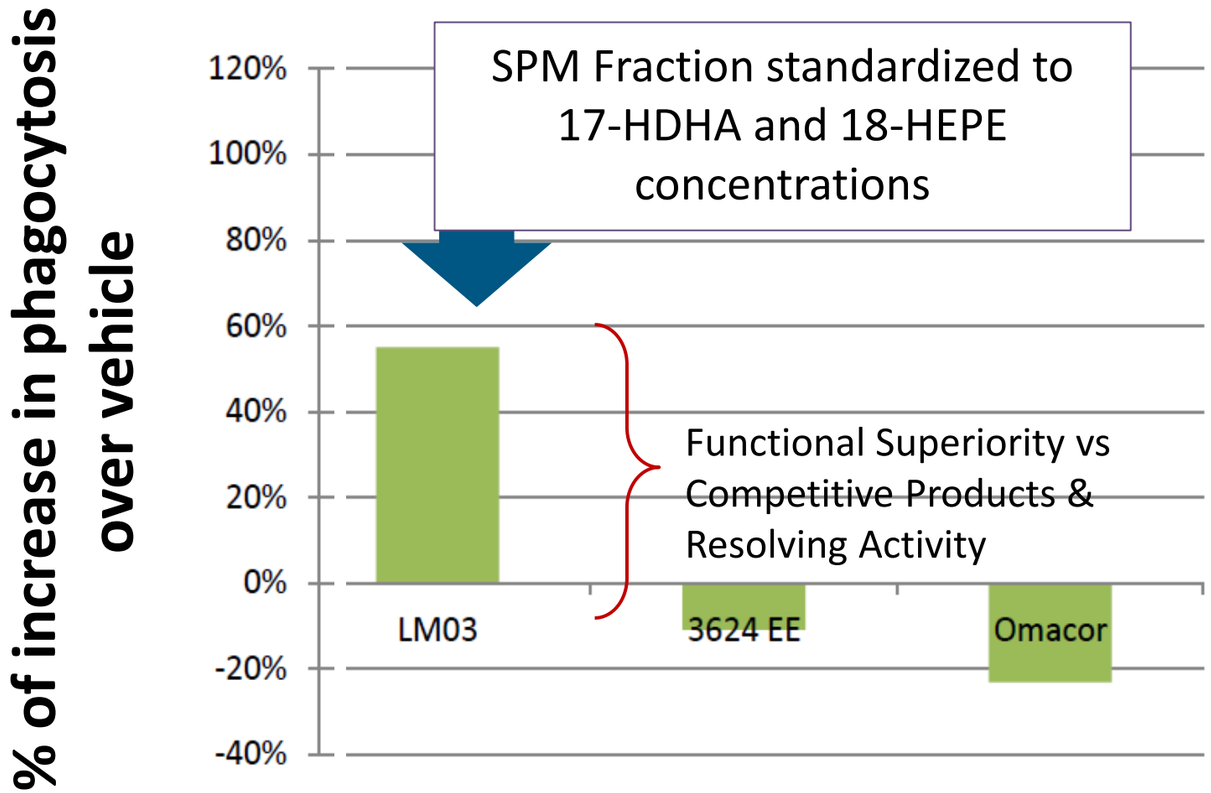


Barden et al. *Am J Clin Nutr* 2015;102:1357-64

Clinical Areas for SPMs

Setting the standard for SPM supplementation

Choosing a fraction based on Resolution Activity



- Not all fractions of fish oil show pro-resolving activity in pre-clinical models
- Process of Oil delivers standardized levels of two key actives *PLUS* total **Resolvin Activity**

Variability in phagocytic response of oils and oil fractions. The phagocytic response of immune cells (Thp-1 cells, a human monocyte cell line) was examined after treatment with various oil fractions and SPMs. Results are shown as increase in phagocytosis compared to control.

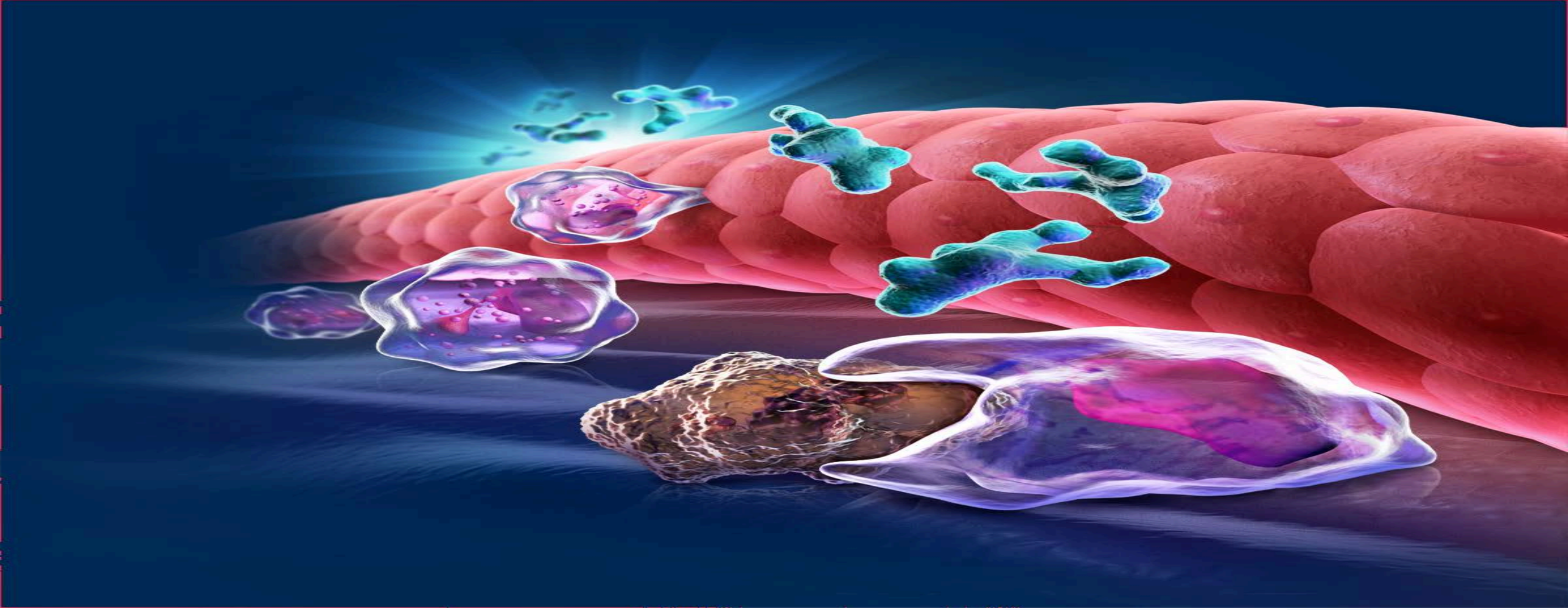
Metagenics Data on File

Clinical Uses and Advantages

Patient Segmentations as Primary Targets of Care and for Nutrition Co-Therapies

Health Conditions Associated with Chronic Inflammation

- Obesity
- Metabolic Syndrome
- Diabetes
- Aging and age-associated diseases
- Vascular disease such as cardiovascular disease and peripheral vascular disease
- Digestive disorders including Inflammatory Bowel Disease (IBD)
- Autoimmune conditions
- Arthritis



Practice-based Research with SPMs

IRB-approved multi-center open case series

Study Goals:

- ✓ Understand the role of SPMs in clinical management of chronic inflammatory conditions
- ✓ Assess the impact of 6 softgels per day for 4 weeks and potential for significant difference when dose was increased to 8 softgels per day. Doses chosen considering the chronic inflammatory nature of the patient types

Patients with inflammatory conditions/symptoms (n=34)

Inflammatory condition included:

- **Chronic pain**
- **Fibromyalgia**
- **Increased inflammatory markers e.g. hsCRP**

Week 1 — **Assessment of blood based biomarkers of inflammation, clinical assessment, subject assessment of pain, symptoms and quality of life.**

Received 6 SPM softgels per day

Week 4 — **Assessment of blood based biomarkers of inflammation, clinical assessment, subject assessment of pain, symptoms and quality of life.**

Received 8 SPM softgels per day

Week 8 — **Assessment of blood based biomarkers of inflammation, clinical assessment, subject assessment of pain, symptoms and quality of life.**

Practice-Based Research Clinical Collaborators

Robert Bonakdar, MD
Director of Pain Management at the Scripps Center for Integrative Medicine in La Jolla, California

Bridget Briggs, MD
Family Practice, Murrieta, CA

Andrew Heyman, MD
Program Director of Integrative and Metabolic Medicine at The George Washington University

Jennifer Stagg, ND
Whole Health Associates, Avon, CT

Cory Rice, DO
Forney Wellness, Dallas, TX

Taz Bhatia, MD
Atlanta Holistic & Integrative Medicine, Atlanta, GA

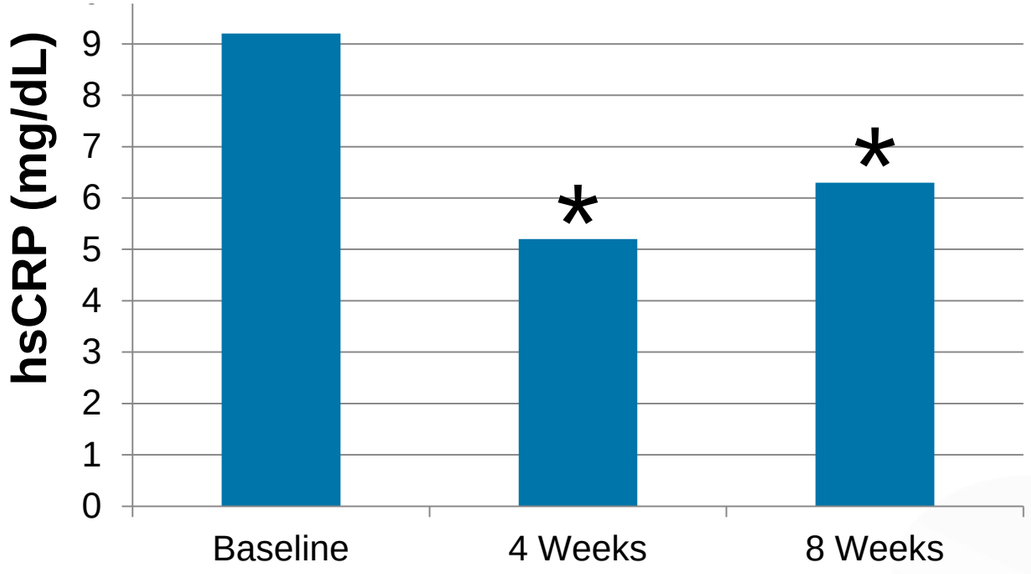
Practice-Based Research with SPMs: Clinical cohort overview

Parameter	Mean ± SD
Age	49.3 ± 10.8 years
BMI	29.4 ± 8.2 kg/m^2
Total participants completing 3 study visits	**n=34**
Sex	Women (n = 28); Men (n = 6)
Arthritis (RA/OA)	n = 14
Chronic Inflammation and associated symptom of pain	n = 15
Fibromyalgia	n = 6
Co-morbidities*	n = 34

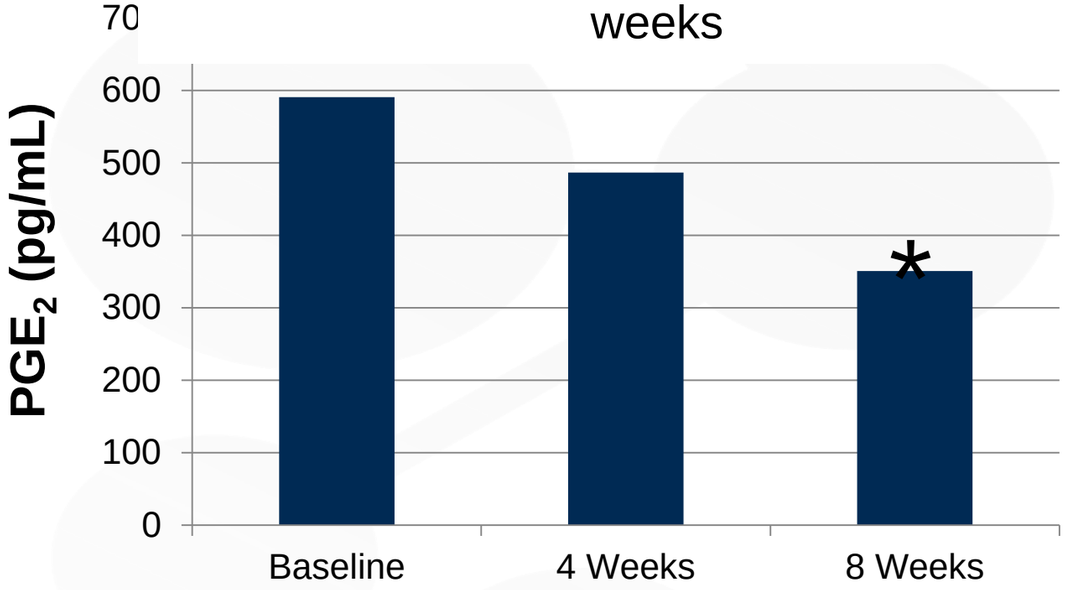
Co-morbidities, including obesity, , metabolic syndrome, hyperlipidemia, hypertension, migraine, insomnia, reflux, fatigue, constipation, hypothyroidism, Sjogren's syndrome, Hashimoto's, and Lyme disease.

Key point: Inflammatory biomarkers significantly reduced – appropriate for tracking SPM response

hsCRP, marker of acute phase response and general inflammatory environment
43% reduction from baseline within 4 weeks and remained significantly reduced

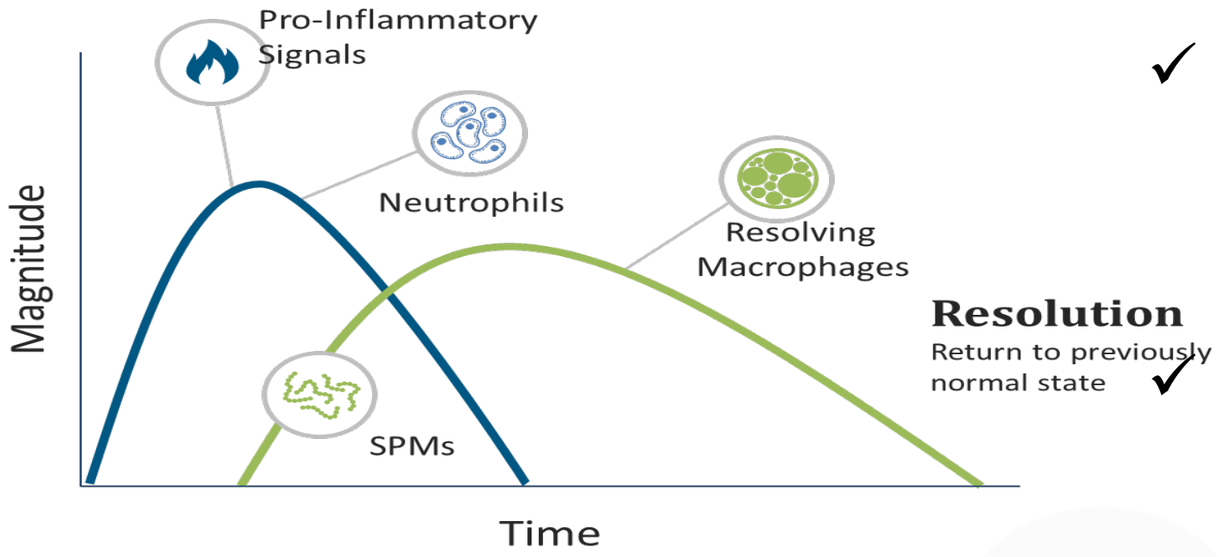


PGE2 is a prostaglandin involved in inflammation initiation
PGE2 was reduced by 41% at 8 weeks and was shown to normalize (200-400pg/mL) at 8 weeks



Other inflammatory biomarkers commonly measured in clinical practice were not raised at baseline in this patient group, and remained within normal limits throughout the study

SPMs driving reduction in hsCRP and PGE_2: potential mechanisms of action

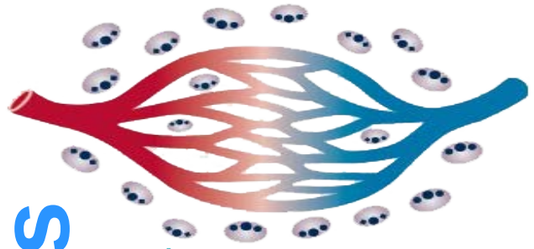


- ✓ Reduction in PMN entering site secreting pro-inflammatory signals including cytokines and PGE_2
- ✓ Lipid mediator class switching during resolution – pro-inflammatory mediators reduce as pro-resolving mediators increase
- ✓ Change in macrophage phenotype to more M2/pro-resolving phenotype for reduction in pro-inflammatory cytokines
- ✓ Knock-on effect of reduction in pro-inflammatory signal production to lowered hsCRP production by liver

Resolution is Necessary to Prevent Tissue Damage

Associated with chronic inflammation

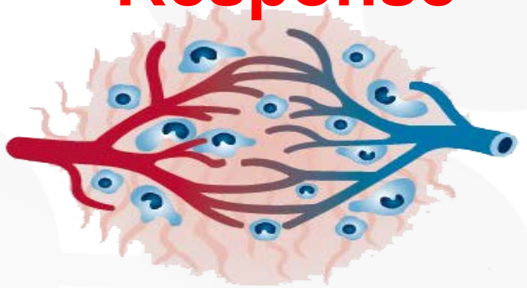
Tissue Impacted
(e.g., over-exercising)



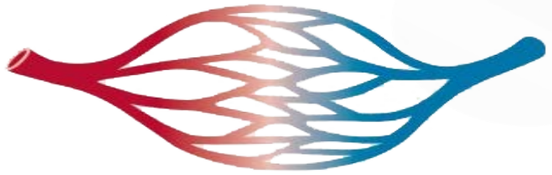
SPMs

Unresolved Immune Response

Progression



Resolution of Immune Response

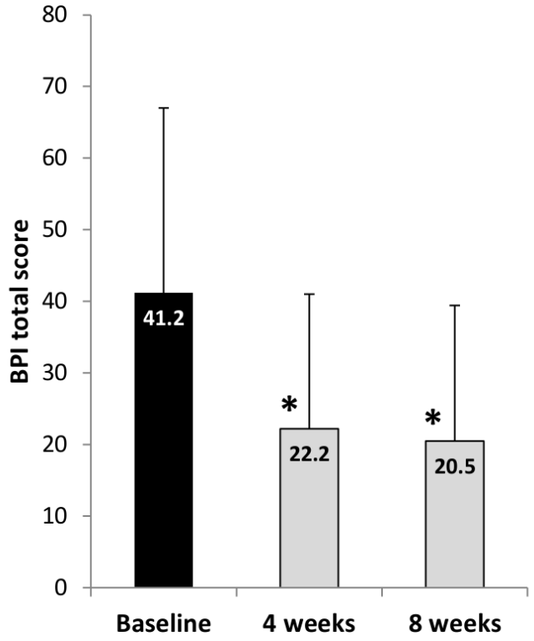


Pain can be a symptom of chronic inflammation

Adapted from Kumar et al; Robbins & Cotran Pathologic Basis of Disease, 8th Edition

Key point: Clinical symptomology improvements with SPM supplementation reflective of the chronic inflammatory condition

- ✓ **Brief Pain Inventory (BPI) scores reduced significantly by 46% at 4 weeks and 50% at 8 weeks**



At 4 and 8 weeks, there was a significant reduction in:

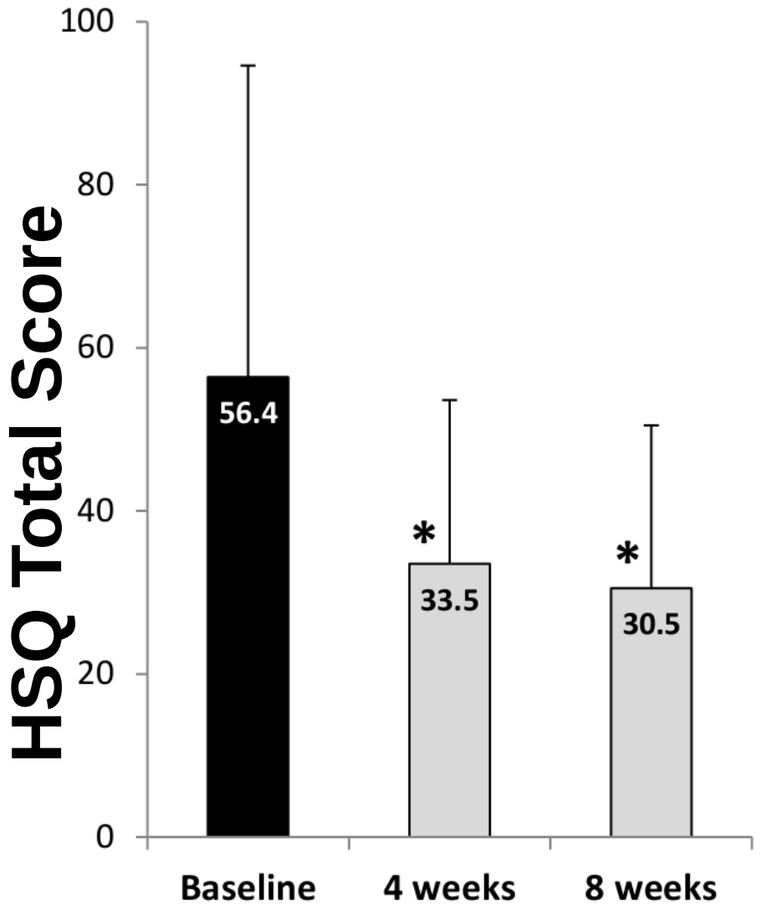
- ✓ Pain at its worst, least and average pain over last 24-hours

At 4 and 8 weeks, there was a significant reduction in interference of pain in

- ✓ General activity
- ✓ Mood
- ✓ Walking ability
- ✓ Normal work
- ✓ Relations with others
- ✓ Sleep
- ✓ Enjoyment of life

BPI is a tool used to assess the severity of pain and the impact of pain on daily functions in patients with pain from chronic diseases or conditions such as osteoarthritis and low back pain

Key point: Clinical symptomology improvements with SPM supplementation reflective of the chronic inflammatory condition



- ✓ Health Symptoms Questionnaire (HSQ) total scores were significantly reduced at 4 weeks and 8 weeks (No significant difference between 4 and 8 weeks)
- ✓ Domains reduced reflected change in the symptoms associated with the chronic clinical condition:
  - Joints/muscle subscale
  - Mind
  - Emotions
  - Head
  - Energy

Quality of life improvements with SPM supplementation

American Chronic Pain Association QOL scale was improved significantly moving from 7.8 to 8.8 within 4 weeks

7	Work/volunteer for a few hours daily Can be active at least five hours a day Can make plans to do simple activities on weekends
8	Work/volunteer for at least six hours daily Have energy to make plans for one evening social activity during the week Active on weekends
9	Work/volunteer/be active eight hours daily Take part in family life Outside social activities limited

Case #1: 50 yo Caucasian man

History & Complaints:

- Osteoarthritis for 4 years
- Obesity (BMI 34.0kg/m2)
- History of hypothyroidism and hypertension

- Presented with daily pain in lower back, knee, toe
- Elevated hsCRP (8.32mg/L) and PGE_2 (794pg/mL)

Family History:

- Father (diabetes, COPD
- Mother: celiac, lupus, OA, HTN, hypothyroidism

Medications

- Desiccated thyroid, zolpidem (10mg/night), DIM (300mg/day), vitamin D3 (5000IU/day), fish oil (330mg omega-3)

Case Study: Dr Cory Rice, DO, Forney Wellness, Dallas, TX

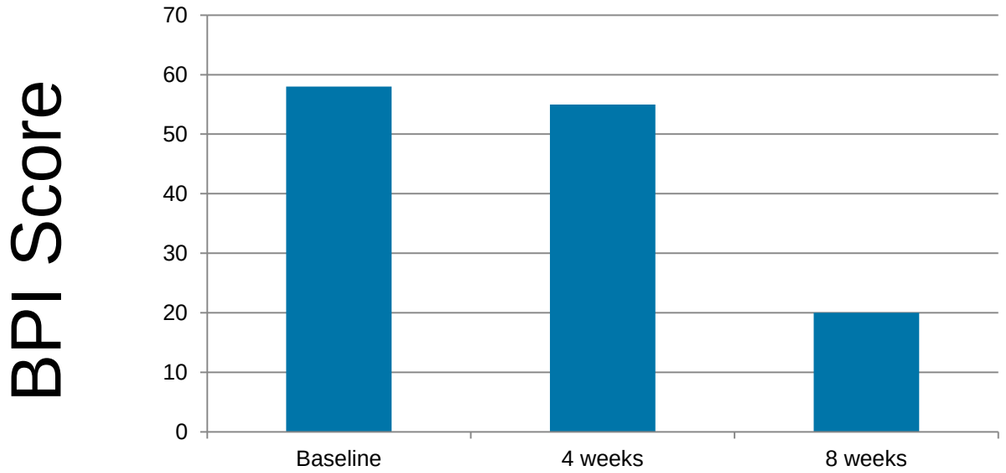
Case #1: Biochemical changes at 4 and 8 weeks

Marker (reference range)	Baseline	4 weeks (note taking 4SPM sg/day)	8 weeks (8 SPM sg/day)	
hsCRP (0-3mg/L)	8.32	0.86	0.74	hsCRP normalized in 4 weeks
PGE2 (200-400pg/mL)	794	847	182	PGE2 normalized in 8 weeks
Fibrinogen (193-504mg/dL)	396	223	226	Stayed within normal limits, modest decrease
IL-6 (0-15.3 pg/mL)	4.8	<0.7	1.8	Stayed within normal limits, modest decrease

Case Study: Dr Cory Rice, DO, Forney Wellness, Dallas, TX

Case #1: Functional improvements at 4 and 8 weeks

Reduced Interference of Pain in Daily Life



- ✓ Pain at its worst, least, average reduced.
- ✓ Interference of pain in general activity, mood, walking, relations with others, sleep and enjoyment of life reduced at 4 and 8 weeks

Scores on HSQ reduced – improved domains (muscle/joint) reflective of clinical changes

Increased quality of life resulting using American Chronic Pain Association Quality of Life Scale

Case Study: Dr Cory Rice, DO, Forney Wellness, Dallas, TX

Case #2: 62 yo woman

History & Complaints:

- Fibromyalgia
- Osteoarthritis
- Sjogren's syndrome
- Hashimoto's thyroiditis
- Chronic fatigue syndrome

Relevant Family History:

- Mother (hyothyroid, RA)
- Sister: Hashimoto's

Medications

- Gabapentin (400mg/night)
- Levothyroxine (125mg)

- Presented with daily pain in legs, knees, ankles, calves, feet, shoulders, back, neck. Pain interfering with QOL
- Elevated PGE2 (1052pg/mL). Other inflammatory biomarkers measured WNL

Case Study: Dr Cory Rice, DO, Forney Wellness, Dallas, TX

Case #2: Biochemical changes at 4 and 8 weeks

Marker (reference range)	Baseline	4 weeks (6SPM sg/day)	8 weeks (8 SPM sg/day)	
hsCRP (0-3mg/L)	1.12	1.04	1.24	Stayed within normal limits
PGE2 (200-400pg/mL)	1052	1510	346	Normalized within 8 weeks

Case Study: Dr Cory Rice, DO, Forney Wellness, Dallas, TX

Case #2: Functional improvements at 4 and 8 weeks

Reduced Pain Reporting

- ✓ 55% reduction in BPI score at 4 weeks and 77% reduction at 8 weeks compared with baseline

	Baseline	4 Weeks	8 Weeks
General Activity	5	0	0
Mood	7	0	0
Walking	7	0	0
Normal work	8	0	0
Relations with others	5	0	0
Sleep	8	2	0
Enjoyment of life	8	0	0

Scores on HSQ reduced – improved domains (muscle/joint; head, energy, mind) reflective of clinical changes

Increased quality of life resulting using ACPA QOL scale.

- Baseline: Work/volunteer limited hours. Take part in limited social activities on weekends (score = 6)
- 8 Weeks: Work/volunteer/be active eight hours daily. Take part in family life. Outside social activities limited (score = 9)

Case Study: Dr Cory Rice, DO, Forney Wellness, Dallas, TX

Case #3: 56 year old Caucasian woman

History & Complaints:

- Perimenopausal female, insulin resistant
- Diagnosed with metabolic syndrome
- Gained 50 lbs over past 6 years
  - About 10 lbs in past year
  - Now considered obese by BMI (31.45kg/m^2)
  - Diet and exercise regimens are not working
- Main complaint of low back pain
  - 30 years duration with decreased range of motion (ROM)

- Laminectomy (2001)
- Foot surgery (2009)

Current therapy:

- Fish Oil (1200mg QD)
- Vitamin D3 (5000IU QD)
- Multi-vitamin (1 tablet QD)
- Fiber Supplement (1 tablet QD)

Relevant Family History:

- None

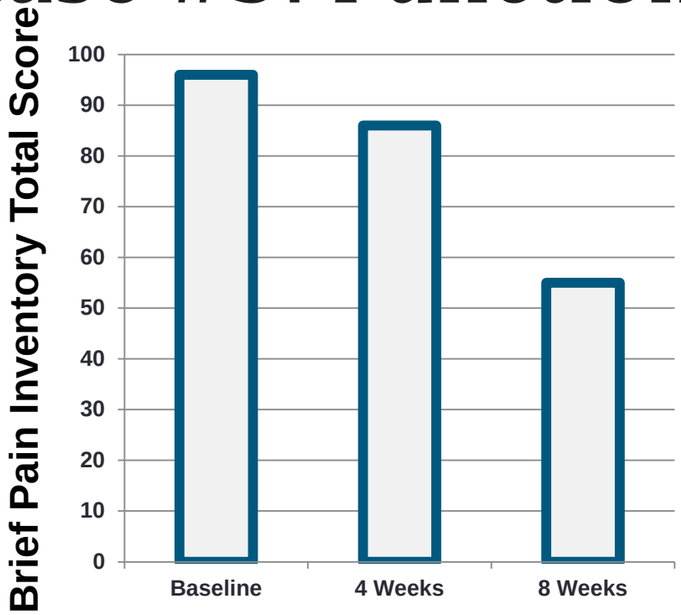
Case Study: Dr Jennifer Stagg, ND, Whole Health Associates, Avon, CT

Case #3: Biochemical changes at 4 and 8 weeks

Marker (reference range range)	Baseline	4 weeks	8 weeks	
hsCRP (0 – 3 mg/l)	32.4	5.2	11.7	hsCRP reduced at 4 and 8 weeks
Ferritin (15 – 150 ng/dl)	136	95	96	Ferritin reduced within normal reference range
Fibrinogen (199 – 504 mg/dl)	460	303	338	Fibrinogen reduced within normal reference range
IL-6 (0-15.3 pg/ml)	3.64	2.16	2.25	IL-6 reduced within normal reference range
TNF-α (0- 8.1 pg/ml)	1.7	6.2	2.7	TNF-α remained within normal reference range
ESR (0 – 32 mm/Hr)	28	11	11	ESR reduced within normal reference range
BNP (0 – 100 pg/ml)	57	29	19	BNP reduced within normal reference range

Case Study: Dr Jennifer Stagg, ND, Whole Health Associates, Avon, CT

Case #3: Functional improvements at 4 and 8 weeks



✓43% reduction in total brief pain inventory score at 8 weeks

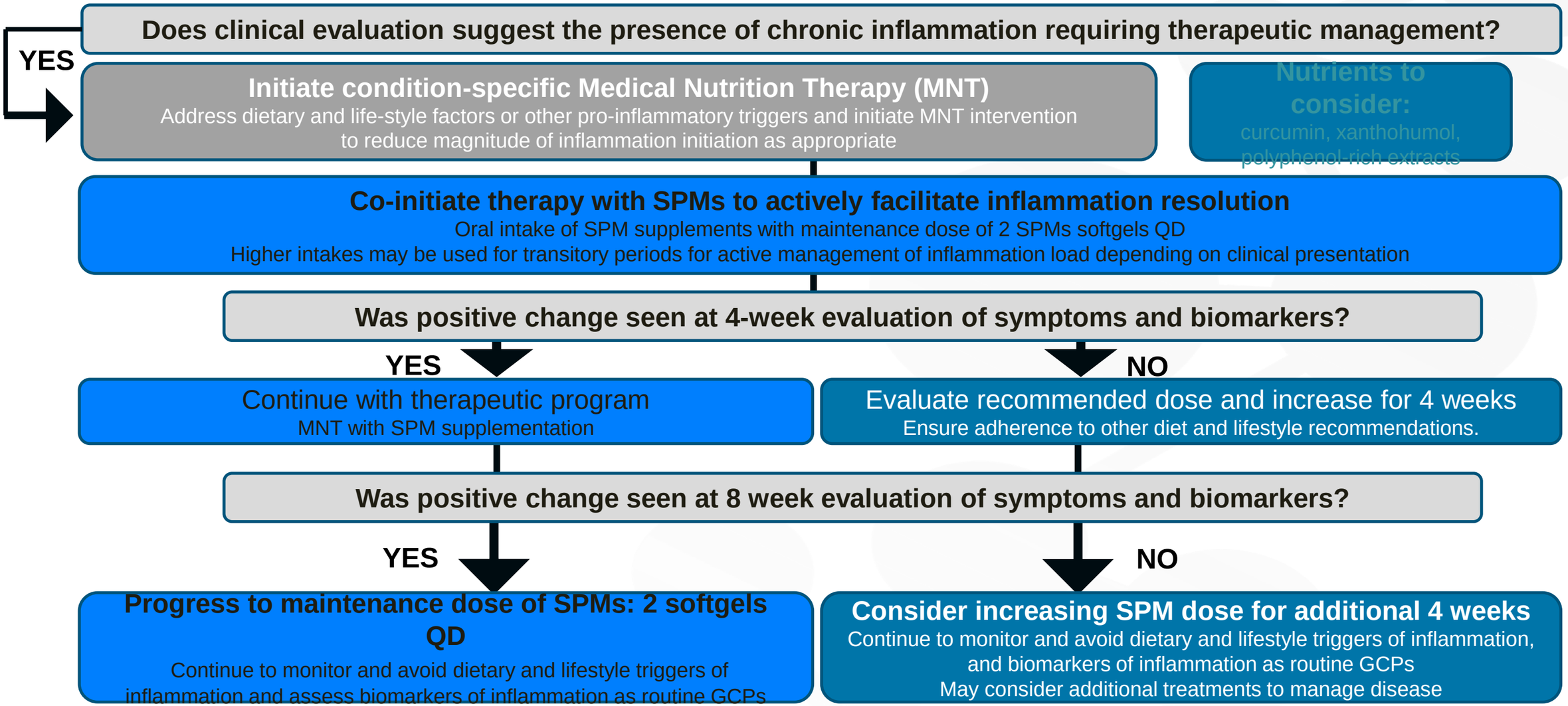
✓50% reduction in scores for interference of pain with relations with others, sleep and enjoyment of life

- Reduction in HSQ scores across 8 weeks Reduction in joint muscle scale and mind most markedly reduced

	Baseline	4 Weeks	8 Weeks
Total HSQ	39	29	22
Joint/Muscle	15	4	4
Mind	6	2	0

Case Study: Dr Jennifer Stagg, ND, Whole Health Associates, Avon, CT

Clinical management of inflammation



Innovation in Clinical Practice—New News in Patient Care

1. Novel Solution and Pathway to Support Inflammatory Responses

- New Clinical Benefits to Resolve Inflammation
- Fills a Gap in Managing Inflammatory Responses

2. Independent yet Complementary Solutions to Managing Inflammatory Conditions

- Not Blocking, inhibiting or suppressing inflammation
- ‘Resolves’ inflammation to avoid prolongation to to chronic health conditions

3. Proprietary Nutritional Solutions

- Specialized Pro-resolving Mediators
- Standardized Level of Activity

4. Clinical Uses with Superior Improvement in Ability to Resolve Inflammation

- Activates effective resolution response
- Resolution critical component of normal inflammatory response

Metagenics committed to ongoing clinical advancement to SPM science and therapies

Research Partnerships

Barts and The London School of Medicine and Dentistry

UCSF University of California San Francisco

NCNM National College of Natural Medicine

CLÍNIC Barcelona Hospital Universitari

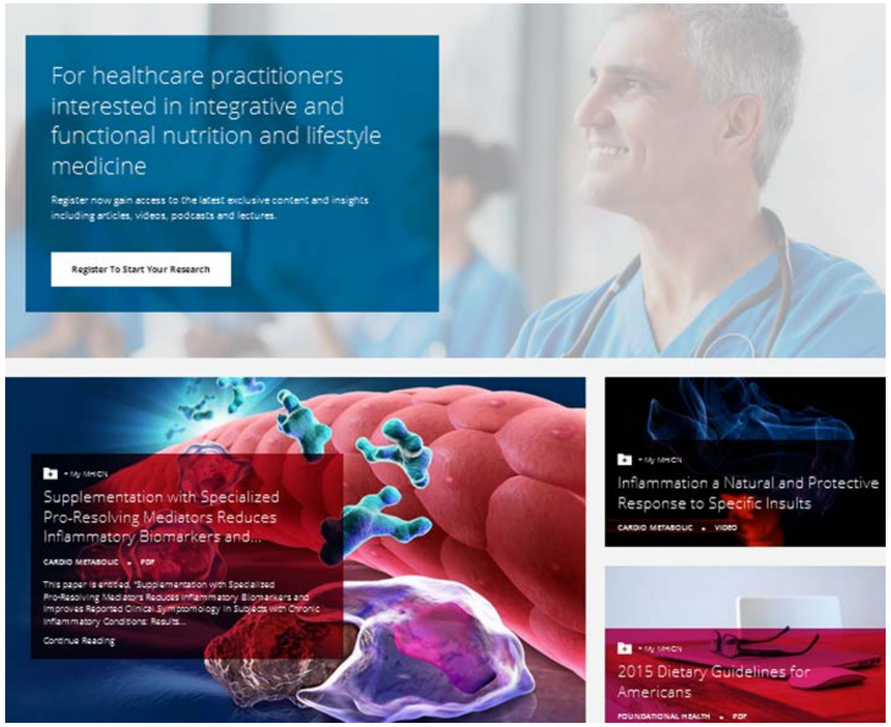
To further understand the impact of SPM therapy and dosing strategies in vascular disease, inflammatory response modulation, SPM production in obese states, and clinical symptomology associated with chronic inflammatory conditions

Educational resources to connect to

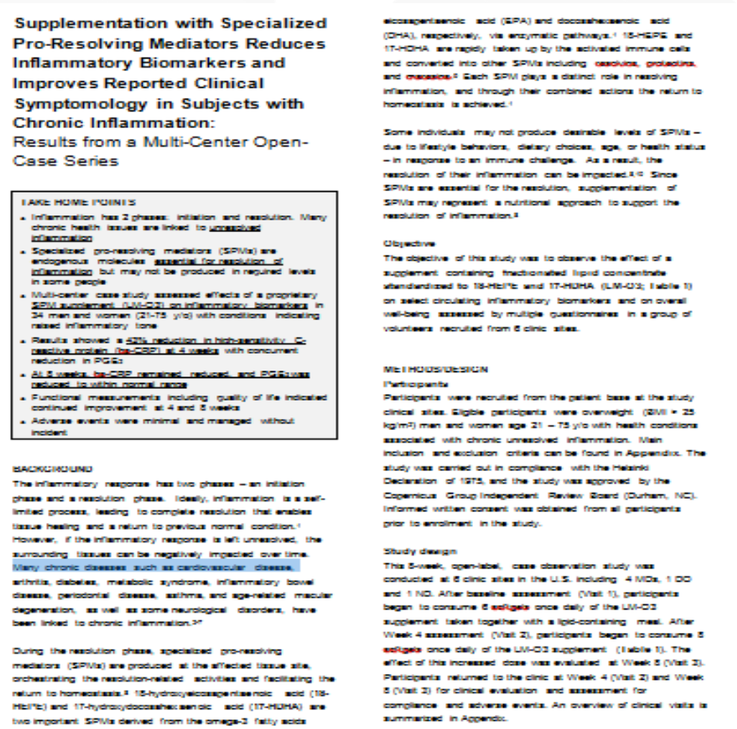
The Metagenics
Healthcare Institute
for Clinical Nutrition

Register and Log-In

SPM Resource



Full Study Results



Supplementation with Specialized Pro-Resolving Mediators Reduces Inflammatory Biomarkers and Improves Reported Clinical Symptomology in Subjects with Chronic Inflammation:
Results from a Multi-Center Open-Case Series

TAKE HOME POINTS

- Inflammation has 2 phases: initiation and resolution. Many chronic health issues are linked to unresolved inflammation
- Specialized pro-resolving mediators (SPMs) are endogenous molecules essential for resolution of inflammation but may not be produced in required levels in some people
- Multi-center case study assessed effects of a proprietary SPM supplement (LM-O3) on inflammatory biomarkers in 34 men and women (21-75 y/o) with conditions indicating raised inflammatory tone
- Results showed a 43% reduction in high-sensitivity C-reactive protein (hs-CRP) at 4 weeks with concurrent reduction in PGE2
- At 8 weeks, hs-CRP remained reduced, and PGE2 was reduced to within normal range
- Functional measurements including quality of life indicated continued improvement at 4 and 8 weeks
- Adverse events were minimal and managed without incident

BACKGROUND

The inflammatory response has two phases – an initiation phase and a resolution phase. Ideally, inflammation is a self-limited process, leading to complete resolution that enables tissue healing and a return to previous normal condition.[1] However, if the inflammatory response is left unresolved, the surrounding tissues can be negatively impacted over time. Many chronic diseases such as cardiovascular disease, arthritis, diabetes, metabolic syndrome, inflammatory bowel disease, periodontal disease, asthma, and age-related macular degeneration, as well as some neurological disorders, have been linked to chronic inflammation.[2,3]

During the resolution phase, specialized pro-resolving mediators (SPMs) are produced at the affected tissue site, orchestrating the resolution-related activities and facilitating the return to homeostasis.[4] 18-hydroxyeicosapentaenoic acid (18-HEPE) and 17-hydroxydocosahexaenoic acid (17-HDHA) are two important SPMs derived from the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), respectively, via enzymatic pathways.[1] 18-HEPE and 17-HDHA are rapidly taken up by the activated immune cells and converted into other SPMs including resolvins, protectins, and maresins.[4] Each SPM plays a distinct role in resolving inflammation, and through their combined actions the return to homeostasis is achieved.[1]

Some individuals may not produce desirable levels of SPMs – due to lifestyle behaviors, dietary choices, age, or health status – in response to an immune challenge. As a result, the resolution of their inflammation can be impacted.[4,5] Since SPMs are essential for the resolution, supplementation of SPMs may represent a nutritional approach to support the resolution of inflammation.[4]

Objective

The objective of this study was to observe the effect of a supplement containing fractionated lipid concentrate standardized to 18-HEPE and 17-HDHA (LM-O3; Table 1) on select circulating inflammatory biomarkers and on overall well-being assessed by multiple questionnaires in a group of volunteers recruited from 6 clinic sites.

METHODS/DESIGN

Participants

Participants were recruited from the patient base at the study clinical sites. Eligible participants were overweight (BMI > 25 kg/m²) men and women age 21 – 75 y/o with health conditions associated with chronic unresolved inflammation. Main inclusion and exclusion criteria can be found in Appendix. The study was carried out in compliance with the Helsinki Declaration of 1975, and the study was approved by the Copernicus Group Independent Review Board (Durham, NC). Informed written consent was obtained from all participants prior to enrollment in the study.

Study design

This 8-week, open-label, case observation study was conducted at 6 clinic sites in the U.S. including 4 MDs, 1 DO and 1 ND. After baseline assessment (Visit 1), participants began to consume 6 softgels once daily of the LM-O3 supplement taken together with a lipid-containing meal. After Week 4 assessment (Visit 2), participants began to consume 8 softgels once daily of the LM-O3 supplement (Table 1). The effect of this increased dose was evaluated at Week 8 (Visit 3). Participants returned to the clinic at Week 4 (Visit 2) and Week 8 (Visit 3) for clinical evaluation and assessment for compliance and adverse events. An overview of clinical visits is summarized in Appendix.

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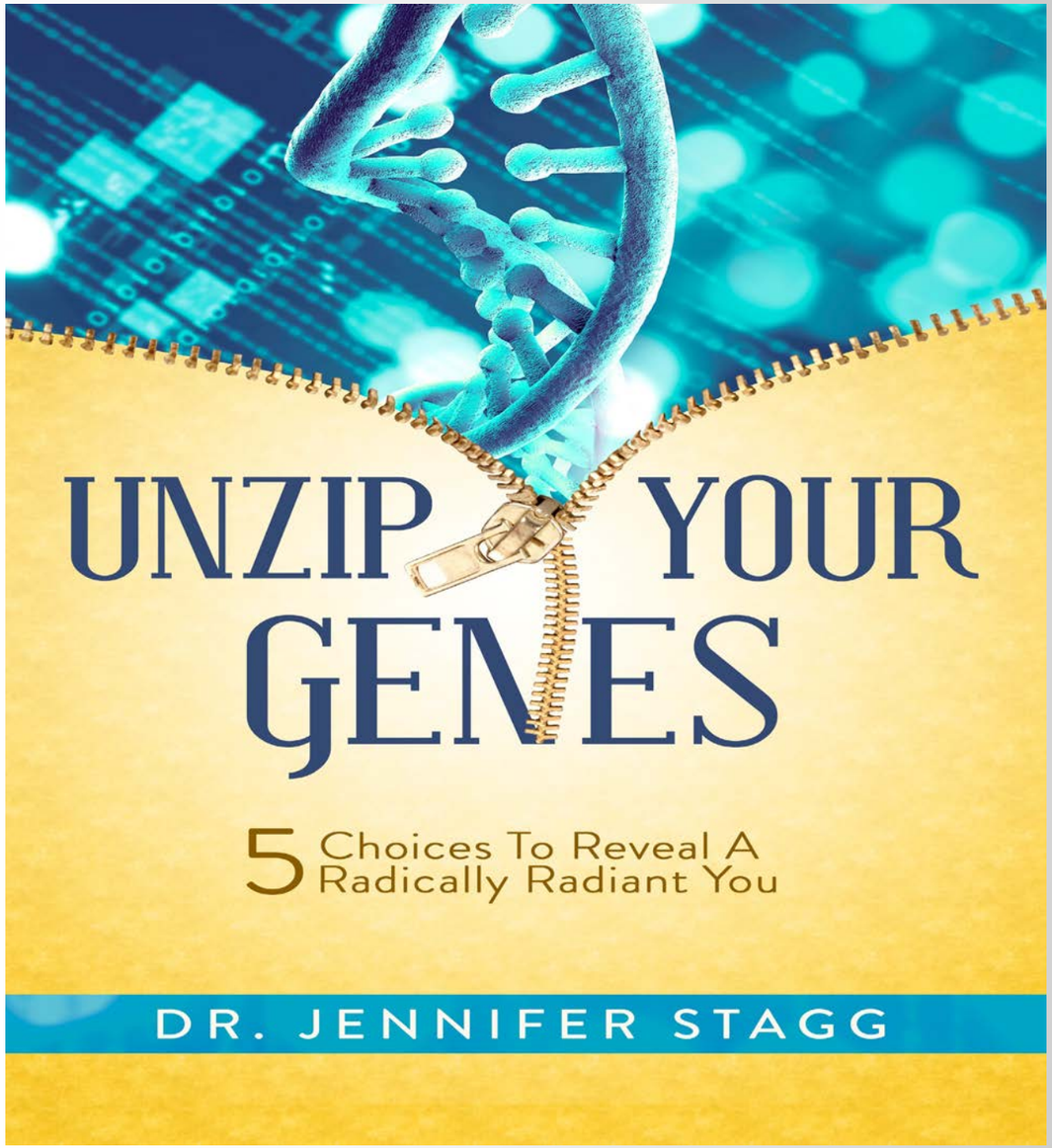

Thank you!