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

Jennifer Stagg, ND
# Innovation in Clinical Practice—New News in Patient Care

<table>
<thead>
<tr>
<th>1. Novel Solution and Pathway to Support Inflammatory Responses</th>
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</thead>
<tbody>
<tr>
<td>• New Clinical Benefits to Resolve Inflammation</td>
</tr>
<tr>
<td>• Fills a Gap in Managing Inflammatory Responses</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>2. Independent yet Complementary Solutions to Managing Inflammatory Conditions</th>
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<tr>
<td>• Not Blocking, inhibiting or suppressing inflammation</td>
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<td>• ‘Resolves’ inflammation to avoid prolongation to chronic health conditions</td>
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<table>
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<th>3. Proprietary Nutritional Solutions</th>
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<tr>
<td>• Specialized Pro-resolving Mediators</td>
</tr>
<tr>
<td>• Standardized Level of Activity</td>
</tr>
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</table>

<table>
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<tr>
<th>4. Clinical Uses with Superior Improvement in Ability to Resolve Inflammation</th>
</tr>
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<tbody>
<tr>
<td>• Activates effective resolution response</td>
</tr>
<tr>
<td>• Resolution critical component of normal inflammatory response</td>
</tr>
</tbody>
</table>
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

Chronic inflammation is associated with disease pathogenesis

- Injuries
- Infection
- Poor Diet
- Atherosclerosis
- Alzheimer’s Disease
- Huntington’s Disease
- Parkinson’s Disease
- Cancer
- Arthritis
- Insulin Resistance
- Type 2 Diabetes

Chronic inflammation
The Inflammatory Response
Inflammation Has Two Stages

Without Resolution, Inflammation Can Become Persistent & Chronic

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

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

Magnitude

Time

Pro-Inflammatory Signals

Neutrophils

Resolving Macrophages

SPMs

Resolution
Return to previously normal state

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

  **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**

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

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

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

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.

- SPM Fraction standardized to 17-HDHA and 18-HEPE concentrations
- Functional Superiority vs Competitive Products & Resolving Activity

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>49.3 ± 10.8 years</td>
</tr>
<tr>
<td>BMI</td>
<td>29.4 ± 8.2 kg/m²</td>
</tr>
<tr>
<td><strong>Total participants completing 3 study visits</strong></td>
<td>n=34</td>
</tr>
<tr>
<td>Sex</td>
<td>Women (n = 28); Men (n = 6)</td>
</tr>
<tr>
<td>Arthritis (RA/OA)</td>
<td>n = 14</td>
</tr>
<tr>
<td>Chronic Inflammation and associated symptom of pain</td>
<td>n = 15</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>n = 6</td>
</tr>
<tr>
<td>Co-morbidities*</td>
<td>n = 34</td>
</tr>
</tbody>
</table>

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 (200-400 pg/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\textsubscript{2}: potential mechanisms of action

- Reduction in PMN entering site secreting pro-inflammatory signals including cytokines and PGE\textsubscript{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

Resolution of Immune Response

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

Pain can be a symptom of chronic inflammation

Unresolved Immune Response

Progression

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

<table>
<thead>
<tr>
<th></th>
<th>Work/volunteer for a few hours daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Can be active at least five hours a day</td>
</tr>
<tr>
<td></td>
<td>Can make plans to do simple activities on weekends</td>
</tr>
<tr>
<td>8</td>
<td>Work/volunteer for at least six hours daily</td>
</tr>
<tr>
<td></td>
<td>Have energy to make plans for one evening social activity during the week</td>
</tr>
<tr>
<td></td>
<td>Active on weekends</td>
</tr>
<tr>
<td>9</td>
<td>Work/volunteer/be active eight hours daily</td>
</tr>
<tr>
<td></td>
<td>Take part in family life</td>
</tr>
<tr>
<td></td>
<td>Outside social activities limited</td>
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</table>
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 #1: Biochemical changes at 4 and 8 weeks**

<table>
<thead>
<tr>
<th>Marker (reference range)</th>
<th>Baseline</th>
<th>4 weeks (note taking 4SPM sg/day)</th>
<th>8 weeks (8 SPM sg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>hsCRP (0-3mg/L)</td>
<td>8.32</td>
<td>0.86</td>
<td>0.74</td>
</tr>
<tr>
<td>PGE2 (200-400pg/mL)</td>
<td>794</td>
<td>847</td>
<td>182</td>
</tr>
<tr>
<td>Fibrinogen (193-504mg/dL)</td>
<td>396</td>
<td>223</td>
<td>226</td>
</tr>
<tr>
<td>IL-6 (0-15.3 pg/mL)</td>
<td>4.8</td>
<td>&lt;0.7</td>
<td>1.8</td>
</tr>
</tbody>
</table>

- hsCRP normalized in 4 weeks
- PGE2 normalized in 8 weeks
- Stayed within normal limits, modest decrease

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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

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

Relevant Family History:
- Mother (hyothyroid, RA)
- Sister: Hashimoto’s

Medications
- Gabapentin (400mg/night)
- Levothyroxine (125mg)
Case #2: Biochemical changes at 4 and 8 weeks

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

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4 Weeks</th>
<th>8 Weeks</th>
</tr>
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<tbody>
<tr>
<td>General Activity</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mood</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Walking</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Normal work</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Relations with others</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sleep</td>
<td>8</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Enjoyment of life</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
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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)
**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/m²)
  - 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

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Case Study: Dr Jennifer Stagg, ND, Whole Health Associates, Avon, CT
Case #3: Biochemical changes at 4 and 8 weeks

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

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

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<th>4 Weeks</th>
<th>8 Weeks</th>
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<tbody>
<tr>
<td>Total HSQ</td>
<td>39</td>
<td>29</td>
<td>22</td>
</tr>
<tr>
<td>Joint/Muscle</td>
<td>15</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Mind</td>
<td>6</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Case Study: Dr Jennifer Stagg, ND, Whole Health Associates, Avon, CT
Clinical management of inflammation

Does clinical evaluation suggest the presence of chronic inflammation requiring therapeutic management?

**Initiate condition-specific Medical Nutrition Therapy (MNT)**
Address dietary and lifestyle factors or other pro-inflammatory triggers and initiate MNT intervention to reduce magnitude of inflammation initiation as appropriate.

**Nutrients to consider:**
curcumin, xanthohumol, polyphenol-rich extracts

**Co-initiate therapy with SPMs to actively facilitate inflammation resolution**
Oral intake of SPM supplements with maintenance dose of 2 SPMs softgels QD
Higher intakes may be used for transitory periods for active management of inflammation load depending on clinical presentation

Was positive change seen at 4-week evaluation of symptoms and biomarkers?

**YES**
Continue with therapeutic program
MNT with SPM supplementation

**NO**
Evaluate recommended dose and increase for 4 weeks
Ensure adherence to other diet and lifestyle recommendations.

Was positive change seen at 8 week evaluation of symptoms and biomarkers?

**YES**
Progress to maintenance dose of SPMs: 2 softgels QD
Continue to monitor and avoid dietary and lifestyle triggers of inflammation and assess biomarkers of inflammation as routine GCPs

**NO**
Consider increasing SPM dose for additional 4 weeks
Continue to monitor and avoid dietary and lifestyle triggers of inflammation, and biomarkers of inflammation as routine GCPs
May consider additional treatments to manage disease
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 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

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.
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#Unzip
Thank you!