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# REDEFINING MEDICINE

Greetings, and a warm welcome from the team at A4M/MMI. We are proud to be celebrating a quarter century of our original mission—redefining medicine—and embarking on a new chapter of exploration and discovery.

Anti-Aging Medicine now plays a critically important role in a healthcare system overly focused on disease management, as opposed to disease prevention. This sphere of medicine stresses the importance of maximizing health vitality at all stages of life, through a specific emphasis on the patient as a whole person: it brings the practice of medicine beyond the current typical skills and attitudes of today's physicians. A4M/ MMI's comprehensive educational offerings, in addition to consistent live conferences and events, reflect a revolution occurring in multiple industries—all of which are unifying around the principles of personalized and preventive medicine, coupled with the most current health technologies and innovative therapeutic applications.

Our healthcare practitioners & professionals who practice Anti-Aging Medicine through A4M/MMI understand the true value of comprehensive wellness. For too long, the practice of medicine has been targeted to specific diseases and disorders, or one type of injury, without viewing the whole patient holistically. The overarching objective of Anti-Aging Medicine, and the programs offered by A4M/MMI, is to enhance quality of life, while decreasing the risk of chronic disease, or mitigating the effects.

We thank you for your engagement and involvement. Our efforts are impossible without your continued support.



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# ANTI-AGING MEDICAL NEWS

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# Welcome Reception

Thursday, December 14 4:00 pm - 6:00 pm Exhibit Hall Sponsored by: DOUGLAS A B O B A T O B I E S

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Friday, December 15 4:00 pm - 6:00 pm Exhibit Hall

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# Mercedes-Benz GVEA December 16<sup>th</sup> • 12:30 pm



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**Drawing - Exhibit Hall** Saturday December 16<sup>th</sup> at 12:30 pm

Your entry form can be found in your attendee bag or at A4M/MMI booth.





# PROFESSIONAL MEDICAL EDUCATION WORKSHOPS

(NON-CME)

# Wednesday, December 13<sup>th</sup> - 6:15pm

Connect the Dots – Lifestyle, Nutraceuticals, Hormone Optimization and Telomerase Activation with TA-65

Presented by: Ron Rothenberg, MD Location: Veronese Ballroom 2403-4



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#### Wellness Analytics: Improving Outcomes and Income

Presented by: Christina Rahm Cook, MS, PhD Location: Veronese Ballroom 2405-6 **UNI**source

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# Thursday, December 14<sup>th</sup> - 6:15pm

#### Body LogicMD: Manage and Grow Your Integrative Practice

Presented by: Andrew Heyman, MD, MHSA and Jennifer Landa, MD Location: Titian Ballroom 2303-4

# Specialty Diagnostics in Clinical Practice

## Presented by: Filomena Trindade, MD, MPH and Andrea Girman, MD, MPH Location: Veronese Ballroom 2403-4

#### **The Future of Regenerative Medicine** Presented by: Alan Gaveck, DPM & Rafael Gonzalez, PhD Location: Veronese Ballroom 2401-2

#### Reversing the Aging Process

Presented by: David J. Metayer, Rick Rhoads, PharmD, Thierry Hertoghe, MD Location: Veronese Ballroom 2405-6

# Friday, December 15<sup>th</sup> - 6:15pm

#### A Metabolic Code Case Study Presented by: Andrew Heyman, MD, MHSA Location: Veronese Ballroom 2401-2

Key Insights into Managing Sleep and Hyperarousal:

# Cognitive Function & Neuroinflammation

Presented by: Jim LaValle, RPh, MS, ND, CCN Location: Veronese Ballroom 2403-4

#### Becoming A Better Diagnostician/Clinician: A New Perspective On Illness And Wellness

Presented by: Silvia Binder, ND, PhD & James Denninghoff, MD Location: Titian Ballroom 2303-4

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# PRODUCT SHOWCASE

# Location: Exhibit Hall

# Thursday, December 14<sup>th</sup>



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# Friday, December 15<sup>th</sup>

11:30 ам	Direct Effects Technology with CBD: A Novel Non-Systemic Delivery of CBD and Cannabis Compounds for Neuropsychiatric Disorders Presented by: Ronald Aung-Din, MD
12:00 рм	The Complete Woman: Solutions For Inner Wellness, Sexual Health, Feminine Rejuvenation & IncontinenceSponsored by:Presented by: Shelena C. Lalji, MDBTL AESTHETICS
12:30 рм	Case Studies:Sponsored by:Learn about the Biomarkers that predict heart attack and have prevented widow maker deathsSponsored by:Presented by: Douglas S. Harrington MD, FASPC, FCAPCARDIAC TEST
4:30 рм	"The Dinner"    Sponsored by:      Presented by: Clayton Thomas    Image: Clayton Thomas
5:00 рм	Sponsored by: How to Implement Peptides Into Your Clinic Presented by: Nima Alavi PharmD, MPS, M.APP, FIN A FIN
5:30 рм	Sponsored by: Intracrinology and Women's Health: A Focus on Menopause Presented by: James A. Simon MD, CCD, NCMP, IF, FACOG Endoceutics*
	Saturday, December 16 <sup>th</sup>
• 11:30 ам	Sponsored by: The Prescription for Change Presented by: Kyle Braatz Sponsored by: Fullscript
12:45 рм	Fitness In and Out      Presented by: Action Martial Arts

# **Refractory Depression, Fatigue, Irritable Bowel Syndrome, and Chronic Pain: A Functional Medicine Case Report**

By Gregory Plotnikoff, MD, MTS, FACP; Melissa Barber, MSc

E-pub: 10/14/2016

Perm J 2016 Fall;20(4):15-242 http://dx.doi.org/10.7812/TPP/15-242

*Editor's note:* A companion editorial to this article is available online at: www.thepermanentejournal.org/issues/2016/fall/6240-fm.html.

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#### ABSTRACT

**Introduction:** Single-disorder or single-organ-system clinical practice guidelines are often of limited usefulness in guiding effective management of patients with chronic multidimensional signs and symptoms. The presence of multiple long-standing medical problems in a given patient despite intensive medical effort suggests that addressing systemic core imbalances could complement more narrowly focused approaches.

**Case Presentation:** A 72-year-old man experiencing longstanding depression, fatigue, irritable bowel syndrome, and chronic pain in the context of additional refractory illnesses was assessed and treated, guided by a system-oriented approach to underlying core imbalances termed functional medicine. This patient was referred from a team of clinicians representing primary care, cardiology, gastroenterology, hematology, and psychology. Prior treatment had been unsuccessful in managing multiple chronic comorbidities. Diagnostic assessment included comprehensive stool and nutritional/metabolic laboratory testing.

**Results:** The blood-, urine-, or stool-based measurements of relevant markers for multiple systemic issues, including digestion/absorption, inflammation, oxidative stress, and methylation, identified previously unrecognized root causes of his constellation of symptoms. These functional measurements guided rational recommendations for dietary choices and supplementation. The patient experienced steady and significant improvement in his mental health, fatigue, chronic pain, and irritable bowel syndrome—as well as the unexpected resolution of his chronic idiopathic pancytopenia.

**Conclusion:** The success in this case suggests that other patients with chronic, complex, and treatment-refractory illness may benefit from a system-oriented assessment of core imbalances guided by specialized nutritional/metabolic and digestive laboratory testing.

#### **INTRODUCTION**

Single-disorder clinical practice guidelines are often of limited usefulness in guiding effective management of patients with chronic multidimensional signs and symptoms. The presence of multiple long-standing medical problems, despite excellent medical care, suggests that new questions or perspectives may be helpful. For example, assessment of underlying key common pathways for all diseases, such as gastrointestinal dysfunction, proinflammatory imbalance, and oxidative stress, could augment the more traditional organ-system-oriented, discipline-focused approach. The organizing principle of the approach taken here, termed functional medicine, is that restoration of health requires defining and addressing seven potential core imbalances that may underlie any given disease state. These seven categories are 1) assimilation (digestion, absorption, microbiomics, respiration), 2) defense and repair (immune function, inflammation, infection), 3) energy (production, regulation), 4) biotransformation and elimination (toxicity, detoxification), 5) transport (cardiovascular and lymphatic systems), 6) communication (hormones, neurotransmitters, cytokines), and 7) structural integrity (membranes, fascia, bacterial translocation). The core belief is that imbalance in one or more of these seven common disease pathways may be the root cause of many seemingly disparate conditions.

This case illustrates how specialized laboratory testing identified previously unrecognized physiologic and biochemical dysfunction in a complex patient. This dysfunction in several common disease pathways was both clinically relevant and inexpensively modifiable. The result was substantial clinical improvement and a markedly improved patient quality of life.

#### **CASE PRESENTATION**

#### Initial Visit (February 2012)

A 72-year-old man was referred to a board-certified internist specializing in complex, refractory illnesses in February 2012. The patient's primary goal, stated at his first visit, was to "walkout of the office with more hope." He wrote that it was "very hard to function. I wake after 9 hours of sleep and still feel tired. I don't have the emotional or physical strength to accomplish much. This is frustrating and I am on a cycle of becoming more depressed, more frustrated, and more helpless."

In addition to chronic fatigue and depression, the patient reported 1) heartburn, frequent gas, bloating, and diarrhea alternating with constipation; 2) right lower quadrant abdominal cramping, worsening after bowel movements; and 3) widespread arthralgias and myalgias. See Table 1 through 6 (Tables 4 and 5 available online at: www.thepermanentejournal.org/ files/15-242.pdf ), and the Sidebar: Important Medical History for a list of the patient's medical considerations.

Table 1. Medical history timeline			
1940s	Heartburn and gastric reflux		
1950s	Depression since adolescence		
1960s	Began smoking; increased alcohol consumption		
1999	Pancreatitis, alcoholic hepatitis, and liver failure (subsequently resolved)		
2004	Idiopathic pancytopenia; no alcohol consumption beginning in 2004		

2012	Type 2 diabetes mellitus
2012	Specialized digestive and nutritional laboratory testing
2012-2015	Treatment for pancreatic insufficiency, nutritional and digestive imbalances
2013	Resolution of idiopathic pancytopenia and irritable bowel syndrome; decreased depression, fatigue, and pain

#### **Initial Clinical Findings**

Patient-reported outcome instruments (higher scores indicate worse symptoms):

- Brief Fatigue Inventory: total fatigue interference score of 37/60
- Brief Pain Inventory: total pain interference score 36/70
- Patient Health Questionnaire-9: total score 13 (moderate depression 10-14).

#### **Physical Examination**

- Blood pressure 118/54 mmHg, pulse 74 beat/min and regular. Body mass index, 21.6 (calculated as weight in kilograms divided by height in meters squared)
- Anicteric with clear lungs and normal cardiac examination
- Abdomen tender to palpation of the right upper quadrant and epigastric area
- No hepatosplenomegaly
- Palpation in the left lower quadrant resulted in right lower quadrant discomfort
- No ascites present
- No edema in extremities (cool, pale fingers with slow capillary refill)
- · No palmar erythema
- No asterixis.

#### DIAGNOSTIC ASSESSMENTS

The patient's concern of a reduced quality of life secondary to depression, fatigue, and gastrointestinal distress was part of a remarkable medical history as a survivor of end-stage liver failure and alcoholism. However, his depression, fatigue, widespread pain, and gastrointestinal symptoms did not resolve from medical treatments of specific diagnoses and individual symptoms. A clinical decision was made to evaluate the root causes of this patient's symptoms from a functional medicine perspective with comprehensive and structured stool1,2 and nutritional diagnostic panels. A Comprehensive Digestive Stool Analysis 2.0 (CDSA 2.0) and Nutritional Evaluation (NutrEval) from a Clinical Laboratory Improvement Amendments-certified laboratory (Genova Diagnostics, Asheville, NC) were ordered. These kits offer bundled laboratory tests that provide insight into the function and status of several of the core pathways. Additionally, given the presence of environmental stressors and a decreased sense of personal efficacy, he was referred for Resilience Training or Mindfulness-Based Stress Reduction.

#### **OTHER RELEVANT LABORATORY RESULTS**

This patient had previously been found to be vitamin D deficient. However, he was not on vitamin D supplementation at his first visit and supplementation (2000 IU) was begun. In addition this patient's dehydroepiandrosterone-sulfate (DHEAS) level was low normal and DHEA 5 mg sublingually each morning was started.3

#### FOLLOW-UP AND OUTCOMES

The patient was evaluated four times between April 2012 and January 2013. With each subsequent visit, he reported steady improvement in his mood, overall energy, and chronic pain. He was compliant with the dietary recommendations and supplements outlined in Table 3. He elected to not pursue Resilience Training or Mindfulness-Based Stress Reduction.

He experienced minor episodes of dizziness with two near syncopal episodes, for which he was referred to his cardiologist.

Table 2. Medications and supplements at presentation				
Medications	Dosage			
Lisinopril/hydrochlorothiazide	40 mg/25 mg/d			
Trazadone	150 mg/d			
Effexor	225 mg/d			
Ranitidine	75 mg 2x/d			
Cilostazol	1 tablet 2x/d before meals			
Atorvastatin	10 mg/d			
Cytomel	5 mg/d			
Nonsteroidal anti-inflammatory drugs	As needed			
Rolaids	As needed			
Supplements				
Centrum silver multivitamins	1 tablet/d			
Folic acid	400 mg/d			
Glucosamine/chondroitin	1500 mg/1200 mg 2x/d			
Vitamin B6 (pyridoxine HCL)	50 mg/d			

#### **Important Medical History**

- 1. Gastric reflux since childhood
- 2. Depression since adolescence with persistently elevated Patient Health Questionnaire-9 scores as an adult, consistent with moderately severe depression
- 3. Twenty pack-year smoking history (quit smoking March 1996)
- 4. Alcoholism (age 28 to 62 years): alcoholic hepatitis, chronic pancreatitis, pancreatic pseudocyst, and liver failure in 1999—successfully sober since 2004
- 5. Successful discharge from hospice with resolution of endstage liver failure, 2004
- Cardiovascular disease: hypertension, dyslipidemia, coronary stents, and claudication
- 7. Diagnosed with idiopathic pancytopenia in 2004
- 8. Type 2 diabetes mellitus since 2012
- 9. Osteoarthritis
- 10. Homocysteinemia with homozygous MTHFR (methylenetetrahydrofolate reductase C677T) polymorphism
- 11. Surgical history: cholecystectomy, tonsillectomy, and anal fissure repair

Repeat testing at his local hospital in December 2012 demonstrated persistent pancreatic insufficiency with an undetectable pancreatic elastase 1 and persistent *Candida glabrata* overgrowth in the stool even though the patient was no longer symptomatic. These findings supported continued prescription of pancreatic enzyme support, probiotics, and a diet rich in prebiotics. The patient's oncologist noted an "inexplicable resolution" of the patient's idiopathic pancytopenia in July 2013 and reported that his physical and laboratory examinations were normal at that time.

In January 2013, patient-reported outcomes had improved significantly:

- Brief Fatigue Inventory: total fatigue interference score of 19/60
- Brief Pain Inventory: total pain interference score 20/70
- Patient Health Questionnaire-9: total score 10.

#### DISCUSSION

Mental health disorders and gastrointestinal complaints are often components of complex, chronic illnesses that can challenge linear pharmacologic management.4,5 System-oriented, functional medicine approaches, supported by laboratory findings, can help engage patient and clinician in a therapeutic partnership to address genetic, environmental, and lifestyle factors that may be important in complex, chronic diseases.6

The intersection of depression, fatigue, widespread pain, and gastrointestinal symptoms in this patient had implications in multiple systems.7,8 This justified a switch in the diagnostic focus from the customary organ-based systems to whole-body systems. Table 3 delineates the systemic issues important in this case, such as inflammation, oxidative stress, or impaired methylation. The blood-, urine-, or stool-based measurements

Table 3. Stool and urine metabolic testing results and therapeutic interventions					
Visit no.	Laboratory biomarkers'	Diagnostic significance	Therapeutic interventions		
1	Pancreatic elastase-1 < 15 (Ref: > 201 mg/g) Fecal fat 50.1 (Ref: 2.6-32.4 mg/g) Long chain fatty acids 43.8 (Ref: 1.3-23.7 mg/g) Phenylacetic acid (PAA) 0.32 mmol/mol creatinine (Ref: ≤ 0.12)	Pancreatic exocrine insufficiency	Pancrelipase 12,000 units with each meal		
2	Candida glabrata 2+ (Ref: potential pathogen) Arabinose 158 (Ref: ≤ 96) Tartaric acid 66 (≤ 15)	Yeast overgrowth (sensitive to fluconazole)	Fluconazole 100 mg daily for 4 weeks		
3	No growth for beneficial bacteria ( <i>Lactobacillus</i> , <i>E coli</i> ) 4+ growth ( <i>Citrobacter braakii</i> and <i>youngae</i> ) Dihydroxyphenylpropionic acid 6.1 (Ref: $\leq$ 5.3) Benzoic acid 0.06 (Ref: $\leq$ 0.05) Hippuric acid 611 (Ref: $\leq$ 603)	Dysbiosis	Probiotics (multiple: <i>Lactobacillus</i> and <i>Bifidobacteria</i> species plus <i>Saccharamyces boulardii</i> ) daily Soluble/insoluble fiber-containing foods in diet		
4	Methylenetetrahydrofolate reductase polymorphism Sarcosine 53 (Ref: ≤ 48)	Impaired folate cycle and methylation pathways	Discontinue folic acid supplementation Switch to L-5-methyltetrahydrofolate 400 mg/d plus vitamin B12 as methylfolate 500 mg/d		
5	Lysine 39 (Ref: 45-286) ⊩Aminoadipic acid < detection limit (Ref: 11-73) Glycine 341 (Ref: 639-3306) Histadine 242 (Ref: 271-993)	Insufficient amino acids	Lysine 1000 mg/day for 2 months Glycine 1000 mg/day for 2 months Chew proteins thoroughly (eat slowly)		
6	Cystathionine 4 (Ref: 6-33) Glutathione 486 (Ref: ≥ 669 mmol/L)	Impaired trans-sulfuration pathways	Pyridoxal-5-phosphate (vitamin B6) 50 mg/d Molybdenum 75 mg/d (multivitamin)		
7	Ethanolamine 71 (Ref: 208-514) Glycine 341 (Ref: 639-3306)	Impaired choline metabolism	Eat lecithin-containing foods (eg, egg yolks, peanuts) Support folate cycle and methylation		
8	Adipic acid 3.9 (Ref: $\leq$ 2.8) Borderline elevated beta-OH-butyric acid 2.0 (Ref: $\leq$ 2.8) Borderline elevated HMG 12 (Ref: $\leq$ 15) Borderline elevated ornithine 20 (Ref: 4-21)	Impaired energy production, ketosis Beta-oxidation of fats Pyruvate dehydrogenase (carbohydrate metabolism) Oxidative phosphorylation	Add magnesium glycinate 400 mg/d B vitamin support (multivitamin) Alpha-lipoic acid 200 mg/d Liberalize carbohydrate intake Eat more frequently		
9	8-OH-dG 18 (Ref: ≤ 15 mg/g creatinine) Cysteine 82 (Ref: 21-78) Glutathione 486 (Ref: ≥ 669 mmol/L) Pyroglutamic acid 48 (Ref: 16-34) Coenzyme Q10 0.20 (Ref: 0.43-1.49 mg/ml)	Excessive oxidative stress/ overwhelmed defense mechanisms	Coenzyme Q10 (Ubiquinol) 200 mg/d Alpha-lipoic acid 200 mg/d Support glutathione production via transsulfuration Support glutathione production via diet: foods rich in vitamins E and C and sulfur Avoid use of acetaminophen		
10	Omega 3 index 3.0 (Ref: $\geq$ 4.0) Vaccenic acid 1.18 (Ref: $\leq$ 1.13 wt %) Eicosapentaenoic acid 0.29 (Ref: $\leq$ 0.26 wt %) Arachidonic acid 22 (Ref: 15-21 wt %)	Long-chain omega-3 fatty acid insufficiency with omega 6 excess	Omega-3 fatty acid: 2 g EPA and DHA/d Cook with olive oil (low heat) or high-oleic acid safflower oil (higher heat)		

<sup>a</sup> All biomarkers reported in mmol/L creatinine unless otherwise noted.

DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; HMG = hydroxymethylglutaryl; Ref = reference; wt % = weighted percentage.

Table 6. Patient-reported outcome instrument scores <sup>a</sup>				
Instruments	February 2012	January 2013		
Brief Fatigue Inventory	37	19		
Brief Pain Inventory	36	20		
Patient Health Questionnaire-9	13	10		

<sup>a</sup> Higher score equals worse symptoms.

of the relevant markers for each issue guided rational recommendations for dietary choices and supplementation.

Addressing systemic issues in chronic, complex illness complements a more traditional organ-system approach. In this case, addressing one fundamental imbalance may have addressed several disparate conditions. For example, diagnosing and addressing this patient's digestive dysfunction and the intestinal ecology imbalances not only improved digestive function but also improved several metabolic and nutritional markers known to be correlated with depression, fatigue, and myalgias.

Likewise, the reduction in his myalgias allowed this patient with diabetes with proven atherosclerosis to remain on atorvastatin. HMG Co-A reductase inhibitors (statins) are known to block production of coenzyme Q10; however, supplementation is not routinely recommended. The very low serum coenzyme Q10 measured in this patient suggested that supplementation might be of benefit.8,9 The reduction in his arthralgias also allowed this patient who presented with low glutathione levels to avoid acetaminophen (which depletes glutathione). His low levels of glutathione were treated with a diet rich in vitamins C, E, molybdenum, selenium, and methionine- or cysteine-containing amino acids. The improved levels of both coenzyme Q10 and glutathione enhanced native oxidative stress management, known to help reduce pain, depression, and fatigue.10 Finally, correction of all these systemic issues may have contributed to the unexpected resolution of his idiopathic pancytopenia after eight years.

#### CONCLUSION

David Sackett, one of the pioneers of evidence-based medicine, said "Without clinical expertise, even excellent evidence may be inappropriate for an individual patient."11 The comprehensive approach outlined here integrated the clinical expertise found in organ-system-based disciplines with the perspective of functional medicine's systems-biology approach. This integration was possible because of external evidence from specialized stool and nutritional diagnostic panels. This combination resulted in effective management of multiple comorbidities that had previously been minimally responsive to treatment. The interference score for this patient's chronic fatigue was reduced by nearly 50% (from 37/60 to 19/60). The interference score for his chronic pain was reduced by nearly 40% (from 36/70 to 20/70). His Patient Health Questionnaire-9 score declined by 25% (13 to 10). His gastrointestinal function improved greatly without significant increases in pharmaceuticals. Therapeutic recommendations were based on measurements of nutritional and digestive status and function. The success in this case suggests that other patients with chronic, complex, and treatment-refractory illness may benefit from a functional medicine, system-oriented approach guided by nutritional and digestive laboratory testing.

#### **Patient Perspective**

"I experienced at least a 50% reduction in pain and improvement in my quality of life. My anxiety is reduced, I am more relaxed, and feel stronger. The most helpful has been the work with my gut issues. I am almost like clockwork now."

#### **Disclosure Statement**

*The author(s) have no conflicts of interest to disclose. Written consent was obtained from the patient for publication of this case report.* 

#### Acknowledgment

This case report was prepared according to the CARE Guidelines by Gagnier, Kienle, Altman, et al, published in the Journal of Clinical Epidemiology in 2014. Mary Corrado, ELS, provided editorial assistance.

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This module provides an overview of the functions and interrelationships of specific hormones in the body, including hormonal changes that manifest in aging men and women. Metabolic, functional, and nutritional approaches to managing hormone deficiencies and endocrine disorders, including diabetes and obesity, are also covered.

## MODULE II Cardiovascular Disease

This module assesses the causes, mechanisms, diagnoses, and management of cardiovascular and cardiometabolic diseases including CHD, CHF, hypertension, metabolic syndrome, dyslipidemia, atherosclerosis, and renal disease. Topics include cardiovascular pathophysiology and biology, inflammation, oxidation, hormones, adipokines, stress, nutrition and nutrigenomics, glycemic control, environmental factors and toxicology, infections, and risk factor testing.

### MODULE III Neurology

This module reviews the most recent developments in the field of neurology, utilizing a metabolic approach to the prevention, management, and treatment of neurologic diseases. The course will cover pathophysiology and the role of neurotransmitters, inflammatory and degenerative disorders, neurovascular diseases, psychological and psychiatric syndromes, the gut-immune-brain connection, and healthy brain function.

### MODULE IV Gastroenterology

This module focuses on comprehensive metabolic, functional, and nutritional approaches to gastrointestinal dysfunction and disease. Physiology and pathophysiology, GI microbiome and dysbiosis, gut permeability, hormones, diet, inflammatory bowel diseases, celiac disease and gluten sensitivity, the gut-immune-brain connection, irritable bowel syndrome, and other digestive and glandular disorders are highlighted.

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# Integrative Management of Healthy Prostate and Urinary Function without Lowering Dihydrotestosterone

By Cristiana Paul, MS

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Lower urinary tract symptoms (LUTS) is characterized by difficulty urinating, incomplete voiding of the bladder, and/ or frequent urination due to irritable bladder. LUTS etiology may involve benign prostate hypertrophy (BPH), prostatitis (PT; of bacterial or non-bacterial origin), or prostate cancer, as well as other unidentified factors. LUTS associated with BPH affects 50% of men in their fifties and 80% of men in their seventies.<sup>30</sup> It increases the risk for urinary tract infections due to incomplete urine voiding and negatively impacts quality of life.

BPH occurs in approximately 20%, 50% and 75% of men by the age of 40, 50 and 80, respectively, and LUTS follows a similar pattern of age-related increase in incidence.<sup>6</sup> Prostate cancer occurs at the microscopic level in 30% of men between ages 20 and 40, while the risk of developing overt prostate cancer with clinical symptoms becomes significant after age 50.

While there are pharmaceutical drugs available for BPH, LUTS and PT, many of them have lackluster efficacy and present undesirable side effects. Regarding prostate cancer, specifically, recent scientific analyses have brought to light considerable controversy surrounding the diagnostic value of elevated PSA.<sup>3</sup> While some healthcare professionals dismiss or downplay the relevance of elevated PSA, one cannot rule out that a faster than normal rise in PSA may indicate the presence of various inflammatory, infectious and/or pre-cancerous or cancerous conditions. Many integrative healthcare practitioners view nutraceutical interventions that lower PSA as potentially beneficial, especially since these present no harmful side effects and may, in fact, offer systemic health benefits. A nontoxic nutraceutical strategy, especially if used early after detection, may be a good option for those who choose a "watch and wait" approach.

Research performed with extracts from cranberry, flower pollen or pomegranate suggests combining these three compounds as a novel approach to managing LUTS in aging men with or without BPH and/or PT. These compounds work via mechanisms of action that are independent of effects on prostate size or testosterone and dihydrotestosterone (DHT) levels, so this approach may be especially useful for those who are also undergoing testosterone replacement therapy.

It is well known that most commercially available nutritional formulas for prostate health incorporate saw palmetto, the main mechanism of action of which is inhibition of 5-alpha-reductase, an enzyme that converts testosterone to DHT. While this may be considered a useful approach for patients with elevated DHT, it may not be appropriate for all men. For example, a potential side effect from reducing the conversion of testosterone to DHT may be an increase in estrogen levels, since testosterone converts to estrogen (via aromatase), while DHT does not.

#### Flower Pollen, Cranberry and Pomegranate Extracts have synergistic and complementary molecular actions, as summarized below:

a) Anti-inflammatory actions due to inhibition of COX-2 and LOX enzymes, as well as NF-kappa B expression from pollen,<sup>1</sup> cranberry,<sup>8</sup> and pomegranate extracts<sup>21</sup>

b) Reduced rate of prostate cell proliferation, which may be

due in part to inhibitory effects of flower pollen extract on inflammatory pathways<sup>11,12</sup> (see Fig. 1)

c) Increased apoptosis and reduced angiogenesis (which reduces metastatic potential) from cranberry extract<sup>18</sup> and pomegranate extract<sup>20,21</sup>

d) Antimicrobial (anti-adhesive and direct microbicidal) effects in the urinary and GI tracts from cranberry extract<sup>18</sup> and pomegranate extract<sup>21</sup>

e) Diuretic effects from cranberry extract<sup>17,18</sup>



Figure. 1: Flower pollen extract inhibits the prostaglandins and leukotrienes involved in prostate problems

#### Synergy of flower pollen, cranberry and pomegranate extracts in providing potential clinical benefits.

Because of their particular mechanisms of action, potential benefits of this nutraceutical approach may be observed within as little as 3-6 months of supplementation, as described below:

**1. Shrinking an enlarged prostate and reversing structural changes.** Studies involving patients with stage II and stage III BPH show flower pollen extract to have an anti-inflammatory effect and result in a marked reduction in prostate volume.<sup>7-9</sup> One of these studies performed a transrectal ultrasonogram of the prostate before and after six months of treatment with pollen extract, illustrating marked reduction of the circumference, internal swelling and fibrosis of the prostate (see Fig. 2).<sup>9</sup> This study also observed a significant reduction in the clinical symptoms associated with BPH.



**Figure. 2:** Sonogram of prostate shrinkage and reduced fibrosis after 6 months treatment with flower pollen extract.<sup>9</sup>

One human study using pollen extract evaluated symptoms of prostatodynia and others associated with BPH and found that 78% of subjects had significant improvement in the measured symptoms, with 60% experiencing a complete resolution.<sup>11</sup>

**2. Improvement in urinary symptoms of LUTS.** A number of placebo controlled, double-blind studies with pollen extract provide evidence that it is effective in reducing nocturia, daytime urinary frequency, and a sensation of residual urine.<sup>10-14</sup> Specifically, one study showed that "after treatment, residual urine volume has been shown to significantly decrease by an average of 47%".<sup>12</sup>

A number of studies employing various cranberry extracts have demonstrated an improvement in LUTS in a relatively short time (3-6 months), which was likely not derived from a change in prostate size, but rather, possibly from other physiological mechanisms.<sup>31-32</sup> One study achieved statistical improvement of LUTS in 70% of the supplemented group with no influence on blood testosterone levels.<sup>17</sup>

**3. Improvement in BPH-induced sexual side effects.** In a study using pollen extract, patients experienced an improvement in symptoms of perineal pain, erection difficulty, ejaculation difficulty and pain during urination throughout the course of treatment.16 In addition, a pomegranate extract was shown to improve erectile function, likely by enhancing nitric oxide availability.<sup>19</sup>

**4. Positive effects on PSA.** One study using cranberry extract demonstrated a lowering of PSA in 80% of men from a group with LUTS or non-bacterial prostatitis, who had negative prostate biopsies for cancer.<sup>17</sup> A study using pomegranate demonstrated that, as a result of intervention with

this extract, PSA doubling time was increased in prostate cancer patients, while 13% of them experienced a reduction in total PSA levels.<sup>20</sup>

**5. Reduced risk of UTIs.** The well-proven antimicrobial effects of cranberry constituents support a reduction in risk of urinary tract infections by reducing adhesion of microbes to epithelial surfaces and possibly direct microbial killing action by hippuric acid, a metabolite of its components.<sup>17</sup> Antimicrobial effects were also shown with pollen and pomegranate extracts.<sup>1,21</sup>

**6. Reduced conversion of testosterone to estrogen.** Excessive testosterone conversion to estrogen may have detrimental effects on men's health, including contribution to BPH.<sup>4</sup> Elagitannins derived from pomegranate were shown in an in vitro study to inhibit the aromatase enzyme, which converts androgens to estrogens.<sup>5</sup>

The beauty of this integrative approach to prostate health is that it can be used preventively many years before symptoms of LUTS and/or BPH occur, and these extracts have additional benefits for overall health.

# Flower Pollen, Cranberry and Pomegranate Extracts: Additional Highlights

**Flower pollen extract** – Flower pollen extracts are supported by over 100 clinical studies for various applications dating back to 1967.<sup>1</sup> An inhibition of inflammatory pathways benefits not only the prostate tissue but the rest of physiology as well. High quality flower pollen is manufactured via an extraction process that ensures removal of the allergenic components of pollen. This process also ensures standardization of the active ingredients to support consistent clinical results.

**Cranberry extract** – In addition to the effects detailed earlier, cranberry extracts have demonstrated the following benefits: antioxidant, anti-inflammatory, cardiovascular benefits, reduced aberrant cell proliferation, anti-viral, anti-H. pylori.<sup>17,18</sup>

**Pomegranate extract** – More than 166 studies support the benefits of pomegranate extracts. In addition to those mentioned earlier, others include: potent antioxidant, improved markers of cardiovascular health, and in vitro inhibition of various aberrant cell types including prostate cells.<sup>21</sup>

# Additional Nutrients of Critical Importance for Prostate Health

In order to optimize prostate health, it is prudent to optimize vitamin D status<sup>22</sup> and omega-3/omega-6 fatty acid levels and ratios<sup>24-29</sup>, since these greatly affect cell proliferation, inflammation and other unhealthy physiological processes. In addition, zinc<sup>23</sup> and selenium<sup>33</sup> provide further benefits for prostate health and should be included at adequate levels as part of foundational multivitamin/multimineral formulas or supplemented individually.

#### Conclusion

#### The combination of flower pollen, cranberry and pomegranate extracts may be taken preventatively or acutely in support of:

- Reduction of symptoms and inhibition of physiological processes involved in benign prostate hypertrophy (BPH) and prostatitis from various causes
- Reduction of lower urinary tract symptoms (LUTS) independently of its effect on lowering prostate size and/ or fibrosis
- Potential to lower PSA level elevated from various causes
- Reduction of aberrant prostate cell proliferation
- Reduced risk of urinary tract infections

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# **Shockwave Therapy for Erectile Dysfunction and Enhanced Sexual Performance**

By Richard Gaines, M.D., FAARM, ABAARM

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From a clinical standpoint, shockwaves are pulsed sound waves that carry energy that can be delivered non-invasively to targeted tissues. The energy of shockwaves has various effects on tissue, but mainly they cause a biological reaction that result in increased blood flow.

Shockwave therapy is a radically new procedure for improving the quality of erections. It helps men with erectile dysfunction overcome their difficulties, and can help any man perform better sexually.

It does this by the use of intense soundwaves to grow and repair blood vessels in the penis and ultimately improve blood flow. This results in penile rehabilitation, regeneration and rejuvenation.

As men age, the vessels in the penis weaken, contract and fill with micro-plaque. This is very similar to the way that cardiac vessels become clogged, leading to heart disease.

In the case of the tiny vessels that supply the blood to erectile tissue, as they become clogged, you have a harder time achieving and maintaining an erection. Also the penis decreases in sensitivity making it harder to achieve a pleasurable orgasm or obtaining another orgasm after climax.

Oral ED medications such as Viagra and Cialis, cannot and do not address this root cause of poor erectile function. Instead, they force blood into diseased vessels.

#### **Shockwave Therapy for ED**

The technical term for this type of treatment is Extracorporeal Shockwave Therapy, or ESWT. The treatments are also sometimes referred to as Low Intensity Extracorporeal Shockwave Therapy (LI-ESWT), Extracorporeal Pulse Activation Therapy (EPAT) or simply "shockwave therapy." One of the earliest uses of Shockwave therapy was urology. Since it has been used in a variety of fields including cardiovascular health, orthopedics, and aesthetics. In the case of treating male sexual performance issues, the procedure uses pulsating acoustical waves to break up micro-plaque, repair and build new blood vessels in the penis that tend to build up with plaque, or otherwise become compromised over time.

When used to treat vascular related erectile dysfunction which is the most common cause of age-related ED, the resulting improvement in blood flow, achieved by the creation of new blood vessels and the rejuvenation of existing vessels, increases the patient's ability to obtain and sustain an erection.

In March 2016, we obtained a device and tried shockwave therapy for the first time on our patients in Miami. The results were beyond all expectations. The first patient, a 56 year old executive stated, "After just one treatment I was able to achieve spontaneous erections and enhanced sexual performance. Other patients reported the ability to have multiple orgasms with almost no refraction time after orgasm. 39 of the first 40 patients reported enhanced sexual function.

#### Shockwave Therapy for ED Has Been Clinically Proven

In clinical trials, ESWT for ED proved to be effective, even for men that did not respond well to other treatments. A recent study published in the Journal of Sexual Medicine, found that all of the men in the study treated with shockwave therapy showed improved erectile function. Men in the study who were using Viagra or some other ED medication, achieved significant improvement, and reported that they did not need to use their ED prescription for "several months" after the shock wave treatment.

A similar study, this one published in Therapeutic Advances in Urology, concluded "ESWT is a revolutionary treatment for ED, and probably possesses unprecedented qualities that can rehabilitate erectile tissue. The clinical improvement in erectile function together with the significant improvement in [blood flow] following ESWT confirm that ESWT has unique properties that may create a new standard of care for men with ED."

The researchers in that study also pointed out that most other treatments for ED, such as oral ED medications, are "on-demand" therapies, where shockwave therapy is one of the few ED treatments that actually addresses the root causes of the problem.

As we started using ESWT in our own practices, developing our own treatment protocols which are now collectively known as GAINSWave<sup>™</sup> Therapy, we found that there was every indication that this could improve sexual performance and erectile quality in all men, and not just those suffering from ED.

Even patients without ED saw a benefit. Even younger patients who did not have ED, or any real evidence of vascular disease, but had a diminished sexual ability, often saw immediate improvements upon treatment.

Shockwave therapy really is unlike any other treatment currently being used to improve male sexual performance and erectile quality. It is noninvasive, it has no side effects, but, most importantly, it treats the root cause of the problem.

This is also really part of age-management medicine. If a man over 30 has ED or other performance issues, he very likely will also have heart disease, and/or other conditions related to vascular degeneration and the buildup of micro-plaque.

Shockwave therapy can be the first step. In addition to treating any trouble in the bedroom, we will often put these patients on a course of diet, fitness, and lifestyle changes that will help them to live a longer, healthier, more vital life.

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Burnout:' loss of enthusiasm, low sense of accomplishment, along with persistent feelings of exhaustion and ineffectiveness pervade the medical profession according to a spate of recent studies and articles. The statistics are jarring: research demonstrates that the level of physician burnout has trended upwards in the past two years, with a 25% increase over a four-year period, and all indications suggest no change in course.

An article in the Archives of Internal Medicine about a 2012 study reveals a gloomy picture. The study supporting this conclusion included responses and data from a large sample of physicians nationwide representing a range of disciplines. The findings demonstrated that not only was burnout more common among physicians than other workers throughout the United States, but physicians in specialties at the front line of care were found to be at the greatest risk. The 2016 Medscape Physician Lifestyle Report delivered similar findings, reporting that almost half of all physicians stated that they had experienced burnout. An analysis from researchers at the Mayo Clinic and the American Medical Association likewise reported that doctors' work-life balance is worsening, with the conclusion that patient care will be negatively impacted.

Even more concerning was data reported in a study published in *The Journal of the American Medical Association*, suggesting that the rate of depression among doctors in training is much greater than in the general population. The negative effect of burnout among doctors is, moreover, linked to alarming consequences

#### By Sarenka Smith, Editor, A4M | MMI

including higher rates of medical error with increased malpractice exposure, larger numbers of staff turnover, physician alcohol and drug abuse, and even suicide. While it is believed that fatalities from physician burnout are underreported, research does reveal that the suicide rate among doctors surpasses that of the general population.

In response to the national epidemic of physician burnout, a chief wellness officer has been added to the staff of Stanford Medicine. In an unprecedented move for an American academic medical institution, Tait Shanafelt, MD is now leading Stanford Medicine's pioneering program in the area of health care provider wellness. At a time when physician burnout has "nationally reached an all-time high," Dr. Shanafelt directs the WellMD Center at Stanford Medicine, while serving as associate dean.

#### "In nothing do men more nearly approach the gods than in giving health to men." — Cicero

Shanafelt has broken new ground in the field of wellness among medical professionals by creating and assessing numerous national surveys that have collected information from over 30,000 physicians and 9,000 workers from other disciplines nationwide. The survev results have confirmed increasing rates of burnout among doctors; in 2014, more than 50% of those surveyed were suffering from "emotional exhaustion, loss of meaning in work, or a sense of ineffectiveness and a lack of engagement with patients." Shanafelt's studies have established that while physicians suffer, patients do as well, since burnout leads to increased errors and higher rates of mortality among hospitalized individuals.

Shanafelt opines that the trend of physician burnout is "eroding the soul of medicine." While many leaders in healthcare recognize that burnout is a serious problem, most do not know how to effectively address it. Complicating the problem, physician distress remains a fairly taboo subject in the workplace. To date, stress management and burnout prevention are not covered comprehensively in medical school or residency training. Shanafelt is working to build and strengthen Stanford's innovative WellMD Center, where more than 200 physicians have worked since 2016, by implementing peer support, stress reduction, and programs aimed at cultivating compassion and resilience. Another focus of the center's work is a reduction of pressure among physicians through an improvement in efficiency and simplification of workplace systems.

The first American Conference on Physician Health took place in October at the center, co-sponsored by the American Medical Association and the Mayo Clinic. The primary goal of this event was the creation of a national dialogue surrounding the issue of physician burnout, and the implementation of tools to address physician distress with programs that promote "physician autonomy, efficiency, collegiality, and a sense of community."

At A4M/MMI, we recognize that the significant and growing problem of physician burnout poses a direct threat to quality of patient care. We believe that there must a collective shift in attitude so that we can move towards an optimal system of healthcare. Only with recognition of the problem will we reach our goal, and help physicians feel motivated and passionate, while moving away from those traditional practices that inevitably lead to doctor burnout. For the past quarter of a century, we have continued the journey to help reshape and redefine the face of medicine, with the goal of reinvigorating physicians so that they can more effectively heal their patients. A4M/MMI faculty emphasize the importance for healthcare practitioners and professionals to rediscover and renew their professional passion, while learning new and innovative methods to prevent burnout before it takes hold.



One notable faculty member who has expanded educational offerings, spearheaded transitions to functional medicine, and helped to shape the entire landscape of integrative healthcare is Pamela W. Smith, MD, MPH, MS. Dr. Smith is a board-certified specialist in Anti-Aging and Metabolic Medicine, an internationally renowned speaker and author on Functional Medicine, and a clinical expert on hormones and hormonal therapies.

Dr. Smith began her medical career as an emergency room physician, with two decades at Detroit Medical Center. After attending a conference that focused on Anti-Aging Medicine, and benefitting from the personalized and tailored approach of hormone compounding, Dr. Smith embarked on a journey that changed her career trajectory: founding and developing the Fellowship in Metabolic and Nutritional Medicine at A4M/MMI, where she currently serves as Fellowship Co-Chair.

A firm believer in personalized, customized medicine for every patient, Dr. Smith serves as Director of the Center for Healthy Living and Longevity, and co-director of the master's program in Metabolic & Nutritional Medicine at the Morsani College of Medicine at the University of South Florida. She holds a Master's in Public Health along with a Master's in Metabolic and Nutritional Medicine. Through Dr. Smith's mentorship and guidance, thousands of clinicians have learned about and embraced functional medicine, and pursued the root causes of chronic disease.



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## First Randomized, Double-Blind, Placebo-Controlled Study to Show Telomeres Getting Longer in Humans

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## A new study, conducted on 97 relatively healthy cytomegalovirus-positive subjects aged 53-87, found participants taking TA-65MD<sup>®</sup> significantly increased telomere length over a 12 month period compared to a placebo group.<sup>1</sup>

TA-65<sup>°</sup> is a patented, all natural, plant-based compound that animal and in vitro studies have indicated activates telomerase.<sup>1-4</sup> Telomerase is an enzyme that counteracts the attrition of telomere length by adding telomere repeats to the end of chromosomes.<sup>5</sup>

Telomeres protect the chromosome, preventing the loss of DNA to ensure cells replicate properly. As people age, telomeres shorten and leave the genetic DNA on the chromosomes vulnerable to damage and mutations. Over time, telomere shortening causes cells to die or to become senescent. By activating telomerase, an enzyme that adds nucleotides to telomeres, cells are able to live longer and continue to function properly.

This new study, published in Rejuvenation Research, confirms previous scientific studies demonstrating that TA-65MD<sup>\*</sup> activates telomerase and lengthens telomeres in a statistically significant manner. Notably, this is the first double blind, placebo-controlled study to show actual lengthening of telomeres in humans.

#### **Study Summary:**

- Study participants: 97 men and women (53-87 years old)
- Study length: 12 months
- First study to show statistically significant (p<0.005) lengthening of telomeres in humans

Placebo Group Decrease in median telomere lenght over 12 months	
Median telomere lenght	<b>↓</b> 290=100bp
20th percentile telomere lenght	<b>↓</b> 170=50bp

TA-65 <sup>®</sup> Group Increase vs placebo group in median telomere lenght over 12 months	
Median telomere lenght	<b>↑</b> 533=160bp
20th percentile telomere lenght	<b>270=90bp</b>

"By activating telomerase, we can help slow and perhaps even reverse cellular aging. These findings are an exciting step in our goal to safely prolong the life of human cells," said Noel Thomas Patton, the founder of T.A. Sciences, "We have been a leader in telomerase research since 2002 and will continue to invest in valuable research to help further the field of telomere biology."

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## **Overview On Weight Management Via Ketogenic Diet And Targeted Probiotic**

By Lewis Chang, PhD and Kirti Salunkhe, MD Metagenics Institute

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#### **OBESITY EPIDEMIC**

The National Health and Nutrition Examination Survey (NHANES) recently estimated that 35% of men and 40.4% of women in the US are obese (defined as BMI  $\geq$  30), and this trend has continued to increase over the past decade.<sup>1</sup> Obesity is an established driver of many conditions including certain cancers, sleep apnea, osteoarthritis, cardiovascular disease, and diabetes,<sup>2</sup> and obesity management continues to be a major healthcare challenge worldwide.

Obesity is an adiposity-based chronic disease. The quantity and distribution of body fat (adipose tissues) have significant physiological impacts in adiposity-based complications. For example, intra-abdominal (visceral) adiposity, but not subcutaneous adiposity in the extremities, is linked to metabolic dysfunction and poses a greater overall risk to metabolic health.<sup>3</sup> Higher waist-to-hip ratio, waist-to-height ratio, and waist circumference are indicators of increased proportion of abdominal adipose tissues, and therefore are useful predictors of cardio-metabolic risks.<sup>4</sup>

Even a modest reduction of 3-10% of total body weight is sufficient to have a clinically measurable benefit for diabetes prevention, symptoms of osteoarthritis, dyslipidemia, hyperglycemia, and hypertension.<sup>5</sup> Financially, the Global Obesity Prevention Center at Johns Hopkins University recently reported that weight loss at any age can yield significant cost savings. For example, a middle-aged adult may reduce direct medical cost around \$31,000 if he/she goes from being obese to a healthy weight.<sup>6</sup>

#### WEIGHT LOSS VIA KETOGENIC DIET

A successful weight loss strategy requires a combination of dietary modification, physical activity, and behavior therapy to achieve negative energy balance. During recent years, there has been strong supportive evidence that ketogenic diets are an effective dietary approach for weight loss.<sup>7</sup>

Ketosis is a natural metabolic state that occurs when there is an absence or shortage of dietary carbohydrates consumed as the main energy source for the body. A ketogenic diet promotes ketosis by restricting carbohydrates (usually to < 50 g/day) and increasing the intake of fat with adequate (low to moderate) consumption of protein.<sup>7</sup> While on a ketogenic diet, glucose levels in circulation decrease and so does the need for insulin to regulate glucose. A reduction of circulating insulin level helps increase release of fatty acids from adipose tissues for utilization. The body, mainly the liver, increases fat oxidation to generate ketone bodies (acetoacetate,  $\beta$ -hydroxybutyrate and acetone) in order to meet the energy demand. Ketone bodies in the circulation provide a stable source of fuel for the body and the brain, thereby sparing the need to break down muscle protein into glucose as energy supplies (**Figure 1**).<sup>8</sup>



Figure 1. Metabolic adaptation while on a ketogenic diet. FFA: free fatty acids

#### Pre-clinical and Clinical Evidence

A systematic review based on 13 randomized controlled trials that assigned adults to a ketogenic diet or a low-fat diet for a duration of 12 months or longer demonstrated that ketogenic diets achieved greater weight loss than low-fat diets.<sup>9</sup> A meta-analysis found that individuals following ketogenic diets were significantly less hungry and exhibited greater satiety.<sup>10</sup> Others have reported that ketone bodies generated during ketosis may have effects on appetite control hormones such as ghrelin and leptin and may have direct appetite-suppressing properties.<sup>11,12</sup>

Adapting to a ketogenic diet has also been shown to lead to several metabolic advantages, such as improvements in glycemic control,<sup>13</sup> improvements in blood lipids (lower triglycerides, lower cholesterol, higher HDL-cholesterol and increased size and volume of LDL-cholesterol particles),<sup>7,14</sup> and anti-inflammatory properties.<sup>15,16</sup>

#### WEIGHT LOSS MAINTENANCE VIA TARGETED PROBIOTIC

Due to multiple environmental and behavioral factors, as well as physiological adaptations favoring weight regain, a large percentage of individuals find it very difficult to maintain their weight loss and gradually regain weight.<sup>17</sup> Increasing evidence is now pointing to a crucial factor linking energy balance and obesity: microbiome.

The microbiome is a complex ecosystem with more than 100 trillion microorganisms colonized in the gut, and contains rich communication networks between the intestine and other organ systems. An imbalance within the microbiome is now recognized to have wide clinical impacts, including obesity.<sup>18</sup> The genomic content and diversity in the microbiome have been shown to be different in individuals with obesity as compared with individuals with normal weight. Lower microbial diversity is associated with obesity and fat mass variables, particularly the visceral fat mass,<sup>19</sup> and lower gene count is associated with more marked weight gain over time.20 An elegant experiment found that transplanting fecal microbiome from the obese humans into germfree mice leads to increased total body and fat mass and obesity-associated metabolic abnormalities in these animals.<sup>21</sup> On the other hand, germ-free mice colonized with fecal microbiome from lean humans did not have the same unfavorable response.<sup>21</sup>

Probiotics are live microorganisms which, when administered in adequate amounts, alter the microbiota of the host and may confer mostly beneficial health effects on the host.<sup>22</sup> However, as stated by the World Health Organization (WHO), not all probiotics are the same. The health benefits of probiotics are genus, species, and strain specific, and probiotics should be chosen based on the desired health benefits.<sup>23</sup> One specific strain, *Bifidobacterium animalis* ssp. *lactis* B420 (B420) has been investigated for its role in body weight regulation.

#### **Pre-clinical and Clinical Evidence**

In pre-clinical animal experiments, B420 reduced mucosal dysbiosis, bacterial translocation, expression of major pro-inflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ , PAI-1, and IL-6) in various tissues, and improved glucose metabolism in mice fed a high-fat diet (HFD).<sup>24</sup> In a mouse model of diabetes, B420 enhanced concentrations of ileum GLP-1, a protein involved in both insulin secretion and satiety signaling.<sup>25</sup> B420 also enhanced concentrations of ileum GLP-1, a protein involved in both insulin secretion and satiety signaling.<sup>25</sup> Diabetic mice receiving both HFD and B420 had decreased fat mass compared with mice receiving only HFD.<sup>26</sup> The potential mechanisms of action of B420 are summarized in **Figure 2**.<sup>24-27</sup>



**Figure 2.** Proposed mechanisms of action of B420. LPS: lipopolysaccharides; SCFA: short-chain fatty acids.

A randomized, double-blind, clinical study was conducted to examine the impact of B420 in adiposity-related outcomes.<sup>28</sup> Healthy adults with overweight or obesity (BMI 28-34.9; waistto-hip ratio  $\ge 0.88$  for men and  $\ge 0.83$  for women) with normal glucose and insulin concentrations at baseline were randomized to 10 billion CFUs/day B420 (n=55) or placebo (n=57) for six months. The post-hoc factorial analysis of participants who completed the trial found that (1) the placebo group had increases in fat mass by 3.1% over the six-month period, whereas the B420 group showed only 0.1% rises in fat mass; (2) compared with the placebo group, B420 group had a lower waist circumference by 2.4% (approximately 1 inch, or 2.4 cm); (3) B420 group reduced energy intake by ~300 kcal/day compared with placebo over the six-month period; (4) there was a significant increase in shortchain fatty acids (SCFAs) in stool samples from the B420 group compared with the placebo group. As SCFAs are produced by the microbial activity, the change in fecal SCFAs is suggestive of alterations in the microbiome occurring with B420 supplementation. These data suggest that B420 may be beneficial for long-term body weight and fat maintenance.

#### SUMMARY

Different evidence-based approaches are available for weight management, and ketogenic diets have demonstrated to be one of the effective dietary plans for weight loss. However, ketogenic diets may not be appropriate for everyone. Individuals should consult healthcare practitioners before committing to such a program. As important, achieving the initial weight loss goal is only the beginning of weight loss maintenance. New physiological and psychological challenges may arise during the maintenance phase and require strategies to ensure long-term success. Bifidobacterium animalis ssp. lactis B420 has been demonstrated clinically to improve body weight and body fat regulation, and may be valuable for long-term weight maintenance. The microbiome is an important factor involved in the regulation of energy balance, and interventions such as the targeted probiotic supplementation represent another tool that may be integrated into a diet and lifestyle management program to improve patient outcomes.

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## **Case Study: Pulsed Electromagnetic Field (PEMF) Therapy Relieves Pleural Effusion Following Open Heart Surgery**

#### By Magda Havas

Trent School of the Environment, Trent University, Canada

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#### Abstract

Sixty-one year old female experienced difficulty breathing that became progressively worse following triple bypass openheart surgery. She was readmitted to hospital and received oxygen therapy. X-rays indicated a large pleural effusion of the left lung that was increasing in size. She then received two 20-minute treatments with pulsed electromagnetic field (PEMF) therapy spaced one day apart. She noticed a significant improvement in breathing following the second treatment but not the first. A follow-up X-ray indicated a "dramatic" reduction in the pleural effusion that the radiologist assumed was due to therapeutic thoracocentesis. No thoracocentesis was performed. This case study indicates that PEMF therapy can be used to reduce a large pleural effusion after just two non-invasive treatments leading to an immediate improvement in symptoms verified by X-rays.

#### **Opinion Piece**

Pulsed electromagnetic field (PEMF) therapy has been used for decades to promote healing of non-union bone fractures and damaged soft tissue [1-3]. It has been shown to be effective at increasing circulation, reducing inflammation, and alleviating pain [4,5]. Currently transcranial PEMF therapy is being tested as an alternative to anti-depressants for those for whom drug therapy is ineffective [6].

Many different PEMF devices are available and a growing number of them have been approved by Health Canada and allowed into the United States as wellness devices. To date, there are no peer-reviewed studies documenting the effectiveness of PEMF on pleural effusions.

#### **Case Study**

A 61-year old female had triple bypass open heart surgery on July 18, 2013 and went home 9 days later. At home she had difficulty breathing and on July 31st was re-admitted to hospital where she received oxygen therapy. X-rays revealed that she had a large pleural effusion of the left lung. On August 3rd she returned home but still had breathing difficulties. X-rays taken on August 2, 9, and 20 indicated an increase in size of the pleural effusion (Plate 1). On September 16 and 17, she had two 20-minute treatments with ONDAMED, a PEMF therapeutic device that is based on pulse biofeedback. She noticed a significant improvement in breathing following the second but not the first treatment. X-rays taken on October 18 showed a "remarkable" improvement that the radiologist assumed was due to a therapeutic thoracocentesis. No thoracocentesis was performed. The only explanation is that the two PEMF treatments initiated the improvement that was subjectively observed and confirmed by X-rays.

Below are direct quotes from the radiologist.

*August 9, 2013:* Large left sided pleural effusion with compressive ateleclasis in the left lower lobe. No significant change when compared with the patient's previous examination on August 2, 2013 (Plate 1).

*August 20, 2013:* Comparison is made with the previous of 9 August 2013. There is a mild increase in the size of the large left pleural effusion and this occupies approximately the inferior two thirds of the left hemi thorax. Fluid is also seen tracking in the superior aspect of the left major fissure. The left upper lung including the right lung is clear and the right costophrenic angle is well defined (Plate 2).

*October 18, 2013:* The study is done on a patient who is seen to have a large left sided pleural effusion on an examination of August 20, 2013 (Plate 3).



The patient has had a prior CABG. The heart is within normal limits in size. The pulmonary vasculature is normal. The left sided pleural effusion shows a dramatic reduction in size when compared to the examine of August 20th. This is presumably due to a therapeutic thoracocentesis. [NOTE: no therapeutic thoracocentesis was performed] The left sided pleural effusion is now a small left sided pleural effusion. Mild compressive atelectasis is seen in the base of the left lung.

#### Conclusion

Two 20-minutes sessions of PEMF therapy one day apart were effective at reducing a pleural effusion in a 61-year old female following open heart surgery. Her ability to breath improved following the second treatment and the reduction in the pleural effusion is obvious in her chest x-rays.

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## **Immune Surveillance and Gut Barrier Function**

By Thomas G. Guilliams, PhD.

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It is difficult to think of the gut lumen as being "outside" the body, but there is an intricate set of barriers designed to ensure it remains so. Therefore, the barrier/permeability functions of the gut represent one of the most important interfaces between a person and the external environment. However, we should not imagine this barrier function as simply a means to keep things out, but as a sophisticated system to communicate with, and allow selective entry of, certain contents from the gut lumen into the body. This requires a tightly controlled but thin barrier of tissues and secretions *intentionally designed for close proximity to the gut lumen*. This proximity permits the absorption of available nutrients and physiological interaction with trillions of non-human microbes and their metabolites and signals, but also creates a vulnerability to those same microbes, toxins and immunologically reactive components from the gut lumen.

The strong relationship between the functions of the immune system and the GI tract is not a new concept, especially within the integrative and functional medicine community. And, as is often pointed out, 70 to 80% of immune cells reside in the GI tract.<sup>1</sup> In fact, in our list of the ten basic principles for building overall immune health, the first two are directly related to core functions of the GI tract: 1) Maintaining and Protecting Barrier Function, and 2) Creating a Commensal Friendly Environment.<sup>2</sup> This is easier said than done, however, especially when we consider the need to permit the absorption of thousands of important nutrients through this same barrier.

Since the GI tract is designed to break down and absorb large amounts of nutrients in a relatively short time, architectural features in the form of folds and fingers, called villi, greatly expands the surface area of the GI tract, especially in the small intestines where most nutrient absorption occurs. However, since this expansive surface area, about the size of a tennis court, is only one cell-layer thin, it represents a highly vulnerable interface with the antigen-rich environment of the gut lumen. This vulnerability requires a highly coordinated cooperation between three cell types: the GI epithelial cells, the adjacent cells of the immune system, and the microbiota within the gut lumen.

The innate and adaptive immune systems are critical components of the barrier function of the gut. Approximately 100 to

150 mesenteric lymph nodes are distributed throughout the gut to create numerous "stations" for concentrated interactions between antigens, antigen-presenting cells, regulatory cells and effector cells. This specialized feature of the immune system is often referred to as the gut-associated lymphoid tissue (GALT), a subcategory of the mucosa-associated lymphoid tissues (MALT) found throughout other mucosal barriers (eyes, mouth, lungs, breast, vagina, skin, etc.). Another special feature of the GALT is the 100 to 200 Peyer's patches found primarily along the mucosa of the ilium.3 These Peyer's patches include a large concentration of B cells surrounded by T cells and antigen-presenting cells-mostly dendritic cells-that interface directly with the gut lumen through the activities of special gut epithelial cells called M cells (microfold cells).<sup>4</sup> These M cells are designed to allow the controlled passage of antigens (commensal bacteria, pathogenic bacteria, viruses, fungi, food particles, etc.) from the gut lumen, where they can be delivered safely to antigen-presenting cells in the lamina propria. These, in turn, present them to both mature and naïve T cells.<sup>5</sup>

A larger number of smaller aggregates of lymphoid cells similar to Peyer's patches, called isolated lymphoid follicles (ILFs), are dispersed throughout the GI tract. In fact, some 30,000 ILFs line the lamina propria of the human GI tract, reaching their highest concentration in the ilium where there is approximately one ILF for every 28 villi.<sup>6</sup> Also, specialized memory T-lymphocytes, called intraepithelial lymphocytes (IELs), are located in the space between mucosal epithelial cells at a rate of approximately 10-15 IELs for every 100 epithelial cells. IELs are critical components in the first-line adaptive immune response (as dendritic cells are for the innate immune response), and directly communicate to adjacent epithelial cells to modulate barrier function.<sup>7,8,9</sup>

One of the unique features of the adaptive immune response within the GALT, as in most other mucosal tissues, is the abundance of antibody-secreting B cells, called plasma cells, which produce antibodies of the secretory IgA class (sIgA). This form of antibody is capable of passing into the lumen of the gut, as it does in breast milk, saliva, tears, etc., to interact with antigens while they are still "outside" the body. Antigens sampled via the M cells are presented to T helper cells and B cells and, when an appropriate cross-reactivity is triggered, B cells are activated to secrete the corresponding sIgA. Research now shows sIgA expression against both pathogenic and commensal organisms is a key regulatory aspect of the intestinal barrier itself.<sup>10,11,12</sup> Also, there is a well-documented relationship between increased HPA axis stress and reduced sIgA levels.<sup>13</sup> Laboratory measurements of sIgA levels are often used as one of many markers of mucosal immune health and/or HPA axis stress-induced immune suppression, and specific sIgA levels measured in a stool or saliva sample can indicate a particular antigenic challenge.<sup>14</sup>

In addition to the M cell-mediated antigen sampling, specialized dendritic cells can change their morphology to permit direct surveillance of the gut lumen by an extension protruding between the gut epithelial cells. This allows the dendritic cell to use its many pattern-recognition receptors to begin reacting to changes within the "pattern" of pathogens in the gut before specific antigens are presented to the adaptive immune cells. This process of immune surveillance is considered an important part of the "education" and maturation of the immune system, and provides an early warning of potential pathogenic agents in the gut, allowing for a preemptive response.<sup>15</sup> The ultimate goal is to mount appropriate and timely immune responses to harmful and foreign antigens, while creating an active tolerance against harmless or self-antigens.

#### Intestinal Permeability: Testing Immune Resilience and Control

Breaches in the gut barrier, resulting from hyper-permeability of the paracellular tight junctions or damage to the epithelium, are one of the most potent challenges to the immune system. These breaches permit unprocessed antigens, or even intact organisms from the gut lumen, entry to the lamina propria without being processed through the specialized GI epithelial M cells. These unprocessed antigens can trigger a vigorous acute immune response and, furthermore, increasing the susceptibility to autoimmune cross-reactivity. In fact, one of the leading theories for the genesis of autoimmune diseases is the immune exposure to unprocessed non-self-antigens that have breached the intestinal barrier (e.g., gliadin and zonulin; see main text).<sup>16</sup>

Once the mucosal immune system of the gut is triggered to respond to a potential threat (regardless of the source), the inflammatory process will be engaged and may persist well after the original trigger is neutralized.<sup>17</sup> Prolonged or inappropriate inflammatory responses by the immune system can, in turn, lead to signals that promote further intestinal permeability thereby leading to chronic cycles of inflammatory bowel diseases.<sup>18</sup> Therefore, it is imperative to consider all intestinal barrier issues as having an immune/inflammatory component, meaning therapies designed to improve intestinal barrier function should also include immune-supporting and anti-inflammatory components.

#### Immune-Friendly, GI Nutrient Supplementation

Like most cells in the body, the cells lining the GI tract need proper nutrients to maintain proper function. These cells have specific nutrient needs that allow for targeted therapy.<sup>19</sup> The most basic is that enterocytes, and to a much lesser extent, colonocytes, use the amino acid glutamine as a major source of energy (this is also true of many cells within the immune system).<sup>20</sup> The deficiency of glutamine is a cause of both gut dysfunction and muscle wasting, since the body will remove glutamine from muscle tissue to attempt to bolster gut glutamine levels. Oral glutamine has been shown to protect and/or repair gut morphology and intestinal permeability triggered by numerous insults.<sup>21</sup>,<sup>22</sup>

The need to produce mucins/mucus within the GI tract is also a specialized function of these cells. Supplementation with mucus pre-cursors such as glucosamine or N-acetyl glucosamine provides cells with the necessary building blocks to produce appropriate mucin levels. The availability of butyrate (a short-chain fatty acid produced by bacterial fermentation of certain fibers) also promotes mucin production in colonocytes, modulates immune function and down regulates inflammatory signaling.<sup>23</sup>,<sup>24</sup> The addition of fermentable fibers such as FOS (fructooligosaccharides) or inulin along with appropriate probiotics (with many other immune-related benefits) will ensure proper butyrate levels.

Of course, numerous other options that support both immune and GI barrier function may be helpful in certain patients. These include oral immunoglobulins (mostly IgG) delivered through colostrum or serum concentrates, anti-inflammatory and immunomodulatory herb or botanical extracts (e.g., curcumin, boswellia, *Scuttelaria baicalensis*, propolis, etc.), omega-3 fatty acids, zinc, berberine and, as already mentioned, probiotics.

Needless to say, it is impossible to have a properly functioning immune system while the gut is burdened with dysfunction or imbalance. An intact barrier function with a vibrant ecosystem of commensal organisms are both vital for the training and regulation of a healthy immune system. Clinicians should always consider GI function as integrated and related to any immune-related dysfunction within the patient, and therefore, as part of the preventative and intervention strategy of any immune-related disorder.

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## **Estrogen and the Microbiome: Implications for Women's Health in Menopause**

By Kate Placzek, PhD

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Complex as a rainforest, the ecological community of the gut is rich with commensal micro-organisms. In health, the functions of these micro-organisms are in a dynamic equilibrium with the human host, exerting both local and distant events. We host these microbes and provide them with food, while they maintain our gut integrity, break down complex carbohydrates to improve energy extraction from food, produce vitamins and minerals, aid in digestion and absorption, ferment dietary fibers and protect us against pathogens. This symbiotic relationship between the bugs and our bodies is very important because the gut serves as a hub for communicating with the rest of the body via neural, endocrine and immune signals. Maintaining a delicate balance in the diversity of the host-microbiome relationship is crucial for disease prevention and healthy aging.

The diversity of the microbiome has profound implications not just for gut health, but also for psychological wellbeing, metabolic and bone health, and the wellness of the female reproductive tract. To properly address these functions, the microbiome works together with reproductive sex steroids. This article aims to shed light on the intertwined roles between gut microbiota and estrogen-modulated events pertinent to women as they transition into menopause.

### **OPTIMIZING METABOLIC HEALTH**

### Estrogen, Microbiome and Metabolic Health

Estrogen and the microbiome regulate body composition and lipid deposition independent of each other.

By increasing the density of small intestinal villi capillaries, gut microbiota influence gastrointestinal physiology and gut motility, and thus promote caloric extraction from the diet. Studies in humans show that a drastic reduction in diversity of gut microbes (also called dysbiosis) is enough to cause functional changes related to weight gain [1]. Owing to the essential role of the gut ecosystem in maintaining host physiology, unfavorable alterations in the composition of the microbial make up can trigger a wide range of physiological disorders, including low-grade inflammation, metabolic disorders, excess lipid accumulation, autoimmunity, and loss of insulin sensitivity, all of which increase the risk of developing metabolic diseases, such as metabolic syndrome. Estrogen, when in proper balance in the body, is also recognized as a key element in preserving metabolic health by keeping weight down, reducing abdominal fat and improving glucose tolerance. Recent studies help illuminate another, less recognized role of estrogen in metabolic health, and it concerns the gut.

### **Microbiome Regulates Free Estrogen Levels**

The gut microbiome impacts estrogen levels through the secretion of b-glucuronidase, an enzyme which removes the sulfate and glucuronide groups from inactivated estrogen glucuronides and sulfates, allowing them to reenter the blood circulation as active estrogens (estradiol, estrone, estriol) available for tissue uptake [2;3]. Of therapeutic interest, when estrogens are elevated, particularly with delayed bowel transit and a preponderance of E.coli, for instance, the use of calcium d-glucarate as a supplement acts by blocking β-glucuronidase and estrogen reabsorption at the intestinal wall. It is the free fraction of estrogen that has activity at the level of estrogen receptors a and b (ERa and ERb, respectively), giving rise to subsequent physiological downstream effects. To assess the free, bioavailable fraction of hormone available for tissue uptake, saliva can be used for a convenient and noninvasive test.

Characterized by diminished microbial diversity, dysbiosis is an event that may lead to an inflammatory response and metabolic profile that is detrimental to health [1]. Disturbances in the microbiota composition, or dysbiosis, when lower microbial diversity is represented, can impair the process of converting estrogen conjugates in the gut to free bioavailable estrogens, resulting in reduced circulating free estrogen levels. Although the formula for the optimal composition of the gut microbiota may be individual, a balanced community is crucial for cultivating homeostasis of estrogen-modulated physiology. Maintaining physiological levels of estrogen with the help of estrogen replacement therapy becomes even more important in menopause when dysbiosis events may be suspected.

### Estrogen is Protective for Microbial Diversity

Adequate estrogen levels are important for a multitude of

functions. Specific to the microbiome, estrogen and estrogen-like compounds prevent the loss of and promote growth and proliferation of certain types of beneficial bacteria [4]. This means that estrogen is critical for preserving microbial diversity in the gastrointestinal tract. Studies show that when treated with estrogen, animals have significantly higher microbial diversity than controls [5], and maintaining microbial diversity is also key for a healthy metabolic profile in humans [1]. A study by Turnbaugh (2009) specifically illuminates how dysbiosis can preferentially turn on genes and inappropriately activate pathways involved in sugar and carbohydrate metabolism in overweight but not in lean individuals. The aberrant upregulation of these genes is believed to contribute to the metabolic profile observed in overweight persons.

#### **Estrogen Reduces Inflammation**

Additionally, estrogen decreases pathogenic populations of bacteria and reduces lipopolysaccharide (LPS) -induced inflammation. LPS, produced by Gram-negative bacteria, can impair the lining of the gut, cross into the rest of the body and elicit a strong immune response. Estrogen working against enteric pathogens is yet another example of estrogen's protective functions on the gut.

#### **Relevance to Patients**

Lack of estrogen and alteration of the gut microbiota are important in driving metabolic issues in menopause. For perimenopausal patients experiencing decreases in basal metabolic rate with concurrent gastrointestinal health issues, a combination of estrogen replacement therapy together with digestive support might have a profound impact on restoring gut health and improving metabolic function.

### PRESERVING BONE DENSITY

Postmenopausal osteoporosis is a common skeletal disease that predisposes women to fracture and disability. The central feature of postmenopausal bone loss is lack of estrogen. Via its receptors, estrogen in pre-menopausal years modulates bone development and remodeling. In menopause, when estrogen levels are very low, bone tissue loses estrogen's protective effects.

Additionally, bone loss is an active process, driven by enhanced cytokine production that is specific to a low estrogen environment. Estrogen deficiency allows production of pro-inflammatory cytokines (which include but are not limited to RANKL, TNF, IL-1, IL-17) [6]. This means that estrogen's immunomodulatory effects are important for keeping inflammation levels down, and not allowing the immune system to wreak havoc on bone tissue.

This is how estrogen aggressively prevents excessive bone

loss – directly, by activating receptors in bone tissue and indirectly, by keeping inflammation levels under control.

#### Estrogen Helps Maintain the Integrity of the Gut

The intestinal epithelium (i.e., cells that line the gut) forms a barrier that creates an interface between the host and the luminal microbiota. The integrity of the gut epithelial barrier is essential for regulating nutrient, electrolyte and water absorption and preventing the entry of pathogenic microorganisms. A healthy and diverse microbiome ensures that the gut barrier maintains its integrity. Sufficient estrogen levels are also needed to form the epithelial layer of the gut and keep it healthy, elastic and impervious to the contents of the gut [7]. This is critical in the context of bone formation because any changes to intestinal permeability are likely to elevate levels of cytokines detrimental to bone health [6]. Loss of estrogen is associated with weakening of the gut barrier integrity, increased intestinal permeability, decreased calcium absorption and increased inflammatory response [2]. All of these consequences of estrogen deficiency play into compromising bone health, but an important piece of the puzzle is the microbiome; gut microbiota are required for estrogen deprivation to induce bone loss [6].

### Bone Loss is an Estrogen and a Gut Problem

Gut microbes regulate the systemic immune response critical for bone homeostasis. Occurrence of dysbiosis is sufficient to aggravate intestinal pathologies related to the immune system. Importantly, the inflammatory response from gastrointestinal inflammation and dysbiosis that estrogen protects against can lead to an immune cascade that can hinder vitamin D receptor expression and activity, wounding not only the immune system but hindering the skeleton's ability to retain its calcium.

#### **Relevance to Patients**

Overall, a balanced hormonal clinical picture is important for maintaining healthy bones. In addition, therapeutic approaches to preserve the integrity of the gut would offer a promising therapy to prevent estrogen depletion-induced bone loss. Estrogen therapy (if not contraindicated) together with probiotics may be worth considering for patients approaching menopause.

### IMPROVING PSYCHOLOGICAL WELLBEING

### **Microbiome and Neuroactive Molecules**

Besides the enteric nervous system, an increasing body of evidence suggests that the microbiome helps the gut and the brain communicate to regulate complex processes such as mood, behavior and cognitive function [8]. A feeling of "butterflies in the stomach" is one perceivable example of this communication. In this case, the brain interprets the reduction in gastrointestinal blood flow as "flutters" while all that anxious adrenaline redirects to the muscle tissue. Several compounds produced by gut microbes can contribute to controlling the host's physiological and pathological states; these include monoamine neurotransmitters. Serotonin, dopamine, norepinephrine, phenethylamine, glutamate and GABA are all examples of neurotransmitters produced by the intestinal microbiota [9]. Identical to the neurotransmitters produced by our own bodies, these same neuroactive molecules released by microbes interact with our bodies to produce enteric-neural communication responses [10]. What's more, estrogen acts specifically to slow down the degradation of serotonin and to upregulate its production. Estrogen's powerful influence on our neurochemistry certainly contributes to the delicate balance in the many similar and complementary influences on neurotransmitters exerted by the microbiota.

### VAGINAL HEALTH

As levels of estrogen drop in menopause the health of vaginal tissues becomes compromised, with vaginal dryness and atrophy being the most common symptoms. Supplementation with estrogen can at least partly reverse these structural and chemical changes [11]. These symptoms arise in part from the loss of direct effects of estradiol on the affected tissues, and in part from a reduction in beneficial bacterial populations [12].

The predominant species giving rise to the vaginal microbiome is *Lactobacillus*. Together with many other species, *Lactobacilli* support a healthy epithelium and the integrity of the urogenital tract, and produce lactic acid to protect against urinary tract infections and exert important health-promoting effects [13]. Estrogen nourishes vaginal microbiota, and promotes the growth of *Lactobacillus*. As estrogen levels drop in menopause, so do levels of *Lactobacillus*. Studies show that re-establishing normal flora with oral probiotics can help support the vaginal ecosystem and protect against dryness and irritation [14]. As commonly seen with probiotic therapy, however, these effects are expected to be transient. Addition of estrogen at physiological levels may foster an appropriate environment for beneficial bacteria that would sustain the health of vaginal tissues long-term.

### CONCLUSIONS

Estrogen, in adequate amounts, together with a flourishing microbiome is paramount to many aspects of women's health

in perimenopause. Like a marigold planted in the vegetable garden, these systems work synergistically to create homeostasis by building a healthy, self-sustaining terrain.

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#### Dr. Kate Placzek's Professional Bio:

Prior to her role as a Senior Research Scientist at ZRT Laboratory, Dr. Placzek performed her postdoctoral studies at Oregon Health and Science University, identifying and characterizing biomarkers in Graves' disease. Dr. Placzek earned her Ph.D. in Medicinal Chemistry and Molecular Pharmacology at Purdue University in 2008 for her work in characterizing biosynthetic mechanisms of endogenous cannabinoid production. Additionally, Dr. Placzek developed robust analytical methods for the detection of these lipid and neurotransmitter-like molecules. Dr. Placzek received a Bachelor's degree in Biology and Chemistry at St. Olaf College in 2003.

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# **Redefining Peptide Immunotherapy. Colostrum — New Research & Application.**

By Andrew Keech, Ph.D., DSc and Nagendra Rangavajla, Ph.D., FACN

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### What is colostrum

Colostrum is the first pre-milk substance that is produced by the mammary gland of female mammals, including humans, following the birth of the newborn. It is the first food tasted in this life by all mammals. It is a special substance that is very unlike other foods, even milk. It is loaded with immune factors, growth factors, and protective proteins as well as all the nutrients the newborn needs to survive. The immune factors in colostrum provide the immunity necessary to ward off potentially fatal infections until the newborn's own immune system can get up to speed, and the growth factors help complete the development of the gut, which is not fully developed at the time of birth.

Colostrum consumption by adult humans is beneficial even though many of the components undergo digestion in the mature stomach, including some antibodies and all other proteins [1,2,3,4]. However, there is evidence that immunoglobulins can survive the digestive tract intact. There are claims that colostrum is useful in the treatment or prevention of a variety of illnesses. [5,6]

### Key constituents of colostrum

Cows colostrum (colostrum) is biologically designed to provide immune benefit, antimicrobial effect in addition to critical nutrients for nurturing the offspring. Cows colostrum (aka bovine colostrum) contains proteins, carbohydrates, fats, vitamins and minerals to help sustain the life of the calf, as a sole source of nutrition. Colostrum is enriched with oligosaccharides, antimicrobials, and immunoregulating factors such as Proline-rich Polypeptides and Apelin peptides (<10k MW protein fraction) (Figure 1). Further, colostrum from the initial milking has much higher concentration of bioactives and the composition gradually matches bovine milk between the 5-7<sup>th</sup> days of post-partum (Figure 2).

### Application of colostrum in human health & performance

Available evidence suggests a beneficial effect of supplementation of colostrum in improving body composition, aspects of athletic performance, diarrhea in persons with immune-deficiency syndromes, NSAID-induced gastrointestinal disturbances, and aspects of the acute phase response that occurs secondary to surgery. Specific hyperimmune colostrum, produced to have high neutralizing titer activity against Cryptosporidia, *H. pylori*, measles, rotavirus, and *Shigella sp.*, appear to have clinical utility in conditions associated with these infectious organisms [7]. Cow colostrum has been clinically studied to be efficacious in variety of conditions such as GI health (e.g., diarrhea, infection, inflammation, etc.), Performance nutrition (e.g., sports) as well as General health (e.g., strength and recovery in elderly).

Antimicrobial/ toxin neutralizing effect: Constituents of colostrum, particularly lysozyme, lactoperoxidase system, oligosaccharides confer both antimicrobial and toxin neutralizing effect throughout the GI track. In addition to direct microbial effect, fractions of colostrum such as peptides provide systemic immune benefits to alleviate inflammation, repair gut tissue and improve gut integrity.

<u>GI Infections</u>: Colostrum as an ingredient offers a unique solution for GI infections particularly in diarrhea in children where the mortality from diarrhea is one of the top leading causes for under 5 years of age. Further, most health agencies do not recommend use of anti-motility and antibiotics for diarrhea in children. Colostrum in combination with egg solids provides dual benefit for the condition – it provides immune bodies such as IgGs & IgYs; bacteriostatic/ bacteriocidal components such as lactoferrin, lysozyme, lactoperoxidase system, etc., to provide broad spectrum efficacy and in addition, colostrum provides much needed nutrients to the child. During a typical diarrhea, it has been reported that children may lose or reduce intake of protein up to 30% of daily value. The DiaResQ\* product replenishes a high-quality protein to support growth and well-being of the child.

Studies have been conducted to substantiate the benefits of colostrum in the management of diarrhea. Most recent study conducted by University of Colorado's Center for Public Health clearly demonstrated the benefit of colostrum + egg combination in reducing the duration of diarrhea in Guatemalan children due to six prominent pathogens [8].

**Sports applications:** Colostrum has been studied in multiple sports applications including recreational athletes, competitive cyclists and elite rowers. Studies show improvement in performance (repetition), VO2 max, LBM and associated increase in IGF levels [9].

<u>Older adults:</u> Elderly demographic is increasing significantly and will impact health care costs in the future. Colostrum is shown to improve leg press strength and lean body mass in elderly subjects compared to whey protein intervention. This finding is key for aiding faster recovery for the elderly subjects [10].



Figure. 1: Typical composition of bovine colostrum

### Animal health

Colostrum is critical in cattle to prevent mortality and improve productivity. While human's fetus receives immunoglobulins through placenta, oral ingestion of immunoglobulins is critical for calf to acquire immunity [11]. Additional opportunities for colostrum include prophylaxis in Cryptosporidium infections in cattle and improved productivity in swine through prevention of scours.

### Safety of colostrum

Colostrum has been classified as milk product under CFR and has been used in large range of doses, 4gms per day in 1-year old children to up to 100gms in adults with no adverse events reported that is attributable to colostrum. A GRAS petition is being assembled by colostrum manufacturers to formalize safety of colostrum for food use. Currently, colostrum is widely available as a supplement.

### **Applications of colostrum**

Since fresh colostrum is difficult to preserve and distribute without affecting the activity of immune components, colostrum is typically made available in a powder form where the liquid colostrum is gently processed and dried to ensure safety while preserving the nutritional and immune components of colostrum. Dairy farmers typically feed the calf the required colostrum right after birth and any left overs are milked (similar to typical milking) and stored frozen for further processing. Colostrum is made available too in multiple formats to deliver to users' convenience. While powder formats are very popular, formats such as tablets, capsule formulation and oral sprays offer unique user experience to the consumer.

### **Future Areas of Research**

There are over 10,000 research articles on the effectiveness of colostrum on human and animal health. The market for colostrum has typically been as a supplement or food ingredient. There are a couple of examples of colostrum used as an orphan drug, but future research should be aimed and formulated for medical food and eventually the industry should perform clinical trials in the area of Biologics on the whole colostrum or subsequent fractions of colostrum. We are of the opinion that health benefits of colostrum have not been fully exploited to help improve quality of health of patients and perhaps to reduce health care costs.



**Figure. 2:** Change in bioactive components of colostrum post partum

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## A Comparison of Telomere Lengths Derived from Buccal and Whole Blood Samples via qPCR.

### By Jonathan Stein, PhD

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### **INTRODUCTION**

Whenever cell division occurs for any purpose (growth, wound healing, repair or replacement, etc.), the telomeres on each arm of each chromosome of each daughter cell shorten. Once an individual is fully grown, the rate of telomere loss can in this sense be considered a marker for an individual's level of cellular turnover, wear and tear. Once an individual cell's telomeres reach a certain critical shortness (3-5 kilobases) the cell goes into a state of senescence and is no longer able to divide. As people age, this process appears to impact rapidly dividing cell systems (e.g., digestive systems, skin, vascular tissues, etc.), both limiting the availability of cellular repair, as well as acting as a break on uncontrolled cellular proliferation. Because of this critical function, telomeres play a fascinating role in commonly associated diseases of aging.

Telomere shortening has been implicated as a mechanism explaining variations in life expectancy and a variety of aging-related diseases. In addition to the telomeropathathies and progeroid disorders associated with defects in telomere length or repair, there is a vast body of peer reviewed scientific publication papers showing a reproducible and significant association between short telomere length and increased disease risk for a wide variety of common diseases (Table 1). It's worth emphasizing that most of these studies use peripheral whole blood to determine average telomere length.

Short telomeres are associated with reduced health, but whether this association is causal, due to reverse causation, or due to the influence of confounding factors is largely unknown (Bojesen, 2013). However, the accumulation of senescent cells is associated with decreased lifespan in animal models, and the reduced availability of cells for repair or replacement has been one proposed explanation (Baker, 2016).

Further, accumulated evidence places oxidative stress as an accelerator of telomere attrition during cell replication (von Zglinicki 2002). Several studies denote inflammation and oxidative stress as the major contributors to pathophysiology of aging and age-related cardiovascular disease (Libby 2002; Stocker & Keaney 2004). In the Cardiovascular Health Study (CHS), in the face of subclinical and clinical cardiovascular disease and Telomere Length, the authors demonstrated negative correlation of IL-6 and C-reactive proteins with Telomere Length, highlighting the role of inflammation in Telomere Length regulation (Fitzpatrick et al., 2007). O'Donovan et al. reported of increased systemic inflammation with shorter Leukocyte Telomere Length in the Health, Aging and Body Composition Study (Health ABC) cohort (O'Donovan et al., 2011).

While increased risk is no guarantee of disease manifestation, it's often useful for an individual to know if they are at increased risk of a disease in order to modify their lifestyle or seek treatment to minimize that risk. As such, testing may be deemed clinically useful for individuals concerned about their risk for these aforementioned conditions.

Several independent longitudinal population studies have shown that telomeres shorten with age, and that the average size of telomeres and rate of attrition varies between individuals (Berenson et. al., 2008, Demerath et. al., 2010, Whooley et. al., 2010). Many studies have also reproducibly reported the correlation between shortened telomeres, specific disease states, morbidity and mortality.

Mechanistically, Telomere Length reflects the cumulative burden of oxidative stress and repeated cell replication, and it has been hypothesized that cumulative oxidative stress may underlie the link between telomeres and aging-related disease in humans (Serra et al., 2003). Further, reduced average telomere length is associated with increased risk for a wide variety of common diseases, and it may be clinically useful to identify patients at increased disease risk in order to determine the necessity of clinical or lifestyle interventions.

### **TELOMERE TESTING**

At present, there are several different methods routinely used to determine telomere length for research purposes (FISH, qPCR, Southern blots) (Blasco, 2012). Although most testing laboratories (and the majority of research studies) use whole blood as the testing material, we were interested in evaluating buccal swabs as potential tissue for testing for a variety of reasons (ease of collection and transport, etc.). Studies have compared telomere lengths in vascular tissue, whole blood and muscle, and shown that all of these different tissues provide similar results (Wilson et. al., 2008), suggesting that the rate of telomere loss and repair might be similar across other tissue types.

### **Materials and Methods**

Briefly, whole blood and buccal swabs were obtained from 38 inhouse volunteers and DNA extraction and amplification was performed via routine methods. Sample DNA was initially extracted from the buffy coat of 10 ml of whole blood or buccal cells obtained from a cheek swab.

Purification of DNA was performed in five steps: 1) Centrifugation to collect the cells, 2) lysis of the cells and precipitation of protein, followed by centrifugation to pellet the protein, 3) precipitation of the DNA with isopropanol followed by centrifugation to pellet the DNA, 4) washing the DNA with 70% ethanol, and 5) addition of rehydration solution to rehydrate the DNA.

High throughput qPCR analysis was then performed to determine the individual sample's telomere length. Telomere length was determined analyzing 10 ng of genomic DNA via high throughput qPCR assay. The assay determines a relative telomere length by measuring the factor by which the sample differs from a reference DNA sample in its ratio of telomere repeat copy number to singe gene copy number (36B4 gene). This ratio (T/S ratio) is thought to be proportional to the average telomere length.

Oligonucleotide primer sets for amplification were as follows:

-36B4 primers (specific for region of 36B4 gene on chromosome 12, which encodes acidic ribosomal phosphoprotein P0.):

-36B4d: 5'-CCC ATT CTA TCA TCA ACG GGT ACA A-3' -36B4u2: 5'-AAT TTG TCA CAG TCA GGC CCA-3'

-Telomere primers:

-tel1b: 5'-CGG TTT GTT TGG GTT TGG GTT TGG GTT TGG GTT TGG GTT-3' -tel2b: 5'-GGC TTG CCT TAC CCT TAC CCT TAC CCT TAC CCT TAC CCT-3'

During the PCR amplification, the genetic area of interest is copied many times, and the accumulation of the genetic material is monitored during the reaction using fluorescent detection of a DNA binding dye (in this case SYBR Green I). A sample is considered positive once it crosses a detection threshold called the Crossing Point (Cp). Within an experimentally determined dynamic range, the Cp is proportional to the amount of input DNA so that plotting Cp versus log (input DNA amount) yields a linear relationship. Using this information, a standard curve can be generated allowing quantitation of unknown samples. Comparing the amount of fluorescent signal generated from a telomere versus that from an amplification of a single-copy genetic sequence (here the acidic ribosomal phosphoprotein P0, 36B4) provided information about the relative amount of telomere sequence per chromosome. A standard curve in duplicate is run with each sample set. In addition, at least one 'no template' (negative) control and two positive controls of two different known telomere lengths (high and low) were included with each run. A set of at least two dilutions of the DNA used for the standard curve were run as positive control. T/S ratio was calculated using a standard curve and served as a surrogate value for relative TL.

### Results

Telomere average length results were obtained from buccal cells and whole blood sampes from 38 in-house volunteers can be seen in Table 2 (Sample Results Comparison). On average, the average telomere sizes of buccal swabs and whole blood derived cells tend to show large within patient differences. Two samples, LaJ-36 and SG-16 reproducibly gave large comparative size differences between buccal swabs and whole blood results, 133% and 103% respectively, and were excluded from further analysis. Excluding the two outliers, the average difference between buccal cell and whole blood derived telomere results obtained from the same patient was 21%, with an average CV of 63%. By comparison, the average difference between whole blood samples obtained from the same patient (as determined by a number of different methods) runs 4-8%. As seen in Figure 1., even after excluding the two outliers, the overall correlation between buccal swabs and whole blood is poor ( $R^2 = 0.11$ ).

#### Discussion

The results obtained show that overall, telomere lengths derived from buccal cells and leukocytes derived from whole blood differ significantly. This suggests that within the same individual, different tissue systems may be subject to different types of wear and tear, resulting in different turnover rates. Although this conclusion may seem obvious, it has important consequences when it comes to getting a patient's telomeres tested. Average telomere length derived from whole blood cells is associated with a wide variety of common clinical conditions (Table 1).

However, if telomere lengths derived from buccal cells do not correlate with whole blood telomere lengths, it's possible that buccal cells will not correlate with these diseases, and as such may lack clinical significance. Supporting this idea, one study comparing leukocytes and buccal cell derived average telomere lengths and ischemic heart failure (IHF), the telomere lengths in IHF patients were found to be significantly shorter than healthy controls in leukocytes (p=0.002), but not buccal cells (p=0.19) (Wong et al., 2011). In a modest study of patients with bone marrow failure due to dyskeratosis congenita, Diamond-Blackfan anemia, Fanconi anemia, or Shwachman-Diamond syndrome), the median qPCR telomere length was longer in buccal cells than in blood (overall T/S ratio= 1.16 vs. 1.05, p=0.001, 0.006, respectively) (Gadalla, 2010).

Although there are reports that telomere lengths derived from buccal cells are foreshortened due to childhood traumas (Drury, 2014) and may also be associated with Alzheimers disease (Thomas, 2008), we suspect that the immune system activation that occurs due to infection or inflammation (and consequently reduces telomere length), may cause the telomere lengths obtained from whole blood to be more relevant than buccal cells, and thus be more clinically relevant as a biomarker for common diseases.

Based on these findings, we continue to offer telomere testing using whole blood and advise against using buccal cells to determine telomere length as a marker for overall morbidity and mortality until additional clinical studies validate the utility of this application.

## Table 1. Telomeres, Telomeropathiesand Common Diseases

Atherosclerosis: Telomere Length is inversely associated with arterial calcification and is highly correlated to arterial age rather than chronological age, supporting the notion of telomere being a

yardstick for biological aging (Mainous & Diaz 2010). Endothelial cells at the atherosclerotic plaque have been shown to have shorter telomeres compared to endothelial cells from subjects without CAD (Ogami et al., 2004), and an association between shortened telomeres in white blood cells and patients with atheroscerosis has also been reported (Goodall et. al., 2001).

**Cancer:** Meta-analysis of 27 different studies evaluating associations between telomere length and cancer in 12,450 patients yielded a pooled OR of 1.96 (95% CI: 1.37-2.81, P = 0.0001) for the association of short TL (telomere length) and cancer. (Savage et. al., 2011. The Association of Telomere Length and Cancer: a Meta-analysis. Cancer Epidemiol Biomarkers Prev June 2011 20; 1238). 47,102 general population participants from the Copenhagen City Heart Study and the Copenhagen General Population Study showed an association with shorter telomeres and reduced survival after cancer was diagnosed (Bojesen, 2013).

**Hypertension and Cardiovascular Disease**: Though hypertension is more prevalent among elderly, a relationship between hypertension and Telomere Length has also been reported in the young; Jeanclos and colleagues (Jeanclos et al., 2000) has shown that Telomere Length is shorter among younger patients with hypertension compared to healthy subjects at the same age. In addition to hypertension, age-associated Cardio Vascular Diseases (CVDs) include atherosclerosis, coronary artery disease, Myocardial infarction (MI), and heart failure. Telomere Length has been established as independent risk predictor for myocardial infarction and stroke (Parks et al., 2011). Studies have reported that shortened Telomeres correspond with a threefold increased risk of myocardial infarction and stroke in some individuals compared to healthy controls (Samani 2003, Aviv et al., 2007). Numerous studies support this finding. Studies (Benetos et al., 2004; Brouilette et al., 2007; Fitzpatrick et al., 2007) have shown that high rates of telomere attrition are associated with elevated CVD risk. Welleit et al. demonstrated higher rate of telomere shortening among people with CVD compared to people without CVD (Willeit et al., 2010).

**CHD and Inflammation:** Samani et al. showed that severe coronary heart disease (CHD) is associated with shorter Telomere Length (Samani et al., 2001). Since then, numerous studies have shown that shortened Telomere Length is linked to severity of CVD, (Hoffmann & Spyridopoulos 2011, et al.);

**Telomeropathies:** Disease manifestations for people with shortened telomeres include premature hair greying, aplastic anemia, immunodeficiency and opportunistic infections, entercolitis, emphysema and idiopathic pulmonary fibrosis, cryptogenic liver fibrosis–cirrhosis, osteoporosis, stem cell failure, and some cancers. (Blackburn, Nature Reviews Genetics 13, 693-704, Oct 2012)).



### Figure 1. Comparing blood and buccal average telomere lengths (units are in kilobases)

### Table 2. Sample Results Comparison

(TL = Telomere Length, L = Length)

sample	blood TL	buccal TL	% difference	L difference	А
MB 01	9.22	8.76	5.12%	0.46	2
JM 02	9.88	6.27	44.66%	3.61	3
KB 03	10.21	7.91	25.39%	2.30	(
LG 04	8.10	9.14	12.09%	-1.04	4
JG 05	9.89	8.10	20.00%	1.80	2
MiB 06	10.48	9.61	8.65%	0.87	2
JC 07	9.48	8.96	5.62%	0.52	2
KrB 08	10.66	8.05	27.86%	2.61	1
RK 09	8.64	6.53	27.80%	2.11	4
TR 10	10.23	9.13	11.36%	1.10	2
oW 11 (K59335)	5.92	8.87	39.89%	-2.95	(
IE 12 (K59616)	7.82	9.26	16.87%	-1.44	4
NR 13 (K59612)	6.84	8.75	24.50%	-1.91	3
HW 14	6.27	7.47	17.40%	-1.20	3
TS 15	9.10	8.39	8.17%	0.71	2
OS 17	8.29	8.42	1.57%	-0.13	L
RP 18	6.54	4.94	27.93%	1.60	1
MC 19	8.91	5.71	43.67%	3.19	1
BeW 20	7.50	9.02	18.48%	-1.53	
DL 21	6.51	7.81	18.26%	-1.31	1
KH 22	8.70	6.17	34.09%	2.54	
SR 23	7.33	7.92	7.78%	-0.59	1
BA 24	6.73	6.01	11.23%	0.72	
JuT 25	8.52	8.88	4.14%	-0.36	
MJ 26	6.69	4.85	32.00%	1.85	
AO 27	7.33	8.72	17.38%	-1.40	
LB-28 (K59959)	6.50	7.69	16.77%	-1.19	
PN-29	6.15	5.61	9.19%	0.54	
RF-30	5.72	3.85	39.13%	1.87	
RuS-31	6.25	8.53	30.89%	-2.28	
KrS-32	7.11	4.90	36.71%	2.21	
MM-33	9.03	8.79	2.68%	0.24	
DA-34	7.68	8.74	12.98%	-1.07	
KC-65	9.30	5.79	46.47%	3.51	
TB-37	8.43	10.98	26.28%	-2.55	
TiP-38	7.05	4.73	39.39%	2.32	
TaW-39	7.62	7.19	5.79%	0.43	
LaJ-36	6.48	32.21	133.04%	-25.73	
SG-16	8.28	26.03	103.49%	-17.75	
SG-16	8.28	26.03	103.49%	-17.75	
		avg	26.02%	-0.70	
		sd	0.26	5.33	
		CV	98.02%		
	Excluding 2 outliers	avg	21.03%	0.44	
		1	0.4.0	1.00	

0.13

63.10%

sd

CV

1.80

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# The Endocannabinoid System's Newly Recognized Role in the Gut-Brain Axis

By Chris D. Meletis, ND and Kimberly Wilkes

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The gut-brain axis has received an increasing amount of attention in the scientific literature, and consequently, functional medicine providers are paying serious attention to the link between the gastrointestinal and neurological systems. Much of this association is driven by the gut microbiota, the population of microbes that reside in the intestinal tract. However, recent research indicates that the endocannabinoid system also plays an important role in the gut-brain axis. This article will discuss some important points that the busy holistic practitioner needs to know including: 1) the involvement of intestinal microbiota dysbiosis in the gut-brain axis, 2) The role of the endocannabinoid system in gut and brain health and the manner in which it interacts with the microbiota, 3) an interesting new role for the use of hemp-derived cannabidiol (CBD) in cognitive health and mental disorders, and 4) botanicals that complement CBD.

#### The Gut-Brain Axis and Dysbiosis

Accumulating evidence indicates that the gut microbiota and central nervous system (CNS) communicate with each other through autonomic, neuroendocrine, and immune pathways.<sup>1</sup> Approximately 500 million nerve endings comprise the enteric nervous system (ENS) found in the gastrointestinal (GI) tract, which also contains the highest levels of immune cells in the body.<sup>2</sup> Approximately 20% of the nerves in the GI tract are intrinsic primary afferent neurons, which signal the brain when subtle alterations within the GI tract occur.<sup>2</sup> This communication is carried out by means of the vagus nerve.

A further connection between the gut and the brain is that immune cells produce cytokines involved in the response to inflammation by the GI tract and brain.<sup>1</sup>Additionally, cortisol and other neuroendocrine-generated hormones affect the integrity of the intestinal lining and interact with immune cells in the synthesis of cytokines.<sup>3</sup> Further supporting the link between the gut and the brain are the findings that *Lactobacillus*, *Bifidobacterium, Escherichia*, and *Enterococcus* synthesize neurotransmitters and neuropeptides such as gamma-aminobutyric acid (GABA), serotonin, and brain-derived neurotrophic factor (BDNF).<sup>4-7</sup>

Gut microbiota dysbiosis leading to gut-brain axis disturbances is implicated in a number of brain disorders while probiotic supplementation has proved beneficial. The microbiota's role in mood and depression has been well-studied. Pinto-Sanchez and colleagues conducted a randomized, double-blind, placebo-controlled trial of 44 adults with irritable bowel syndrome (IBS) and diarrhea or a mixed-stool pattern and mild to moderate anxiety and/or depression.<sup>8</sup> The participants were randomized to receive either 42 sachets of spray dried *Bifidobacterium longum* containing 10<sup>11</sup> colony-forming units (CFU)/1 g of powder or a placebo for 6 weeks. Immediately after the intervention period, 14 of the 22 subjects given the probiotic experienced a 2-point or more decline in scores on the Hospital Anxiety and Depression Scale, whereas only 7 of the 22 individuals in the placebo group had similar declines. *B. longum* did not significantly affect anxiety or IBS symptoms. However, a mean increase in quality of life score was observed in subjects taking the probiotic compared with the placebo. Using functional magnetic resonance imaging, the researchers also determined that *B. longum* mitigated responses to negative emotional stimuli in several brain areas, including the amygdala and fronto-limbic regions. Ten weeks after the study's initiation, depression scores remained lower in patients given the probiotic.

In another study, researchers found that 1 capsule per day containing 2 x 10° CFU/gram each of *Lactobacillus acidophilus*, *L. casei*, and *Bifidobacterium bifidum* in individuals with major depressive disorder improved scores on the Beck Depression Inventory and yielded improvements in insulin metabolism, the Homeostasis Model Assessment of Insulin Resistance, and levels of hs-CRP and glutathione.<sup>9</sup>

Probiotics have also been shown to reduce pre-surgery anxiety and stress.<sup>10</sup> Furthermore, investigations conducted in germ-free animals and in animals exposed to pathogenic microbial infections, antibiotics, or fecal microbiota transplantation indicate that dysfunction of the gut microbiota may be involved in the pathogenesis of Alzheimer's disease (AD).<sup>11</sup> Microbiota dysbiosis leads to impaired gut barrier function resulting in translocation of bacteria and bacterial products into the systemic circulation and ultimately penetration of the blood-brain barrier.<sup>11</sup> Furthermore, some gram-negative bacteria in gut microbiota dysbiosis can generate copious quantities of amyloids and lipopolysaccharides, resulting in the generation of proinflammatory cytokines linked to the etiology of AD.<sup>11</sup>

A recent human trial by Akbari and associates found that AD patients who consumed 200 mL/day probiotic milk containing  $2 \times 10^9$  CFU/g each of *Lactobacillus acidophilus, L. casei, B. bifidum*, and *L. fermentum* for 12 weeks had improved cognitive function and inflammatory markers such as high-sensitivity C-reactive protein.<sup>12</sup> In addition, the probiotics resulted in improved measurements on the Homeostasis Model of Assessment-Insulin Resistance, B-Cell Function, serum triglycerides, and the Quantitative Insulin Sensitivity Check Index.

Gut microbiota dysbiosis has also been shown to be involved in psychological stress,<sup>13</sup> autism,<sup>14</sup> epilepsy,<sup>15</sup> schizophrenia,<sup>16,17</sup> and attention-deficit hyperactivity disorder.<sup>18</sup>

#### The Endocannabinoid System and the Gut-Brain Axis

While the role that the microbiota plays in the gut-brain axis is frequently discussed in the scientific literature and addressed in clinical practice, the involvement of the endocannabinoid system in both gut and brain health has only recently been addressed. The endocannabinoid system is comprised of endogenously produced cannabinoids (endocannabinoids) as well as cannabinoid receptors 1 and 2 (CB<sub>1</sub> and CB<sub>2</sub>) located in the brains of mammals and throughout the central and peripheral nervous systems. Enzymes involved in the production and breakdown of endocannabinoids and molecules necessary for endocannabinoid uptake and transport are also key players in the endocannabinoid system.

Evidence is accumulating that the endocannabinoid system plays an integral role in GI function and brain health.<sup>19</sup> The first indication of this connection came from the discovery that the endocannabinoid anandamide is found in both the brain and the gut.<sup>20</sup> This system is now thought to be involved in gut motility, gut-brain communications, and intestinal permeability and inflammation.<sup>19</sup> Administration of *L. acidophilus* to rats ameliorates abdominal pain via induction of  $CB_1$ .<sup>21</sup> Satiety, diarrhea, emesis, and inflammation are all associated with endocannabinoid concentrations in the brain and gut.<sup>21</sup> Satiety and gut peptides such as cholecystokinin and ghrelin govern the expression of  $CB_1$  and  $CB_2$  on vagal afferents.<sup>20</sup> Endocannabinoids in the brainstem acting on  $CB_1$  and  $CB_2$  and other receptors regulate vagal nerve control of gut motor function and emesis.<sup>20</sup> The endocannabinoid system also may be involved in the impact of stress on GI function.<sup>20</sup>

The endocannabinoid system's role in protecting gut barrier function has implications for brain health. Impaired intestinal permeability has been linked to depression<sup>22</sup> and autism.<sup>23</sup> Furthermore, interactions occur between endocannabinoids and the gut microbiota,19 which result in changes that can affect mental health.<sup>24</sup> Guida and colleagues established in an animal model that dysbiosis of the gut microbiota can result in alterations in the endocannabinoid system.<sup>24</sup> Mice were administered a mixture of antimicrobials for 2 weeks. The antimicrobials disrupted the gut microbiota, led to inflammation, and changed some endocannabinoidome components in the gut. These changes were accompanied by alterations in behavior, including increased immobility in the tail suspension test (an indicator of depression) and a decline in social recognition. The behavioral impairments were related to alterations in signaling of brain-derived neurotrophic factor (BDNF) and its receptor tropomyosin receptor kinase B (TrkB) as well as changes in hippocampal neuronal firing. Additionally, nonneuronal cells involved in emotional behavior underwent morphological rearrangements in the animals with antimicrobial-induced dysbiosis of the microbiota. Oral gavage administration of Lactobacillus casei DG or a placebo for up to 7 days resolved most of the damage to the gut as well as the pathological behavioral, biochemical, and functional changes. Furthermore, other researchers have observed that L. acidophilus increased the expression of opioid and cannabinoid receptors in human intestinal epithelial cells, and 109 CFU/day of L. acidophilus demonstrated analgesic activity similar to morphine in the rat gut.25

The interaction between the gut microbiota and the endocannabinoid system may explain results of studies where reduced function of the endocannabinoid system occurs in mental conditions such as post-traumatic stress disorder (PTSD),<sup>26</sup> melancholic depression,<sup>27</sup> and autistic spectrum disorder.<sup>28</sup>

Endocannabinoids effects on the gut-brain axis may involve mitochondria. CB<sub>1</sub> receptors have been found to regulate mitochondrial transport in enteric nerves.<sup>29</sup> Other rodent models and in vitro studies have indicated endocannabinoids may have beneficial effects on mitochondrial function and biogenesis.<sup>30,31</sup>

#### The Role of Cannabidiol

The phytocannabinoid cannabidiol (CBD) is a nonpsychoactive component of the cannabis plant. In vitro, it has demonstrated neuroprotective, antioxidant, and anti-inflammatory properties and reduced amyloid- $\beta$  production and tau hyperphosphorylation.<sup>32</sup> There has been an astronomical amount of growth in CBD research, especially on its effects in psychiatric conditions and mental health.

In humans with Alzheimer's disease, research on the use of cannabinoids in humans primarily revolves around their utility for reducing behavioral and motor symptoms. These studies have used a synthetic cannabinoid.<sup>33,34</sup> In a mouse model of Alzheimer's disease, CBD administration blocked the decline in neurogenesis and reduced amyloid- $\beta$  related inflammation.<sup>35</sup> Data from animal models also indicate that CBD can suppress stress-related synaptic remodeling.<sup>36</sup>

Cannabidiol's mechanism of action does not involve the activation of cannabinoid receptors, but rather it moderately suppresses the breakdown of the endocannabinoid anandamide.<sup>37</sup> There is an inverse relationship between increases in anandamide concentrations in cerebrospinal fluid and psychotic symptoms in schizophrenia patients.<sup>37</sup> In this group of subjects, CBD increased anandamide and produced clinical improvement.<sup>37</sup>

Some of the most promising clinical studies of CBD involve its effects on anxiety. Crippa and coworkers investigated the effects of a single 600 mg dose of CBD or placebo on 24 patients with untreated social anxiety disorder (SAD) taken before participating in a simulated public speaking test (SPST) and compared the results to those of 12 healthy controls who participated in the same SPST.<sup>38</sup> In this randomized, double-blind study, pretreatment with CBD markedly lowered anxiety, cognitive impairment, and discomfort during the speech. The placebo group was more anxious and experienced greater cognitive impairment and discomfort compared to the control group. Similar results were achieved in a double-blind study of healthy volunteers undergoing a simulated public speaking test.<sup>39</sup> In this trial, CBD mitigated the anxiety felt immediately after a SPST. Studies using brain imaging techniques in healthy people and in individuals with social anxiety disorder confirm CBD's calming effects.<sup>40,41</sup>

Another application for CBD is to improve sleep. Insomnia is both a cause and a consequence of many mental disorders including depression, anxiety, and PTSD. A review of the literature conducted by Babson and associates found that the psychoactive component of cannabis, Delta-9 tetrahydrocannabinol (THC), may decrease the time it takes to fall asleep but may decrease sleep quality.<sup>42</sup> Conversely, CBD was found to reduce REM sleep behavior disorder and excessive daytime sleepiness.<sup>42</sup>

CBD also has demonstrated anticonvulsant activity in 2 case studies of individuals with epilepsy and in surveys of caregivers and patients.<sup>43</sup>

#### **Complementary Botanicals**

In clinical practice, it is often useful to combine CBD with other botanicals and probiotics to support gut health and cognitive and mental function. A special extract of *Bacopa monnieri* (CDRI 08) is well-supported in the scientific literature for its role in enhancing cognitive function, reducing stress, and inhibiting hyperactivity.<sup>44-47</sup> For example, a meta-analysis of 9 studies involving 518 participants, concluded that Bacopa improves cognitive function, especially speed of attention.<sup>45</sup>

Another botanical that works well with CBD in clinical practice is L-theanine, an amino acid derived from green tea. An open-label study of 20 individuals with major depressive disorder observed that 250 mg/day of L-theanine reduced depressive symptoms and anxiety and improved sleep quality and cognitive function.<sup>48</sup> L-theanine reduces the response to stress, lowers cortisol levels,<sup>49</sup> and improves symptoms in schizophrenia patients on antipsychotic medication.<sup>50</sup>

Probiotic support is generally best accomplished using a multispecies formula supplying good numbers of *Lactobacillus* and *Bifidobacterium* species. The formula should include *L. acidophilus*, *L. casei*, *B. bifidum*, and *B. longum*.

#### Conclusion

Disturbances in the gut-brain axis are implicated in a variety of psychological disorders as well as impaired stress responses and poor cognitive function. Dysbiosis of the gut microbiota as a cause of these gut-brain disturbances is well-recognized. However, accumulating evidence indicates the endocannabinoid system also plays an important role in the connection between the gut and the brain. CBD oil, complementary botanicals such as Bacopa and L-theanine, and probiotics can be used to resolve gut-brain axis disturbances and restore optimal brain health.

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Endoceutics is a private pharmaceutical company specializing in women's health and hormonesensitive cancer prevention and treatment, and committed advancing basic sciences, clinical R&D, and product commercialization worldwide. Intrarosa (prasterone) was approved in 2016 for the treatment of dyspareunia, a symptom of vulvovaginal atrophy due to menopause. Endoceutics is focusing on developing non estrogen-based therapies for sexual dysfunction and the other symptoms of menopause, including hot flashes, osteoporosis, muscle loss, and type 2 diabetes.





















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Gnosis is a biotechnology company specializing in the manufacture of active and functional ingredients for the nutraceutical, cosmetic, personal care, biotech and pharmaceutical industries. With our proprietary technologies and sophisticated know-how, we have developed a comprehensive nutritional product line including reduced folates, SAMe, SAG, K2 as MK7, chondroitin, etc. Our products focus on bone, cardiovascular, gastrointestinal, liver, neurological, and cellular health, offering an extensive range of differentiated solutions for head-to-toe health

#### Great Plains Laboratory • Booth #8039

11813 West 77th St., Lenexa, KS 66214 US Ph: 913-341-8949 • Fax: 913-815-4043 Email: sales@gpl4u.com • Website: www.greatplainslaboratory.com

The Great Plains Laboratory, Inc. is a global leader in metabolic, environmental, and genetic testing for people with chronic diseases. We provide clients with access to the most reliable, comprehensive, and understandable scientific results using the latest technology and proven techniques to maintain optimal health for patients of all ages.



The Great Plains Laboratory, Inc.

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72320 Manufacturing Rd., Thousand Palms, CA 92276 US Ph: 855-292-7935 • Fax: Email: help@groundtherapycenter.com • Website: www.groundtherapycenter.com

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High Tech Health International pioneered detoxification of heavy metals and chemicals via infrared sauna therapy 20 years ago. More than 4000 health practitioners in 57 countries now use our Transcend and Thermal Life saunas. High Tech Health was just awarded patent 9,770,386 for the lowest total EMF infrared sauna heater.



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#### Immunosciences Lab., Inc. • Booth #1035

822 S. Robertson Blvd., #312, Los Angeles, CA 90035 US Ph: 310-657-1077 • Fax: 310-657-1053 Email: Immunsci@gmail.com • Website: Immunoscienceslab.com

Immunosciences Lab., Inc. (ISL) is a state-of-the-art clinical reference and research laboratory, a leader and innovator in the field of molecular medicine. Licensed in California and CAP-approved, ISL specializes in utilizing the most highly sensitive and accurate testing methods for detecting lyme disease, autoimmunity, and viral infection. The information provided by these tests can help clinicians not only to pinpoint the cause of the illness but to treat and perhaps even reverse the course of the disease' development.

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Integrative Therapeutics (integrativepro.com) is a leading manufacturer and distributor of sciencebased nutritional supplements and elemental diet products committed exclusively to healthcare professionals. Integrative develops unique formulations that can be safely and effectively integrated with diet and lifestyle recommendations for improved patient health.

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2215 Auto Park Way, Escondido, CA 92029 US Ph: 855-979-6751 • Fax: 855-979-6751 Email: info@isodiol.com • Website: www.isodiol.com

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5883 Rue Ferrari, #175, San Jose, CA 95138 US **Ph:** 800-347-2223 • **Fax:** 408-362-0140 **Email:** info@janmarini.com • **Website:** www.janmarini.com

San Jose, CA-based Jan Marini Skin Research, Inc. (JMSR) is a recognized leader and innovator of professional skin care solutions. In addition to multiple patented formulations, JMSR?s track-record of technological firsts includes, but is not limited to, topical TGF beta-1, antioxidant sunscreen, topical resveratrol and cosmetic lash enhancement. JMSR products and its Skin Care Management System are used and trusted by professionals worldwide.



#### Jigsaw Health, LLC • Booth #3044

9035 E. Pima Center Pwy., Ste. 3, Scottsdale, AZ 85258 US Ph: 480-951-0840 • Fax: 480-785-4634 Email: help@jigsawhealth.com • Website: www.JigsawHealth.com

Jigsaw Health (Aka. The Magnesium People), are the makers of America's #1 Time Release Magnesium Supplement: MagSRT®. We'll be handing out generous 60 count samples bottles at booth #3044. While you're visiting our booth, we'll keep you hydrated with our delicious Jigsaw Electrolyte Supreme Berry-Licious and Lemon Lime.

#### Kashi Clinical Laboratories • Booth #6044

10101 SW Barbur Blvd., Portland, OR 97219 US Ph: 503-206-4989 • Fax: 503-206-6939 Email: info@kashilab.com • Website: www.kashilab.com

Kashi Labs is an expert in health-focused genetic testing with a reputation for improving the health of countless patients. Established in 2006, our innovative and scientifically rigorous genetic panels are designed to promote health and wellness by delivering actionable results for targeted treatments. Based in Portland, OR, our CLIA, CAP and ASHI accredited laboratory serves clients worldwide with non-invasive genetic testing for medication response, behavioral health, cardiac health, pain management, nutritional health and weight management.

#### KBMO Diagnostics • Booth #4045

4 Business Way, Hopedale, MA 01747 US Ph: 617-933-8130 • Fax: 267-219-6005 Email: jwhite@kbmodiagnostics.com • Website: kbmodiagnostics.com

KBMO Diagnostics is a fully integrated medical diagnostics company. The company offers Food Sensitivity Testing that measures sensitivities to up to 132 different foods using the Food Inflammation Test (FIT) Test. The company continues to add new assays to their menu, including IgA, Zonulin and the PGX Predict drug metabolism test. KBMO Diagnostics produces easy-to-read and fully individualized color reports for each test. Patients can access reports and meal plans on a mobile phone app.

#### Klaire Labs • Booth #5032

795 Trademark Dr., Reno, NV 89521 US Ph: 888-488-2488 • Fax: 775-850-8810 Email: customerserviceUSA@sfihealth.com • Website: www.klaire.com

Klaire Labs brand high-quality nutraceuticals are available exclusively through healthcare professionals to empower them in providing better choices and optimal health outcomes for those under their care. - Scientifically researched, clinically relevant formulas/ - Broad hypoallergenic probiotic selection/ - Specialized antibiofilm, digestive, and systemic enzymes/- Multinutrients, antioxidants and hormone support, and advanced skin care products/ - Ingredients based on purity, bioavailability, documented actions, and safety characteristics/ - 48 years of clinical experience garnering brand trust and brand loyalists.

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Miguel Angel 11 2nd floor, Madrid, ES29 28010 ES Ph: 1 561 886 6685 • Fax: 913 10 17 53 Email: info@lifelength.com • Website: www.lifelength.com

Life Length is the world leader in providing telomere diagnostics and telomerase activity measurements for use in clinical and diagnostic medicine. Life Length has developed unique and proprietary technologies. Our robust, sensitive and reproducible tests can be combined with other analyses to provide a comprehensive picture of a patient's health. Life Length's TAT®, is the only test that measures critically short telomeres, for people wanting to optimize their health for the longest, healthiest possible lives.







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LifeVantage Corporation (Nasdaq: LFVN) is a pioneer in Nutrigenomics - a new science dedicated to cracking the human aging code. We engage in the identification, research, development and distribution of advanced nutraceutical dietary supplements and skin care products that activate the messenger proteins NRF1 and Nrf2, including Protandim®, our line of scientifically-validated dietary supplements, and TrueScience®, our line of anti-aging skin care products. Protandim® is the world's only nutraceutical proven to extend life in a mammal as clinically proven by the National Institute on Aging a division of the National Institutes of Health.

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#### Living Younger Lifestyle Medicine • Booth #4047

8323 N Shannon Rd., #9208, Tucson, AZ 85742 US Ph: 520-229-1900 • Fax: 844-270-8061

Email: gwpetersburg@LivingYoungerPreventive-Aging.com • Website: ww.Living-Younger.com

Physicians are gathering knowledge but don't have the 'tools' to apply it to the patient or know what's needed to start a cash practice. Living Younger Lifestyle Medicine© has only all-inclusive specialty-specific practice 'tools'. An emphasis on wellness medicine for new and seasoned practitioners, low overhead, no franchise fees! Provides everything: online tutorials, consulta-tion forms, automated comprehensive human performance, biologic age assessments, clinical guidelines, protocols, patient charting, patient education, business/marketing

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2534 Anthem Village Dr., Ste. 100, HENDERSON, NV 890525539 US Ph: 866-682-6193 • Fax: 866-682-6193 Email: rachael@livonLabs.com • Website: www.livonlabs.com

LivOn Laboratories has been the industry leader formulating high performance dietary supplements that offer genuine health benefits for over 12 years. LivOn Labs Lypo-Spheric<sup>™</sup> Vitamin C was the world's first unidose Liposomal vitamin C gel. Other LivOn Labs' products are Lypo-Spheric<sup>™</sup> B Complex+, Lypo-Spheric<sup>™</sup> Glutathione, Lypo-Spheric<sup>™</sup> R-ALA (R-Alpha Lipoic Acid), and Lypo-Spheric<sup>™</sup> ALC (Acetyl-L-Carnitine). LivOn Labs' invites all attendees to visit our booth, sample our products and get a free copy of the latest book from Dr. Thomas E Levy MD, JD. "Hidden Epidemic".

#### ANTI-AGING MEDICAL NEWS • Winter 2017

#### L-Nutra • Booth #6032

8322 Beverly Blvd., Los Angeles, CA 90048 US Ph: 323-580-6855 • Fax: Email: admin@l-nutra.com • Website: www.l-nutra.com and www.prolonfmd.com

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#### Lumineu, LLC • Booth #1103

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#### Maharishi Ayurveda Products • Booth #1040

1680 Hwy 1 North, Ste. 2200, FAIRFIELD, IA 52556 US Ph: 877-767-7555 • Fax: 877-767-7555 Email: hp@mapi.com • Website: www.mapi.com

Maharishi Ayurveda is the first and oldest ayurveda products company in the United States. Our ayurvedic formulations are based on written records dating back thousands of years. Our formulations are not new; they are ancient, time-tested and effective.

#### Master Supplements, Inc. • Booth #6057

1600 Arboretum Blvd., Ste. 202, Victoria , MN 55386 US Ph: 800-926-2961 • Fax: 570-300-2333

Email: info@mastersupplementsinc.com • Website: www.master-supplements.com

Master Supplements, Inc. is committed to raising the standard on probiotics, digestive enzymes and prebiotic fiber. We utilize patented acid-proof delivery, a unique, multi-faceted prebiotic and third party testing on every lot. Theralac®, TruBifido®, TruFlora®, Enzalase®, TruFiber® and the professional-only: TheralacPRO® & TruBifidoPRO® provide powerful digestive and immune support you can feel. Stop by our booth #6057 for more information or visit our website at www.master-supplements.com.

#### MasterPharm Compounding Pharmacy • Booth #2042

115-06 Liberty Ave., Richmond Hill, NY 11419 US Ph: 866-630-5600 • Fax: 866-630-5700

**Email:** tmasta@masterpharm.com • **Website:** www.masterpharm.com

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#### McGuff Compounding Pharmacy Services, Inc • Booth #3047

2921 West MacArthur Blvd., Ste. 142, Santa Ana, CA 92704 US Ph: 877-444-1133 • Fax: 877-444-1155 Email: pharmacyanswers@mcguff.com • Website: www.mcguffpharmacy.com

McGuff Compounding Pharmacy Services provides a level of commitment and value that is unsurpassed. We are independently certified as ISO 9001:2008 compliant and accredited by the Pharmacy Compounding Accreditation Board (PCAB). We compound all dosage forms including sterile injections and deliver to all US states, territories and protectorates. Product quality and patient safety are our number one concern. Stop by the booth to find out more!















#### McGuff Medical Products, Inc • Booth #7099

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#### MedEsthetics Magazine • Booth #8064

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MedEsthetics Magazine serves medical professionals and private practices that offer noninvasive, minimally invasive and surgical cosmetic procedures by providing coverage on practice management, practice building, industry news, and the latest equipment and treatment trends.



MedEsthetics.

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Mediplay provides a totally customizable, education and marketing digital signage solution displayed on the TV in waiting rooms or exam rooms. Videos are selected from our on-line library of over 600 multi-specialty topics. Your own videos can be displayed, too, along with custom pieces, news feeds and Social media posts. There is also an instant message bar at the bottom of the screen. It's quick to install and everything is easily managed through an online portal.

#### MediZap LLC • Booth #3073

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MediZap in partnership with Steri-Tek provide Turn-key E-Beam Sterilization Services & Packaging Solutions to the compounded pharmaceutical and medical device industries. Services include process validations, ongoing E-Beam Sterilization and Regulatory and Compliance support for its customers in this ever-changing industry. MediZap packaging solutions for compounding pharmacies provide advanced technologies and comprehensive pre-validated validated offerings. Visit us to advance your sterility assurance and elevate your product offerings through our technology and world-class services.

## MediZap

#### ANTI-AGING MEDICAL NEWS • Winter 2017



#### MedTek LED • Booth #7097

3 Depot St., Hudson Falls, NY 12839 US Ph: 800-950-2893 • Fax: 518-747-2294 Email: info@mypolyled.com • Website: www.mypolyled.com

MedTek LED is a subsidiary of UVBioTek - a 25 year provider of light-based aesthetic and medical systems. MedTek LED is proud to showcase its newest system at A4M in Las Vegas: POLY. POLY is a polychromatic light therapy system that utilizes both red and blue wavelengths to deliver a variety of treatment options through a one-of-a-kind 5-panel flexible head.

#### Meridian Valley Lab • Booth #5045

6839 Fort Dent Way, Ste. 206, Tulwila, WA 98188 US Ph: 855-405-8378 • Fax: 206-209-4200 Email: info@meridianvalleylab.com • Website: www.MeridianValleyLab.com

Meridian Valley Lab is a world leader in urine hormone and food sensitivity testing. Founded in 1976 by Dr. Jonathan Wright, Meridian Valley Lab has always been at the forefront of laboratory testing in large part due to Dr. Wright's pioneering spirit and his fearless dedication to serving humanity. Every test ordered comes with a free consultation with Meridian Valley Lab's very own consulting physicians.

#### MERIT PHARMACEUTICAL • Booth #4037

2611 N. San Fernando Rd., Los Angeles, CA 90065 US Ph: 800-69-MERIT • Fax: 323-227-4831 Email: solutions@meritpharm.com • Website: www.meritpharm.com

For almost 40 years, Merit Pharmaceutical has been the key supplier to Anti-Aging and similar Integrative healthcare professionals offering pharmaceuticals (2, 3, 3N, 4), medical/ surgical devices. Our popular Merit brand line of products is the equivalent quality you need at cost effective pricing to further ensure your profitability and growth. Please visit our booth, see what your colleagues already know: Merit has excellent pricing on items your practice needs to improve margins and increase profitability.

#### Metabolic Code • Booth #4013

4850 T Rex Ave., Ste. 125, Boca Raton, FL 33431 US Ph: 561-237-1885 • Fax: 877-234-2879 Email: sales@metaboliccode.com • Website: www.metaboliccode.com

The Metabolic Code is a proprietary approach to clinical assessment and treatment planning implemented as a component of all treatment programming where appropriate within medical and non-medical services. Metabolic Code delivers evidence-based tools, delivered via the web, that support practitioners? abilities to assess, interpret, and recommend proven integrative protocols to their patients while dramatically increasing their patients? adherence and engagement levels resulting in patient centered care and higher levels of wellness.

#### Metabolic Solutions, Inc • Booth #8072

41865 Boardwalk, Ste. 120, Palm Desrt, CA 92211 US Ph: 760-836-3232 • Fax: 760-836-3234 Email: questions@plattwellness.com • Website: www.plattwellness.com

Our company helps people obtain wellness by dealing with the underlying cause of their issues. Our main focus is helping to lower excess adrenaline levels naturally. Insomnia, ADHD, fibromyalgia, anger, anxiety, IBS, weight gain, PMDD, neuropathy, and even bed-wetting in chlldren are associated with excess adrenaline. We have a 5% progesterone cream to block adrenaline formulated by Michael Platt, md, the author of "Adrenaline Dominance" and 'The Miracle of Bio-identical Hormones". He will be at the booth.

#### Metagenics • Booth #6007

25 Enterprise, Ste. 200, Aliso Viejo, CA 92656 US Ph: 800-692-9400 • Fax:

Email: Info.customerservice@metagenics.com • Website: www.metagenics.com

Metagenics was founded on a revolutionary idea: Our genes do not predetermine our health potential, and through nutrition, we can impact how our genes express themselves. Embodied by our company motto?genetic potential through nutrition?this groundbreaking principle drives us to deliver high-quality, science-based nutritional supplements, medical foods, and lifestyle programs to support healthcare practitioners in their efforts to help patients achieve their health and wellness goals.











# THE NEW FACE OF LIGHT THERAPY

ANTI-AGING MEDICAL NEWS • Winter 2017

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**IT JUST GOT A WHOLE LOT EASIER WITH...** The Most Comprehensive Online Certification Course The Most Dynamic Online Interpretation Software



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#### MethylGenetic Nutrition Analysis™

This easy-to-use, inexpensive software allows you to Assess, Analyze & Design Support<sup>™</sup> based on a person's unique genetics, lab work and presenting symptoms.

- Integrates symptom survey and lab data
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www.dnasupplementation.com

Take the guesswork out of genetic nutritional support. Visit **www.dnasupplementation.com** to receive the first three modules of the online certification course free, and a free trail of the MethylGenetic Nutrition Analysis<sup>™</sup> software. Or for more in-depth information, call us at **717-466-5700.** 

#### MethylGenetic Nutrition AnalysisTM • Booth #5047

15 Pleasure Rd., Ephrata, PA 17522 US Ph: 717-466-5700 • Fax: 717-466-5700 Email: support@dnasupplementation.com • Website: www.dnasupplementation.com

People are turning to genetic testing to help find answers to their health and need an experienced practitioner to help them. MethylGenetic Nutrition AnalysisTM online software is the tool you need to easily guide you through this seemingly complex process. MGNATM creates nutritional protocols, based upon one's unique DNA, lab work, and presenting symptoms, giving you the ability to Assess, Analyze and Design SupportTM. This will take your practice into the future of care.



101 E. Town Pl., Ste. 210, St. Augustine, FL 32092 US Ph: 855-729-5090 • Fax: 909-940-2209 Email: info@gomegaspore.com • Website: www.microbiomelabs.com

Microbiome Labs was originally established as Physicians Exclusive in 2013 as an organization focused on providing probiotic bacteriotherapy. In the past several years our business model has grown and so has public awareness for gut health issues. Microbiome Labs comes to you as an all inclusive resource center designed to address the needs of physicians and health care practitioners.



6352 Corte del Abeto, Ste. A, Carlsbad, CA 92011 US Ph: 949-215-8560 • Fax: 949-215-8564 Email: info@mmt-us.com • Website: www.mmt-us.com

Millennium Medical Technologies is an FDA registered manufacturer committed to providing comprehensive solutions and support for harvesting, isolation, and deployment of 361 compliant tissue and cells. We manufacture and distribute devices in liposuction and body shaping, adipose tissue collection, fat grafting, autologous cell isolation and processing as well as provide device development and clinical support services.

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4050 S. Sarival Ave., Goodyear, AZ 85338 US Ph: 623-932-1522 • Fax: 623-932-3533 Email: rhunsaker@mineralbiosciences.com • Website: www.mineralbiosciences.com

For over 20 years, Mineral BioSciences® has worked behind the scenes as a key ingredient supplier to human health, athletic, and personal care companies worldwide. In that time, we have become the world's foremost supplier of a unique fulvic ionic mineral complex, loniplex. We are now pleased to offer this patented ingredient in our signature line of products, Totála® Cellular Health and IoniCell® to bring cellular health and vitality to the next level.

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MitoQ Limited is a New Zealand based company dedicated to introducing MitoQ, the world's first mitochondria-targeted antioxidant skincare and supplement range, to people around the world. We are a small passionate team committed to educating, informing and inspiring you to invest in your health and wellbeing now, so you can get the most out of life.

#### Mushroom Science • Booth #8027

1025 Conger St., Ste. 6, Eugene, OR 97402 US Ph: 541-344-1396 • Fax: Email: shannon@mushroomscience.com • We

Website:

Mushroom Science has been providing high potency mushroom extracts through its practi-tioner brand JHS Natural Products for the past 2 decades. Mushroom extracts have historically been prepared as a tea/ decoction, also known as a hot water extract. The scientific literature has numerous human clinical trials on the dehydrated tea form, indicating the percent of actives. Mushroom Science ingredients are certified organic, tested for purity, and guarantee levels of active compounds on every bottle.















#### My Practice Connect • Booth #1032

2744 Summerdale Dr., Clearwater, FL 33761 US Ph: 727-754-3696 • Fax: 727-230-1437 Email: info@MyPracticeConnect.com • Website: www.MyPracticeConnect.com

My Practice Connect bridges the gap between compounding pharmacies and practices that currently offer, or want to start offering, wellness solutions without having to change EMR systems. Our convenient platform offers nutrient IV protocols and formularies, vitamin and peptide injections, patient and practice resources, and more. My Practice Connect was designed by an integrative physician, so we understand the needs of today's medical practices. We also offer hands-on physician training and sales consulting to help practices thrive.

#### National Academy of Hypothyroidism and Integrative Sciences • Booth #1050

2232 E. Maple Ave., El Segundo, CA 90245 US Ph: 310-375-2705 • Fax: 310-375-2701 Email: jenyk@holtorfmed.com • Website: NAHypothyroidism.org

The National Academy of Hypothyroidism and Integrative Sciences (NAHIS) is a non-profit, multidisciplinary translational medical society dedicated to the dissemination of new information and training on the diagnosis and treatment of endocrine dysfunction and chronic multisystem disease, including chronic fatigue syndrome (CFS), fibromyalgia, Lyme disease and other vector-borne illnesses, autism, PANS and other autoimmune disorders. NAHIS also facilitates the implementation of effective innovative treatments via collaborative processes.



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#### Natural Health Partners, LLC • Booth #2036

125 SW 3rd Pl., Ste. 205, Cape Coral, FL 33991 US Ph: 239-673-2110 • Fax: 813-433-2526 Email: miguelg@mercola.com • Website: www.mercola.com

Natural Health Partners, providing quality nutritional supplements to licensed physicians worldwide.



#### Natural Partners • Booth #3045

8445 E Hartford Dr., Scottsdale, AZ 85255 US Ph: 888-633-7620 • Fax: 800-862-1261 Email: lpossehl@naturalpartners.com • Website: www.naturalpartners.com

Natural Partners is a resource for practitioners who strive to improve patient wellness by providing education, services and professional-grade products. For over 22 years Natural Partners has researched trusted brands and welcomed them into their portfolio, currently offering over 14,000 premium products from hundreds of high-quality manufacturers. NP Script(TM), a virtual supplement store, allows practitioners to offer trusted wellness products to their patients without maintaining a physical inventory. For more information visit naturalpartners.com.

#### Natural Source International • Booth #8090

315 Madison Ave., #16th Floor, New York, NY 10017 US Ph: 212-308-7066 • Fax: 212-593-3925 Email: info@natural-source.com • Website: www.natural-source.com

Drawing on 40 years of pioneering environmental medicine research conducted by Dr. Mirko Beljanski, Natural Source International has developed a unique expertise, bringing together science and nature, to deliver tested formulas that promote health and well-being. Beljanski's discoveries, and ongoing research at the Beljanski Foundation, remain the driving forces behind the Beljanski® Products and the Beljanski® Professional products. Please stop by our booth in order to discover the full power of the Beljanski® Products.

#### Naturally Plus USA (NPUSA) • Booth #7074

1140 North Town Center Dr., Ste. 100, Las Vegas, NV 89144 US Ph: 800-378-0321 • Fax: 702-515-4100 Email: info@npusainc.com • Website: www.npusainc.com

NPUSA brings a unique opportunity to members in the U.S.---blending the excitement of a new opportunity with the stability of a company that creates more than a quarter of a billion US dollars in annual sales. So many of our members have found success with our products by experiencing benefits to their finances and health. We have nearly 20 years of pioneering quality products. IZUMIO is a high-quality, natural water infused with hydrogen. IZUMIO contains water from the serene countryside of Japan, which is the source of hydrogen that provides antioxidative benefits. Super Lutein is a broad spectrum multi carotenoid nutritional supplement specially designed for eye and overall health.

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#### Nature Hill NV • Booth #9022

8550 W Desert Inn Rd. 102 163, Las Vegas, NV 89117 US Ph: 312-361-7775 • Fax: 312-361-7775 Email: nadav@naturehillnv.com • Website:

Our company's mission is to deliver Natural and pampering experiences with each of our L.E.D medical device and skin care products, to transform the way you look at your skin and skin care regimen.

#### Nature's Cures • Booth #3071

1400 Kearns Blvd., Park City, UT 84060 US Ph: 435-655-6000 • Fax: 435-655-2439 Email: MBailin@nutracorp.com • Website: www.nutraceutical.com

The Nutraceutical Nature's Cures Collection brings together many of the best anti-aging ingredients from Mother Nature – with numerous formulations available to sample at our booth. The Collection includes several practitioner exclusive lines, such as Nutra BioGenesis & AllVia. We offer a verified gluten-free brand, while for babies & toddlers, we've developed gentle, children's remedies and liquid herbals. Check out our unique zinc lozenges, colloidal silver solutions and herbal syrups to get through the cold & flu season, naturally.

#### Natures Wonder LLC • Booth #9046

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Nature-Throid and WP Thyroid are natural hypothyroid medications containing both T4 and T3 hormones. Two natural thyroid solutions. Because no two people are alike. RLC Labs also manufactures a-Drenal and i-Throid, (iodine 12.5mg & 6.25mg), which can be used alone or with either Nature-Throid or WP Thyroid for a well-rounded thyroid protocol.

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4930 ch Bois Franc, St. Laurent, QC H4S 1A7 CA Ph: 800-263-8888 • Fax: 514-333-4008 Email: info@derme.ca • Website: www.nellydevuyst.com

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#### Neogenis Medical is now HumanN • Booth #3043

1120 S Capital of Texas Hwy., Bldg. 1, Ste. 210, Austin, TX 78746 US Ph: 512-487-7032 • Fax: 512-271-6800 Email: susan@humann.com • Website: www.HumanN.com

Neogenis Medical is the world leader in nitric oxide science with over 17 years of research, we

have 10 U.S. and international patents and 7 published clinical trials. • Neo40® Professional is clinically shown to increase N-O levels, which is essential for proper endothelial function and cardiovascular health.• Neo40®, created at the University of Texas through 17 years of research, is the only technology that has been patented and proven to generate authentic N-O gas.





Neogenis Medical has changed its name to HumanN





Nature's Wonder







## ogy.





#### Neurohacker Collective LLC • Booth #2079

179 Calle Magdalena, Ste. 100, Encinitas, CA 92024 US Ph: 855-281-2328 • Fax: 855-281-2328 Email: support@neurohacker.com • Website: www.neurohacker.com

Neurohacker Collective exists because we believe that it is now both possible and necessary for human beings to dramatically upgrade our individual and collective capacities to design and create the future. We are creating and curating the best resources available for neurological optimization to empower people to realize their fullest potential.

#### New Voice - SmartDOTs • Booth #6039

13 Blackswan, Irvine, CA 92604 US US Ph: 949-551-3397 • Fax: 949-552-9041 Email: marcus@newvoice.net • Website: www.smartDOTs.us

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#### Novus Optimum • Booth #6042

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#### Nube Health Inc • Booth #1056

1286 University Ave., #734, San Diego, CA 92103 US Ph: 619-373-8306 • Fax: 619-330-4647 Email: info@mynubehealth.com • Website: www.nubehealth.com

Nube Health Inc is a worldwide resource and educational connection in healthcare. We support the access to medical facilities, specialists, nutritional guidance and specialty products. We specialize in corrective health, medical research and holistic medicine and non-traditional viewpoints. Your connection to wellness.



#### NuMedica<sup>®</sup> • Booth #5021

9503 E. 55th Pl., Tulsa, OK 74145 US Ph: 800-869-8100 • Fax: 877-270-2005 Email: jose.rivas@numedica.com • Website: www.numedica.com

NuMedica® provides the most innovative, science-based nutritional formulas exclusively available to licensed healthcare practitioners. We manufacture our formulas in cGMP facilities with SGS and NSF certifications ensuring the highest quality formulas. Our mission and passion drives us to remain the benchmark of excellence in nutritional science, technology and safety.



#### NuSkin • Booth #2055

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Oligoscan's online testing system quickly and non-invsilvey utilizes sophisticated software and spectrophotometry to measure current mineral & heavy metal trends from your patient's hand tissue for immediate assessment and interpretation. Visit Booth #5092 or www.oligoscan.com for more information

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4130 SW 28th Way, Ft. Lauderdale, FL 33312 US Ph: 800-613-6269 • Fax: 877-254-8822 Email: support@omaprem.com • Website: www.omaprem.co

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50 West Bridge St., New Hope, PA 18938 US Ph: 855-978-6615 • Fax: 267-247-5029 Email: Imh@omaxhealth.com • Website: www.omax3pro.com

Omax Health is a science based, health and wellness company focused on developing premium guality nutraceuticals for healthcare professionals, including Omax3® Professional Strength Omega-3. Developed by scientists affiliated with Yale University, Omax3® is a pharmaceutical-grade fish oil supplement that is 93.9% concentrated, double molecularly distilled, tested by independent laboratories, and blister packed for freshness. With a patented 4:1 ratio of EPA to DHA, Omax3® has been developed specifically to fight inflammatory cytokines.

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Nutrafol • Booth #2043





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## OBJECTIVES

- Possess a thorough understanding of cell anatomy & biology, and basic stem cell properties and processes.
- Develop expert understanding of harvesting methods for various stem cell procedures.
- Demonstrate a working knowledge surrounding cardiovascular, vascular, and respiratory conditions with relation to stem cell therapies.
- Understand the treatment of musculoskeletal & neurodegenerative conditions through the use of various stem cell sources.
- Learn best practices for implementing and integrating regenerative medical treatments into practice.
- Assess the ethical considerations and controversies surrounding cellular therapy, while discussing the risks, benefits, applications, and current legalities surrounding cell cryopreservation and cell banking.
- Participate in interactive sessions with leading experts practicing live stem cell demonstrations.

#### MODULE I:

The Biological and Molecular Basis for Regenerative Medicine

MODULE II: Best Practices in Regenerative Medicine

#### MODULE III:

In-Office Applications of Regenerative Therapies: Focus on Cardiovascular, Vascular, & Respiratory Conditions

#### MODULE IV:

In-Office Applications of Regenerative Therapies: Focus on Musculoskeletal, Neurological & Neuro-Degenerative Conditions

#### MODULE V:

Stem Cell Harvesting and Isolation (Hands-On)



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#### Modules I-IV are available online.

## Evening workshop sponsored by

# ONDAMED®

## "Becoming a better diagnostician/clinician: A new perspective on illness and wellness"

with Silvia Binder, N.D., Ph.D. and James Denninghoff, M.D.

## Friday, December 15, 2017 at 6:15 to 8:30pm | Titian 2303-4

### Come learn about the integration of ONDAMED as part of a successful medical practice.

#### This Workshop is for any anti-aging medical specialist.

Here is a testimony by James Denninghoff, M.D. "Most of our patients in my 30 year ENT-Allergy practice have been mislabeled because their symptoms (chronic sinusitis, fatigue, asthma, gastric reflux, headache, allergies, depression, and others) have been used as the diagnosis. Identifying the actual underlying cause has often never been done. An accurate, specific diagnosis is essential for effective treatment and symptom resolution. Our ONDAMED use has been a revelation, both diagnostically and therapeutically, especially for patients who have not gotten answers elsewhere or were unresponsive to conventional treatment."

We plan a hands-on demo after sharing our clinical experience with patients suffering from chronic disease and acute injuries using ONDAMED as part of an integrative medical approach.

#### RSVP: christianekoch@ondamed.de

A delightful assortment of refreshments, with wine, coffee and tea will be served.

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#### ONDAMED • Booth #2015 5 Fairlawn Dr., St. 200, Washingtonville, NY 10992 US Ph: 845-534-0456 • Fax: 845-534-0457 Email: support@ondamed.net • Website: www.ondamed.net

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T.A. Sciences® is the first healthcare company dedicated exclusively to creating researchbased, clinically tested wellness products that help address cellular aging through the science of telomerase activation. TA-65® is a patented, all natural, plant-based compound which can help maintain or rebuild telomeres. It is currently available in TA-65MD® Nutritional Supplements, in 250 unit and 100 unit capsules, and TA-65® for Skin which provides cosmetic benefits in all layers of the skin.

#### Tailor Made Compounding • Booth #6021

200 Moore Dr., Nicholasville, KY 40515 US Ph: 859-887-0013 • Fax: 859-406-1242

Email: admin@tailormadehealth.com • Website: www.tailormadecompounding.com

Tailor Made Compounding pharmacy has established itself as a leading compounding pharmacy specializing in tailor made medications and peptides, providing a high level of patient care to compliment physician's therapies, and forming a holistic prescriber-pharmacy-patient interface. Located in Nicholasville, Kentucky we are able to provide you with all your compounding needs.

#### Terra Biological LLC • Booth #3079

3830 Valley Centre Dr., Ste. 705, PMB 561, San Diego, CA 92130 US Ph: 858-947-5722 • Fax: 888-850-3455

Email: acash@benagene.org • Website: www.benagene.com

Terra Biological developed and markets "benaGene" oxaloacetate, a patented nutritional supplement for anti-aging, energy management, and general health. Oxaloacetate has been shown to mimic the calorie restricted metabolic response via both gene expression changes and short-term metabolic changes. Terra Biological is a privately-held life sciences company based in San Diego, California.

#### Tesla Wellcare Inc. • Booth #7072

Las Vegas Blvd., Las Vegas, NV 10000 US Ph: 909-539-3701 • Fax: Email: curtis@teslawellcare.com • Website: teslawellcare.com

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#### The Cardio Group • Booth #4033

6440 N. Central Expressway, Ste. 100, Dallas, TX 75206 US Ph: 214-770-4934 • Fax: 888-629-1419 Email: melissa@thecardiogroup.com • Website: www.thecardiogroup.com

The Cardio Group is the leader in Pulse Wave Analysis technology. The Max Pulse cardiovascular device is a three minute functional diagnostic with a focus on endothelial function, arterial elasticity, eccentric constriction as well as remaining blood volume valuations. Within three minutes the patient and clinician are presented with valuable information regarding cardiovas-cular risk factors. The clinician may use this objective data to prove clinical efficacy as well as improve clinical outcomes.

#### The SaltFacial – A Med-Aesthetic Solutions Company • Booth #9054

2033 San Elijo Ave., Ste. 200, Cardiff, CA 92007 US Ph: 760-942-8815 • Fax: 760-230-8048

Email: adanto@yourmas.com • Website: www.thesaltfacial.com

The SaltFacial Skin Renewal Therapy System is a non-invasive, multi-modality aesthetic/medical device that can be used alone, or as an adjunct to other aesthetic procedures, to yield unparalleled results in the treatment of a wide variety of skin conditions, naturally. As a patent-pending 3-step procedure, The SaltFacial Skin Renewal Therapy is safe and effective for all skin types. Results are immediate, with no side effects and virtually no downtime, promoting excellent patient satisfaction and a rapid ROI.

#### THOR Photomedicine • Booth #7065

Water Meadow House, Chesham, Buckinghamshire HP5 1LF UK Ph: 877-723-4804 • Fax: Email: valerie@thorlaser.com • Website: www.novothor.com

THOR Photomedicine specializes in developing technologies for delivering PMBT, Photobiomodulation Therapy (formerly, LLLT). Our hand-held LX2 and NovoTHOR Whole-Body Light Pod have quickly become

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6170 Research Rd., Frisco, TX 75033 US Ph: 877-443-5227 • Fax: 877-443-5227 Email: info@TrueHealthDiag.com • Website: www.TrueHealthDiag.com

True Health Group is focused on transforming patient care through integrated diagnostics and healthcare services. True Health Diagnostics, a subsidiary, specializes in earlier-stage diagnosis and prevention of chronic disease, including cardiovascular, diabetes, cancer, genetic disorders and autoimmune disease. True Health is headquartered in Frisco, Texas, with operations across the country.

#### Truffoire Las Vegas • Booth #8032

3301 Beach Port Dr., Las Vegas, NV 89117 US Ph: 702-330-6435 • Fax: 702-330-6435 Email: truffoirelv@gmail.com • Website: www.truffoire.com

We are a skin care company that specializes in skin protection from aging as well as repair damaged skin. We are focusing on the future of skin care using state of the art technology in our products. Our products provide numerous advantages to the skin using natural ingredients. Some of the most common advantages are simulating collagen growth, tightening, and lifting sagging skin as well restoring the skin and leaving it with a much younger luster.

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733 Washington Rd., Ste. 211, Pittsburgh, PA 15228 US Ph: 412-668-3831 • Fax: 412-668-2165 Email: support@trugen3.com • Website: www.trugen3.com

From the founding family of Douglas Laboratories\* comes a new generation of nutraceuticals, available exclusively through Health Care Professionals: TruGen3®. TruGen3® continues our family legacy of three generations and more than half a century of nutraceutical experience, with products produced under the highest ethical standards. FREE Hemp Oil/CBD samples will be available at booth 7061.

#### TUSHY • Booth #1105

163 N. 6th St., Brooklyn, NY 11211 US Ph: 888-218-8749 • Fax: 888-218-8749 Email: hello@tushy.me • Website: www.hellotushy.com

TUSHY is a Brooklyn based bidet company set on changing the way Americans poop. We are changing American bathroom culture by providing a healthier alternative to using toilet paper. We pride ourselves on being advocates for personal health and hygiene, environmental conservation, and combating the global sanitation crisis. Through our partnership with Samagra, a non-profit that provides life-improving services to rural India, every TUSHY sold provides a family one month of access to clean community toilets.

#### Ultradiol LLC • Booth #1048

450 West 14th Ave., Denver, CO 80204 US Ph: 833-858-7234 • Fax: 833-858-7234 Email: ultradiol@ultradiol.com • Website: www.ultradiol.com

Ultradiol was established with a shared team mission of providing an exceptionally crafted, medicinal-grade CBD product for distribution through professional networks of doctors. Ultradiol products are manufactured according to the Whole Flower Principle and use a proprietary technology to enhance overall bioavailability. With Ultradiol now available nationwide through healthcare professionals, patients can feel confident they are taking a physician preferred product that is safe, effective and valuable.

#### UNIsource Health • Booth #5055

1894 E William St., Ste. 4, # 307, Carson City, NV 89701 US Ph: 805-660-0793 • Fax: 775-881-9300 Email: Roberto@UNIsourceHealth.com • Website: www.UNIsourceHealth.com

UNIsource Health offers the RM-3A Medical Device. It is a five time FDA cleared device which provides an innovative unique fast analytical screening system for risk factors pertaining to diabetes, cardiovascular disease, neuropathy and ANS dysfunction as well as other wellness and longevity markers. The non-invasive RM-3A and ABI devices are designed for in-practice early detection of risk variables offering up-to-the-minute data essential to whole-person analysis.

#### Universal Medical Testing • Booth #3097

2810 E. Trinity Mills Rd., #209-235, Carrollton, TX 75006 US Ph: 844-783-6722 • Fax: 888-332-8099 Email: rick.anstest@gmail.com • Website: www.universalmedicaltesting.com

Universal Medical Testing provides medical testing devices for early detection of complications of diabetes and other chronic conditions. We offer testing equipment for Peripheral Neuropathy, Cognitive testing (dementia), Tonometer for glaucoma testing, Autonomic Nervous System Testing, Digital Fundus Camera, Laboratory Blood and Urine Services.

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1875 Third Ave., San Diego, CA 92101 US Ph: 619-683-2005 • Fax: 619-683-2008 Email: info@ucprx.com • Website: www.ucprx.com

University Compounding Pharmacy specializes in the formulation of drugs that are not commercially available. Our pharmacists use state of the art technology with quality chemicals so that your finished medication meets the doctor's exact specifications. We employ the highest standards in compounding, following nationally recognized United States Pharmacopoeia. In addition to the highest quality of compounds, UCP prides itself with providing the best physician and patient experience.



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Vielight Inc is a leader in providing non-invasive brain stimulation in home-use devices. Its technology is based on photobiomodulation (or low level light therapy) using near infrared light. Evidence of its potential efficacy for Alzheimer's disease has recently been published in a peer-reviewed journal, which showed the Neuro to improve dementia-related cognitive impairment and functional factors significantly. Vielight will soon be co-investigating its efficacy for Parkinson's disease. For more information, go to www.vielight.com.

#### Viora • Booth #4039

213 West 35th St., Ste. 500, New York, NY 10011 US **Ph:** 702-525-7784 • **Fax:** 702-525-7784 **Email:** Info@vioramed.com • **Website:** www.vioramed.com

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With 20+ years of experience in the natural health industry, Vita Aid Professional Therapeutics strives to provide high-quality and effective nutraceuticals for health care practitioners worldwide. We focus on products for safe and effective therapeutic use and follow strict pharmaceutical-grade standards. What differentiate Vita Aid from others are: \*Exclusive to health care practitioners/ \*Clinical evidence based formulations/ \*No added stearic lubricants, for higher bioavailability of the active ingredients/ \*Vegetarian formulas.

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#### Vital Nutrients • Booth #4036

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Vital Nutrients produces a wide range of nutritional supplements using the highest standards of manufacturing practices and quality assurance. We are constantly evolving our products to keep pace with current scientific research, and maximize clinical effectiveness. Our product line consists of over 200 supplements including vitamins, minerals, botanicals, fatty acids, antioxidants, protein powders, and more. Our supplements are proudly used by healthcare practitioners worldwide.

## Vital Reaction

#### Vital Reaction • Booth #9051

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Vital Reaction<sup>™</sup> is the leader in molecular hydrogen products, a noteworthy therapy with clinical significance as a preventative and therapeutic medical gas. We advance health and human potential at the sub-cellular level via our Vital Reaction<sup>™</sup> Inhaler (inhalation of H2 gas) and Vital Reaction<sup>™</sup> Tablets (ingestion of H2 gas). Molecular hydrogen (H<sub>2</sub>) is a unique antioxidant. H<sub>2</sub> eliminates only the most harmful free radicals, reduces oxidative stress and puts the body in balance. Due to its small size, it easily crosses cell membranes, blood brain-barrier and accesses parts of the cell that other antioxidants are too large to reach. Molecular hydrogen acts as an antioxidant mediator, anti-inflammatory and cell signaling molecule.

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#### Vitalere, Parent company of Power On/Power Off • Booth #7073

228 Park Ave. S, #24032, New York, NY 10036 US

Ph: 800-209-9808 • Fax: 800-209-9808

**Email:** customerservice@poweronpoweroff.com • **Website:** www.poweronpoweroff.com www. modusnutrition.com

Vitalere creates products to solve problems in health and nutrition. We operate as a portfolio company. Our Portfolio includes Power On: the first NSF-Sport certified nootropic for enhancing focus, attention, memory and muscle twitch response without stimulants such as caffeine. Power Off: the first NSF-Sport certified sleep supplement that works. Modus Professional Plant Based Protein: the first NSF-Sport certified 100% plant protein powder that has a higher quality than whey and casein.

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For 20 years Vitelle Labs has been the formulator and manufacturing partner behind many of the most recognizable brands in the professional skincare market. Our products are found on the shelves of clinical/medical esthetic practices worldwide. We have helped hundreds of clients create unique, powerful boutique skin care brands that have allowed them to market proprietary products to their clientele. Vitelle Labs guides you through product and packaging selection; graphic design/label set up; product training and post launch.

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Viveve is a womens health and wellness company whose flagship device, the Viveve® System, delivers Cryogen-cooled Monopolar Radiofrequency deep into soft tissue. Available in the US for electrocoagulation and hemostasis in general surgery, it is cleared in more than 50 countries to improve vaginal laxity and sexual function. InControl Products by Viveve are FDA cleared devices that treat incontinence conditions and improve pelvic floor strength. Viveve exclusively distributes InControl Medicals products to US healthcare providers.

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9220 James Ave. South, Minneapolis, MN 55431 US Ph: 612-298-1838 • Fax: 612-298-1838 Email: info@wellness-usa.com • Website: www.wellness-usa.com

Wellness USA, Inc. designs and distributes a line of exciting new affordable products (Residential and Commercial) for the wellness, fitness, beauty and spa markets. These new products focus on services that further the integration of mind/body wellness that has seen explosive growth during the past several years. The principals of the company bring a combined total of over 100 years of experience in the global development and distribution of wellness, fitness, spa equipment and products.

#### Wells Pharmacy Network • Booth #4005

1210 SW 33rd Ave., Ocala, FL 34474 US Ph: 800-622-4510 • Fax: 877-401-5653 Email: info@wellsrx.com • Website: www.wellsrx.com

Wells Pharmacy Network is a compounding pharmacy operating as a 503A pharmacy in Florida and a FDA Registered 503B Outsourcing pellet facility in Tennessee. Wells specializes in wellness, anti-aging, weight management, sexual wellness, thyroid/adrenal health and aesthetic dermatology preparations. Our comprehensive formulary encompasses an array of strengths and sizes of medications including Testosterone, hCG, Vitamin Injectables, Peptides and Sermorelin. Preparations come in many dosage forms such as creams, capsules, injectable, troches and sterile implantable pellets.

#### Women's International Pharmacy • Booth #9035

2 Marsh Ct., Madison, WI 53718 US Ph: 800-279-5708 • Fax: 800-279-8011 Email: info@womensinternational.com • Website: www.womensinternational.com

Women's International Pharmacy specializes in custom compounded bioidentical hormone prescriptions for men and women. Our pharmacy earned accreditation through the Pharmacy Compounding Accreditation Board (PCAB) by following stringent proficiency and quality assurance standards. Our pharmacists focus on meeting individual needs for licensed medical practitioners and their patients. Whether you are a practitioner or patient you can be assured Women's International Pharmacy is here for you and we respect your freedom of informed personal choice.

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#### ZyCal Bioceuticals Healthcare Co., Inc. • Booth #8060

5 Executive Dr., Ste. A, Toms River, NJ 08755 US Ph: 888-779-9225 • Fax: 888-373-0594 Email: marketing@zycalbio.com • Website: zycalbio.com

ZyCal Bioceuticals Healthcare Co., Inc. is a nutritional supplement company focused on manufacturing and marketing of biologically active proteins that address bone and joint conditions for healthcare providers and their patients. The company is headquartered in Toms River, New Jersey. Since it's founding in 2006, ZyCal Bioceuticals has developed and launched the first biologically active class of proteins containing BMPs (Bone Morphogenetic Proteins) and growth factors as a nutritional supplement.

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- Open up your office use account and personalize assessment forms, operating procedures, and placing your first order.
- Consult with our Clinical Pharmacist on specific protocols while designing custom formulations for your practice.

#### IV NUTRITION MYERS' COCKTAIL • ASCORBIC ACID IMMMUNE SUPPORT • GLUTATHIONE VITAMINS • MINERALS • AMINO ACIDS

#### CENTRAL DRUGS OFFERS

- Experience, customizing compounded formulations for over 18 years
- Personalized customer service
- Quality products tested onsite to meet regulatory standards
- Timely delivery all orders are mailed within 24 hours of order confirmation
- Consultation services by an expert staff or clinical pharmacists
- Practical educational programs for building your practice

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THE PREMIER DEVICES FOR YOUR TRANSDERMAL MEDICATIONS

Hormones | Aesthetics | Pain Management | Dermatological



REDEFINING MEDICINE

## 2018 Educational Schedule

#### FEBRUARY 8-11

Belmond Charleston Place Charleston, SC

BHRT Symposium February 8-11, 2018

Fellowship Modules February 9-11, 2018



#### **APRIL 12-14**

Diplomat Resort Hollywood, FL

Spring Congress April 12-14, 2018

ABAARM/ABAAHP Written Exams April 12-14, 2018

ABAARM Oral Exams April 12-14, 2018

Fellowship Modules April 12-14, 2018

#### **MAY 4-5**

Wynn Las Vegas Las Vegas, NV

**A4M Workshop** May 4-5, 2018

#### AUGUST 10-12

Venetian/Palazzo Resort Las Vegas, NV

**Fellowship Modules** August 10-12, 2018

A4M Lab Fundamentals Workshop August 10-12, 2018

A4M Pellet Therapy Workshop August 10-11, 2018

#### **SEPTEMBER 27-30**

Gaylord Opryland Nashville, TN

BHRT Symposium September 27-30, 2018

ABAARM/ABAAHP Exams September 27-30, 2018

**Fellowship Modules** September 28-30, 2018

Sexual Health Workshop September 28-29, 2018

#### **OCTOBER 19-20**

Westin Galleria Dallas Dallas, TX

A4M IV/Chelation Workshop October 19-20, 2018

A4M Weight Management Workshop October 19-20, 2018

A4M Pellet Therapy Workshop October 19-20, 2018



#### **DECEMBER 13-15**

Venetian/Palazzo Resort Las Vegas, NV

ABAARM/ABAAHP Written Exams December 12, 2018

**ABAARM Oral Exams** December 13-15, 2018

**World Congress** December 13-15, 2018

**Fellowship Modules** December 13-15, 2018

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SPRING CONGRESS 2018



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