Back to Basics
From MPKB, edits by Chris Benediktsson and Janet Raty

The Autoimmunity Research Foundation team presents at international conferences. Progress on pure olmesartan continues and we are in contact with the FDA, but we are most concerned about you, our readers. That is why we are taking this time to review the basics of the MP in an easy-to-read Q&A format for this newsletter.

Q. What is the Marshall Pathogenesis?
A. First, it is helpful to know the word "pathogenesis" means the source or cause of an illness or abnormal condition. A fuller description is "The development of morbid conditions or of disease; more specifically the cellular events and reactions and other pathologic mechanisms occurring in the development of disease." (http://medical-dictionary.thefreedictionary.com/pathogenesis)

"The Marshall Pathogenesis... posits that chronic diseases (Th1 illnesses), are the result of infection by an intraphagocytic, metagenomic microbiota of chronic microbial forms that we often refer to as the Th1 pathogens." (http://mpkb.org/home/protocol)

We often focus only on the "Marshall Protocol" because it is an action or choice. However, the Marshall Pathogenesis explains the logic or reason for an action or choice.

On a relatively modest scale, the pathogenesis describes the science underpinnings of the Marshall Protocol to medical providers, friends and family as a framework for action and choice. We understand the science is replicable, with the correct skills and tools, to verify facts that guide the clinical application of the Marshall Protocol.

In a more global perspective, the Marshall Pathogenesis provides profound direction-changing implications on what is known about disease or disorders. It occupies a unique position in history to clarify previous scientific research, using in silico modeling and other advanced technologies with what is seen in a clinic setting. And in a very real way, the Marshall Pathogenesis refocuses medical solution goals to cure, instead of management, this way:

“The Marshall Pathogenesis, upon which the Marshall Protocol is grounded, is a description for how microbes interfere with the innate immune response. These pathogens survive and reproduce by disrupting the Vitamin D Nuclear Receptor, an evolutionarily consistent mechanism for survival, which leads to the development of chronic inflammatory diseases. Because these diseases are fundamentally bacterial in nature, the conditions are referred to as the 'Th1 diseases.' The Marshall Pathogenesis is supported by an emerging array of evidence, including clinical evidence, evolutionary evidence, some in silico data, and environmental sampling studies.” (http://mpkb.org/home/pathogenesis)

Timeline
From MPKB.org, vimeo.com and trevormarshall.com, with edits by Trevor Marshall, Chris Benediktsson and Janet Raty

2012
2012 May, Granada, Spain
International Congress on Autoimmunity.

- Lindseth I. Keynote, “Treatment of Chronic Fatigue Syndrome as an Immunological Disorder”
- Marshall TG. Plenary "The Microbiome, which Feeds a Myriad of Autoimmune Diseases" and keynote "The Human Microbiome is the infection at the Heart of Autoimmune Disease"
Q. What is Microbiota?

A. Microbiota are the microscopic living organisms in a specific region or area, like a human body. They are also called microbial flora. Microbes can be bacteria, fungus, virus or protozoa. According to a recent National Institutes of Health (NIH) estimate, 90% of cells in the human body are bacterial, fungal, or otherwise non-human. (Tumbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI. The human microbiome project. Nature. 2007;449:804-10.)

Although experts agree that microbes enjoy a commensal relationship with human hosts, only a fraction of human microbiota have been characterized, much less identified. The sheer number of non-human genes represented by human microbiota communities—there are millions in our “extended genome” compared to the nearly 23,000 in the human genome—implies we have just begun to fathom the full extent microbes act to facilitate their own survival. (www.ncbi.nlm.nih.gov/pubmed/20388071)

The NIH’s ongoing initiative, the Human Microbiome Project, has started to catalog the human microbiome, also referred to as the human metagenome, because traditional in vitro methods for culturing individual species in the lab have drastically under-represented the size and diversity of actual microbe populations.

Cores across body sites → Our Metagenome makes us genetically unique

Core is small at any definition, body site specific. Abundance of core members varies dramatically

One study employed a newer technology, high throughput genomic sequencing, on removed prosthetic hip joints. Those results revealed the previously-unknown presence of hydrothermal vent eubacteria, a species once thought only to persist in the depths of the ocean. (http://mpkb.org/home/pathogenesis/microbiota)


2011 May, Dalian, China Marshall TG, NeuroTalk 2011, “The human microbiome is the mechanism fueling neurodegenerative disorders.”


2011 December Raty J, Benediktsson C, Marshall TG. ARF Newsletter Publication begins: Th1nk MP.
Q. What is the VDR and how does it work?

A. The NR111 or VDR (also called the calcitriol receptor) is a nuclear receptor, a class of proteins found within the interior of cells. These proteins are responsible for sensing the presence of hormones and certain other molecules. Nuclear receptors are unique from other classes of receptors because of their ability to directly interact with and control the expression of genomic DNA.

Some molecules (or ligands) which bind to the nuclear receptor activate (agonize) and some inactivate (antagonize). It is believed approximately 95% to 98% of ligands inactivate nuclear receptors. Nuclear receptors play a significant role in immune response and many drugs, supplements and substances in food and drink are immunosuppressive. Expression of a large number of genes is regulated by nuclear receptors and ligands that activate receptors have profound effects.

Different cell types have different nuclear receptors. Immune cell VDR use two endogenous or “native” ligands, the two main forms of vitamin D in the human body: 25-hydroxyvitamin D (25-D) and 1,25-dihydroxyvitamin D (1,25-D). Non-native or exogenous ligands also inactivate or activate, depending on their molecular structure.

Ligands compete to dock into nuclear receptors. A greater molecule concentration can displace competing molecules. Affinity occurs in a logarithmic or sliding scale. VDR binding with ligand 1,25-D tends to be much less common than 25-D by a factor of 1,000 or more. But an increase in 1,25-D and decrease in 25-D can tilt the odds in favor of 1,25-D, and vise versa. Affinity and whether a ligand inactivates or activates a nuclear receptor can be validated with in silico modeling. Although less precise, it is also possible to measure this in vitro.

When activated by 1,25-D, the VDR transcribes thousands of genes. The VDR functions in regulating calcium metabolism. It is becoming increasingly clear, however, that the clinically-accepted role of vitamin D metabolites—regulating calcium homeostasis—is just a small subset of the functions actually performed by these hormones.
One of the VDR’s key functions is the transcription of antimicrobial peptides. In humans, when the VDR is activated, TLR2 is expressed on the surface of certain cells to recognize native or foreign substances, and then passes on appropriate signals to the cell and/or the nervous system. When activated, TLR2 also allows the immune system to recognize gram-positive bacteria, including Staphylococcus aureus, Chlamydia pneumoniae, and Mycoplasma pneumoniae and TLR2 protects against intracellular infections such as Mycobacteria tuberculosis. (http://mpkb.org/home/pathogenesis/innate_immunity#nuclear_receptors_and_ligands. Additional references found in MPKB.org article.)

In Homo sapiens, or humans but not other species, Cathelecidin, TLR2 and beta-Defensins are transcribed by the VDR. (http://mpkb.org/home/publications/marshall_cancer_2009)

Q. What is vitamin D?
A. During the last century, through early perceptions and tools, “vital amines” were identified and given alphabetical designations. “Vitamin D” was misidentified as a necessary dietary nutrient instead of being recognized as a secosteroid, tightly regulated by the body. We now know all forms of D belong to a family of lipids called secosteroids—very similar in structure to steroids, except two B-ring carbon atoms of the typical four steroid rings are not joined as they are in steroids.

The level of each D metabolite is affected by a complex network of feedback interactions involving multiple enzymes and receptors, further revealing mis-categorized vitamin D is regulated more like a steroid than a nutrient.

In scientific literature, researchers sometimes distinguish between “steroid” and “secosteroid,” but not always. This is an indication of how secosteroids behave. All vitamins D act very much like steroids, binding nuclear receptors and modulating immune response. Growing evidence reveals secosteroids D causes adverse side effects like chronic disease over time, just like anabolic steroids and corticosteroids.


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Q. What is olmesartan? How does it work?

A.

Patients on the Marshall Protocol (MP) take olmesartan (Benicar), a drug whose actions are well known, every six hours. A growing body of research supports the use of olmesartan as a part of a curative therapy for chronic disease. In general, olmesartan tends to be prescribed for its antihypertensive properties due to the fact that it is an angiotensin receptor blocker.

For the purposes of the MP, olmesartan has two primary actions: it reduces inflammation by blocking the Nuclear Factor-kappaB cytokine pathway and it is an agonist of the Vitamin D Receptor (VDR). As a VDR agonist, olmesartan activates the innate immune response. Research supports the safety of doses used by MP patients. Olmesartan has minimal interactions with other drugs and is one of the safest drugs on the market.

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Q. Why, why, why does the MP take so darned long?

A.

The MP takes on an individualized timetable to safely remove pathogens, working with each individual’s immune system via stimulation. It is tempting to compare the MP to immunosuppression—a quick goal to mask or manage symptoms—but working with a body’s immune system takes time.

Length of treatment varies per individual by:

Degree of illness – If disease is advanced, symptoms debilitating, or...
vital organs severely compromised, immunopathology takes more time. MP patients must improve with all due caution and decide what level of symptoms are tolerable while a doctor monitors biological processes to make sure they stay within acceptable limits.

Degree of health desired.

Prior use of immunosuppressants and immunomodulatory medications.

Fibrosis – When the immune system fails to kill a pathogen, it encases diseased tissue in collagen. This is known as fibrosis. Individuals with fibrosis can expect to be working fibrosis pockets for an extended length of the treatment, as tissue slowly remodels. (http://mpkb.org/home/patients/mp_duration)

Chris Benediktsson (Tiburon, California, USA) – Executive Vice President of ARF. Over 30 years experience as a senior manager with both the private and public sector, ranging from operations management of an international media company, to senior staff with the State of Alaska Court System. He has a lifelong interest in practical science, prepared environmental assessments for the FAA, drafted municipal code for regulation of recreational water resources for the Municipality of Anchorage, and lobbied and presented technical testimony to state legislature, served as an accounting, business development and management consultant for private and public sector organizations including Municipality of Anchorage, Lottery Alaska, ABC Alaska, Builder’s Bargains Stores, and several Alaska Native corporations.

Janet Raty (Portland, Oregon, USA) – ARF research. BYU (UT) BFA in Illustration and MsEd in Supervision and Administration from Bank Street College of Education (NY). Her career spans traditional print and online content publishing, but features educational leadership and assisting C-level executives and strategists visually describe, publish and implement.


1999 California, USA. Sartans 8-hr cycle calculated.


2001 March First early adopter, Elaine E. begins ARB.