Supporting Immune Function
A Lifestyle and Nutrient Approach

Principles and Protocols for Healthcare Professionals

SECOND EDITION

Lifestyle Interventions for Immune Health • Basic Principles of Autoimmunity and Autoinflammation
Slowing Immunosenescence • The GI and Immune Function • Mitochondrial Function and Immune Health
Immunology and Autoimmune Testing • Diminishing Stress and Cortisol-Induced Immune Suppression
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THE STANDARD
ROAD MAP SERIES

Thomas G. Guilliams Ph.D.

POINT INSTITUTE

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POINT INSTITUTE
STEVENS POINT, WI

The Point Institute was founded by Thomas Guilliams, Ph.D. as an independent research organization focused on examining and disseminating information about the use of natural therapeutic options for treating and preventing chronic disease. Along with therapies generally defined as lifestyle interventions, the Point Institute specializes in the evidence and application of nutraceuticals (dietary supplements, herbs, vitamins, minerals, etc.) as therapeutic and preventative agents in clinical practice.

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Optimizing Immune Function:
Fundamental Principles for Building a Strong Immune System

Throughout this guide there is an abundance of detailed information about the specific mechanisms that allow the immune system to function properly and a number of suggested protocols for clinicians to follow to address specific immune challenges. Of course, these sections of the Road map are important details for the clinician dealing with complex immune-related health concerns, but it is equally important to keep in mind the fundamental principles at work within those details—those that build and maintain the foundation of a strong immune system. So, while many will thumb past this section, in search of the "how-to" protocol sections of this book, we believe that those who understand these important principles will have the greatest success in adapting those protocols to each patient's specific underlying vulnerabilities.

Almost every week, new research is published that expands and challenges our understanding of the mechanisms and vulnerabilities of the immune system. This is especially true in the midst of the Covid-19 pandemic, where new information is being published nearly every day. Nonetheless, while we sift through how this new research will change our therapeutic strategies, the fundamental principles laid out in this section will always be a cornerstone for building the foundation for those new strategies. Furthermore, since these are fundamental principles (rather than specific protocols) they can function within a wide variety of healing disciplines with equal success. With this in mind, we describe ten fundamental principles for building/maintaining immune function; principles that are built upon and foundational for the rest of this Road map.†

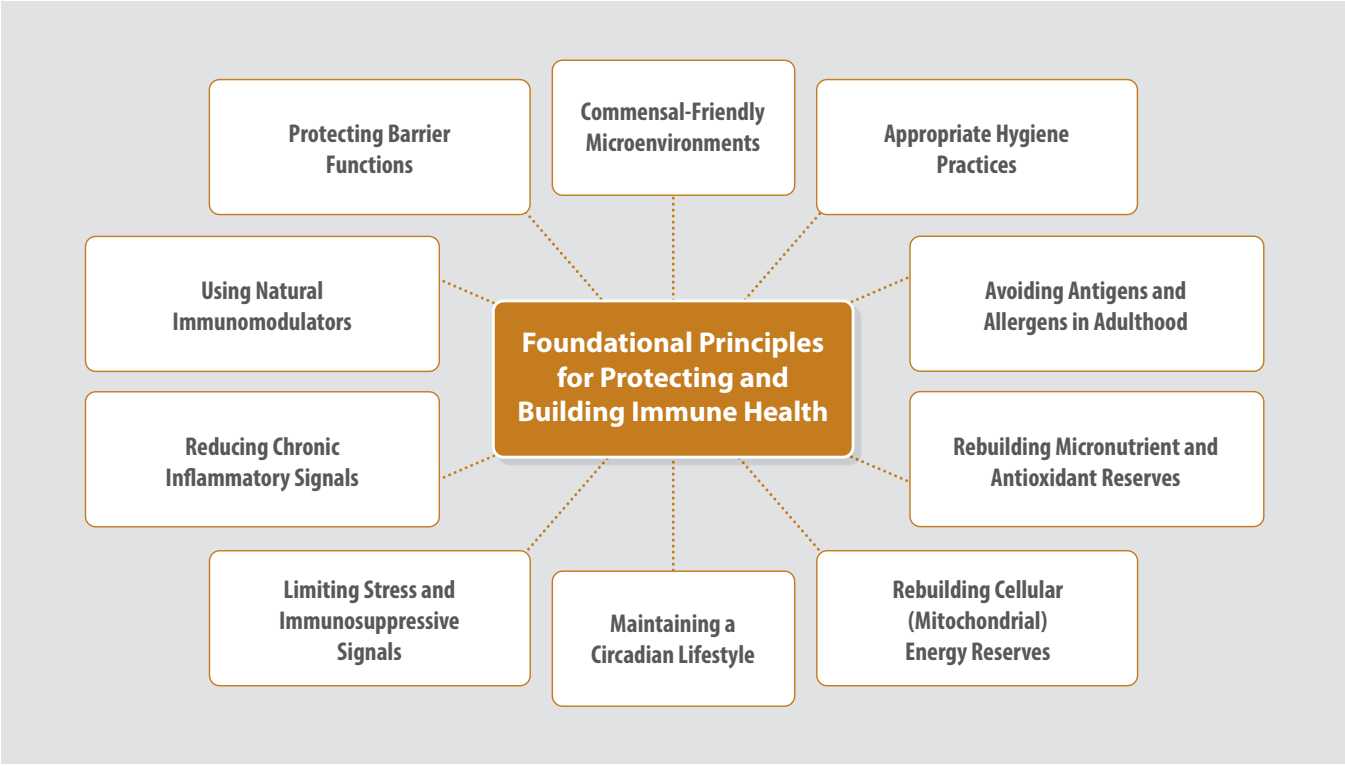

Figure 3: Ten Foundational Principles for Protecting and Building Immune Health.

† This list of ten principles is slightly different in this second edition, compared to the list described in the first edition; most notably, the inclusion of the importance of circadian signals.

The Adaptive Superiority of the Innate Immune System

The fundamental way to teach immunity is to first explain that the immune system is easily divided into the innate immune system and the adaptive immune system. That the innate immune system is "primitive" and lacks specificity and memory, while the adaptive immune system helps us "adapt" a specific response to a specific antigen or pathogen and has a "memory" for this encounter which allows us to mount a second or third response with greater vigor. However, like many things in biology, this simplistic way of understanding these two "systems" has been radically shifting in the past few decades and our nomenclature needs to catch up.

The adaptive immune system, indeed, is capable of both specificity and diversity. The process by which naïve B and T cells rearrange their DNA to convert a finite number of gene segments into an almost limitless number of antigen binding sites (a process known as VDJ recombination, see page 33) is behind this phenomenon. This process means that once a B or T cell expresses a functional immunoglobulin or T-cell receptor gene (most don't and are eliminated) the expressed protein binds to a very limited set of structures. This is why we say the adaptive immune system has great specificity. However, these cells cannot "adapt" when a new immune threat emerges. We have seen the evidence of this when a highly specific antibody is elicited against a very specific viral epitope with the use of mRNA vaccines. If the host encounters a virus with an altered (mutated) form of this protein for which the previous antibodies cannot attach, the adaptive immune system has no ability to adapt to this change, it must find another naïve B-cell with an appropriately formed antibody binding site to begin the "adaptive" immune response all over again.

Likewise, if a B-cell produces an antibody that recognized a self-antigen, this B-cell must be neutralized (it can't adapt, it can't be retrained) or it could be the genesis of an autoimmune response down the road. And even though B-cells can produce various types of antibodies (IgM, IgG, IgA, etc.), this process (known as class switching) is also a unidirectional process which can't be reversed and is directed by signals from T-helper cells. But where do the T-cells get their instructions and how do they know friend from foe or what type of response to trigger when a threat is detected? All of this requires the innate immune cells!

Yes, while the cells within the adaptive immune system produce high levels of specificity, they do this before encountering antigens and they are pre-programmed to respond to signals coming from the innate immune system. Ironically, it is actually the innate immune cells, with their plethora of pattern recognition receptors (PRRs), most notably Toll-like receptors (TLRs), that can generate a highly adaptive response; especially in their communication with T-cells and B-cells as they direct the "adaptive" immune response. In fact, TLRs on dendritic cells (the master innate immune cells at the gut interface) regulate nearly every aspect of antigen presentation, including how the antigen is processed, how the MHC proteins are expressed and the types of cytokines expressed to tell the T-helper cells how to respond.[1] Using these PRRs to recognize a variety of antigen molecular patterns (e.g., cell wall proteins, spike proteins, nucleic acid patterns and more), dendritic cells can ***adapt*** their response and help trigger the appropriate cells within the more rigid "adaptive" immune system.[2,3] In other words "the innate immune system is much more adaptive than the adaptive immune system."

So, what implications does this change in thinking have for understanding the support of the immune system? One way is in how we understand the decisions made at the gut/immune interface, the primary location the immune system learns to recognize friend vs. foe. Remember, the immune system must carefully recognize harmful non-self pathogens while interacting closely with a large number of "non-self" commensal organisms in the gut. B-cells and T-cells must be kept away from direct contact with this environment, accessing only processed and presented antigens from innate immune cells; whereas the innate immune cells that can dive right in. It is the adaptive ability of the innate immune cells, with all their pattern recognition receptors, that trains and tweaks the immune response. And since our gut microbiota is constantly changing, itself adapting to various inputs from the environment around us, their constantly changing interaction with the innate immune cells allows for a constantly adaptive immune response. Each decision or environmental influence has some influence on our immune health, starting from early childhood. It is influenced greatly by the introduction of antibiotics and what is usually called the "hygiene hypothesis," as well as nearly every dietary choice we make. [4,5] Therefore, the role of lifestyle, diet,

stress, access to sunlight and a host of other factors that influence the gut microbiota are critical in the process that creates a balanced response to a hostile world—adaptively translated by our innate immune system!

1 Watts C, West MA, Zaru R. TLR signalling regulated antigen presentation in dendritic cells. *Curr Opin Immunol*. 2010 Feb;22(1):124-30.

2 Dolasia K, Bisht MK, Pradhan G, Udgata A, Mukhopadhyay S. TLRs/NLRs: Shaping the landscape of host immunity. *Int Rev Immunol*. 2018 Jan 2;37(1):3-19.

3 Corridoni D, Simmons A. Innate immune receptors for cross-presentation: The expanding role of NLRs. *Mol Immunol.* 2019 Sep;113:6-10.

4 Shekhar S, Petersen FC. The Dark Side of Antibiotics: Adverse Effects on the Infant Immune Defense Against Infection. *Front Pediatr.* 2020 Oct 15;8:544460.

5 Pfefferle PI, Keber CU, Cohen RM, Garn H. The Hygiene Hypothesis - Learning From but Not Living in the Past. *Front Immunol.* 2021 Mar 16;12:635935.

Modulating PRRs with Exogenous Signals

If one of the keys to supporting immune function is the appropriate modulation of inflammatory activity, then modulation of PRR activation within innate immune cells is vital. As our understanding of the mechanisms of PRR-signaling increases, so does our hope of finding ways to modulate their activity. In fact, a number of the phytochemicals already considered to be anti-inflammatory appear to have some ability to affect PRR function or signaling.[9]

PRR activation is dependent on the receptor's ability to form dimers (homodimers or heterodimers). Several recent studies have shown a number of phytochemicals, such as curcumin, sulforaphane, and cinnamaldehyde, are able to interfere with PRR dimerization, accounting for reduced TLR-signaling.[10] Other bioactive plant compounds, like resveratrol, EGCG, luteolin, quercetin and chrysin, have been shown to inhibit downstream-signaling triggered by PRR activation (apart from NF-κB inhibition). Finally, curcumin and parthenolide (from *Tanacetum parthenium,* feverfew) have been shown to inhibit signaling from the intracellular PRRs NOD1 and NOD2. These mechanisms, along with the other anti-inflammatory mechanisms described for these phytochemicals (see page 52), help explain their role in preventing and treating inflammatory-mediated chronic diseases.

The Adaptive Immune System

The adaptive immune system (or sometimes called the acquired immune system) is designed to elicit a targeted immune response that is selected and triggered by specific encountered antigens. The primary cells involved in this system are the T and B lymphocytes (see Figure 6). They are able to recognize invading organisms with a high degree of specificity using T-cell receptors (TCR) or immunoglobulin (Ig) proteins (i.e., antibodies). The adaptive immune cells also have "memory," allowing a second invasion of the same (or cross-reactive) antigen to stimulate a quicker, more potent response. This memory is actually achieved by clonal expansion of a T- or B-cell after it encounters an antigen for which it has specificity. By expanding the number of cells that have previously encountered an antigen, the response to the next encounter with the same antigen can be swift and potent. Also, memory cells undergo antigen-stimulated metabolic reprogramming that allows them to quickly engage the necessary metabolic machinery to mount a more immediate secondary immune response.[11]

One of the key interactions between the innate and the adaptive immune response comes through the process of antigen presentation. Various antigen-containing particles (e.g., viruses, bacteria, fungi, food peptides, etc.) are taken up by certain antigen presenting cells (generally macrophages or dendritic cells, but sometimes B-cells) through phagocytosis or receptor-mediated endocytosis before being processed for presentation to T-cells (see Figure 11). This presentation is done by displaying the processed antigenic portions (sometimes called epitopes) within a specific pocket formed within a transmembrane-associated protein known as a major histocompatibility complex (MHC), also known in humans as human leukocyte antigens (HLA). When an antigen-presenting cell docks with a T-cell that recognizes the particular antigen being presented (using MHC class II molecule) the appropriate secondary receptors and cytokines are triggered, the T-cell is activated and responds in one of several ways, which may include differentiation into one of several different mature T-cell types (see below). Molecular patterns on the antigenic organism influence the antigen-presenting cell (via pattern recognition receptors, discussed previously), which then influence what types of cytokine signals are given to the T-cell.

Antigen-presenting cells trigger T-cell effects by presenting processed *foreign* antigens via MHC class II molecules; however, all nucleated cells display various

Mediators of Inflammation

Pro-inflammatory signals between cells are achieved through a network of cytokines and chemokines (see page 35 for list of common cytokines). Immune cells produce a majority of these molecules, though many different cells can produce inflammatory signals when they are under various metabolic stressors; such as pro-inflammatory adipokines from insulin-resistant adipose cells or injured arterial cells.[3,4] While the list of pro-inflammatory cytokines is quite long, some of the more important pro-inflammatory biomarkers (i.e., cytokines or molecules induced by cytokines) used in clinical practice include monocyte chemotactic protein-1 (MCP-1), interleukins 1β (IL-1β), IL-6, tumor necrosis factor-α (TNF-α), intracellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), bradykinin, histamine, C-reactive protein (CRP), fibrinogen, serum ameloid A (SAA) and plasminogen activator inhibitor-1 (PAI-1). As many of these compounds are coordinately regulated or have direct influence on the expression or secretion of others, they are often up-regulated together in various disease states. Conversely, many anti-inflammatory agents result in the coordinate down-regulation of several of these biomarkers. This is primarily because the intracellular signaling pathways of inflammation is highly coordinated by the nuclear transcription factor NF-κB, which is turned on through many diverse signaling pathways.

The NF-κB Pathway to Inflammatory Activation

Nuclear factor-kappa B (NF-κB, or nuclear factor kappa-light-chain-enhancer of activated B cells) is a nuclear transcription factor that alters gene regulation to promote a wide-range of immune system function, especially those connected with inflammation.[5] NF-κB is a heterodimer of the proteins p50 and p65 (or RelA). In order to have NF-κB readily available without the need for new protein synthesis, the preformed dimer is kept sequestered in the cytoplasm, attached to inhibitor proteins called Inhibitor of κB (IκBα is the most common). Phosphorylation of the IκBα protein causes a change in its conformation, and following ubiquitination, the IκBα subunit releases from the NF-κB dimer and is degraded by proteases. The freed "active" NF-κB dimer is then capable of being transported into the nucleus where it can recruit other transcription factors and promote gene transcription. Figure 15 shows a simplified version of this canonical pathway for NF-κB activation.

Phosphorylation of IκBα (and the subsequent release of active NF-κB) is controlled by another phosphorylating protein called IκB kinase (IKK). This kinase is made of three different peptide subunits: IKKα, IKKβ, and the controlling subunit IKKγ (or NEMO, NF-κB essential modulator). Secondary signals, mostly received through receptor-mediated interactions from outside the cell (signals such as TNF-α, IL-6, IL-1β, molecular patterns that trigger various pattern recognition receptors, T-cell receptor interaction with antigen, etc.) are transmitted to the IKK protein through one of several members of the TNF receptor associated factor (TRAF) protein family. Most of the botanical anti-inflammatory agents that are listed later in this section act as inhibitors of NF-κB activation by interacting with one or more of the steps between receptor activation and the release of active NF-κB.[6,7]

Each of the activation pathways shown in Figure 15 includes other proteins (not shown in the figure) that help control this signaling pathway or act as secondary signals for related pathways. One of the most potent set of signals activating the NF-κB pathway within (mostly) innate immune cells are those that trigger pattern recognition receptors (PRRs). These receptors (e.g., toll-like receptors) bind a variety of molecular patterns from pathogens,

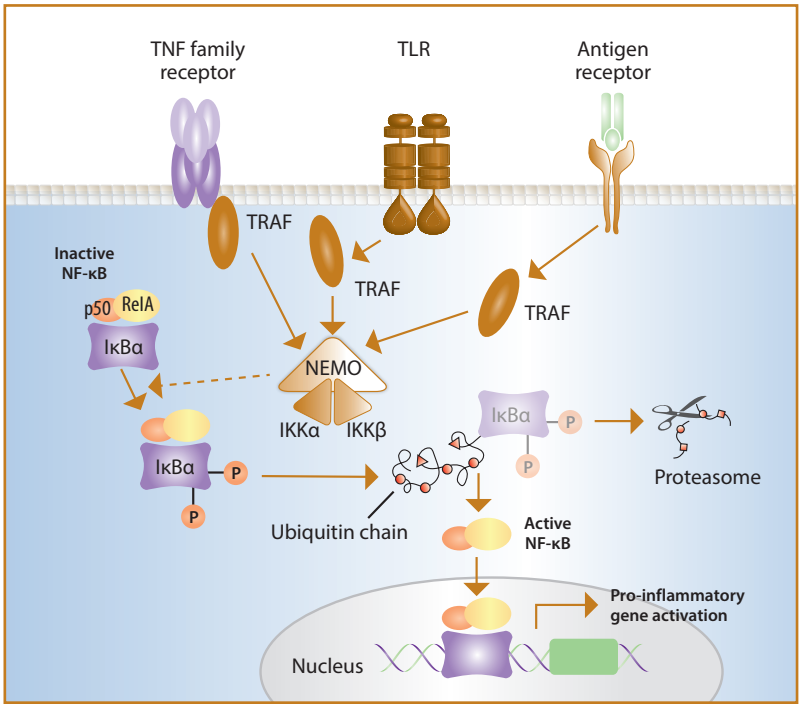

Figure 15: NF-κB Inflammatory Signaling. This shows the canonical pathway for NF-κB signaling, showing three different cell surface triggering possibilities. See the surrounding text for a full explanation of the process that releases NF-κB to drive inflammation.

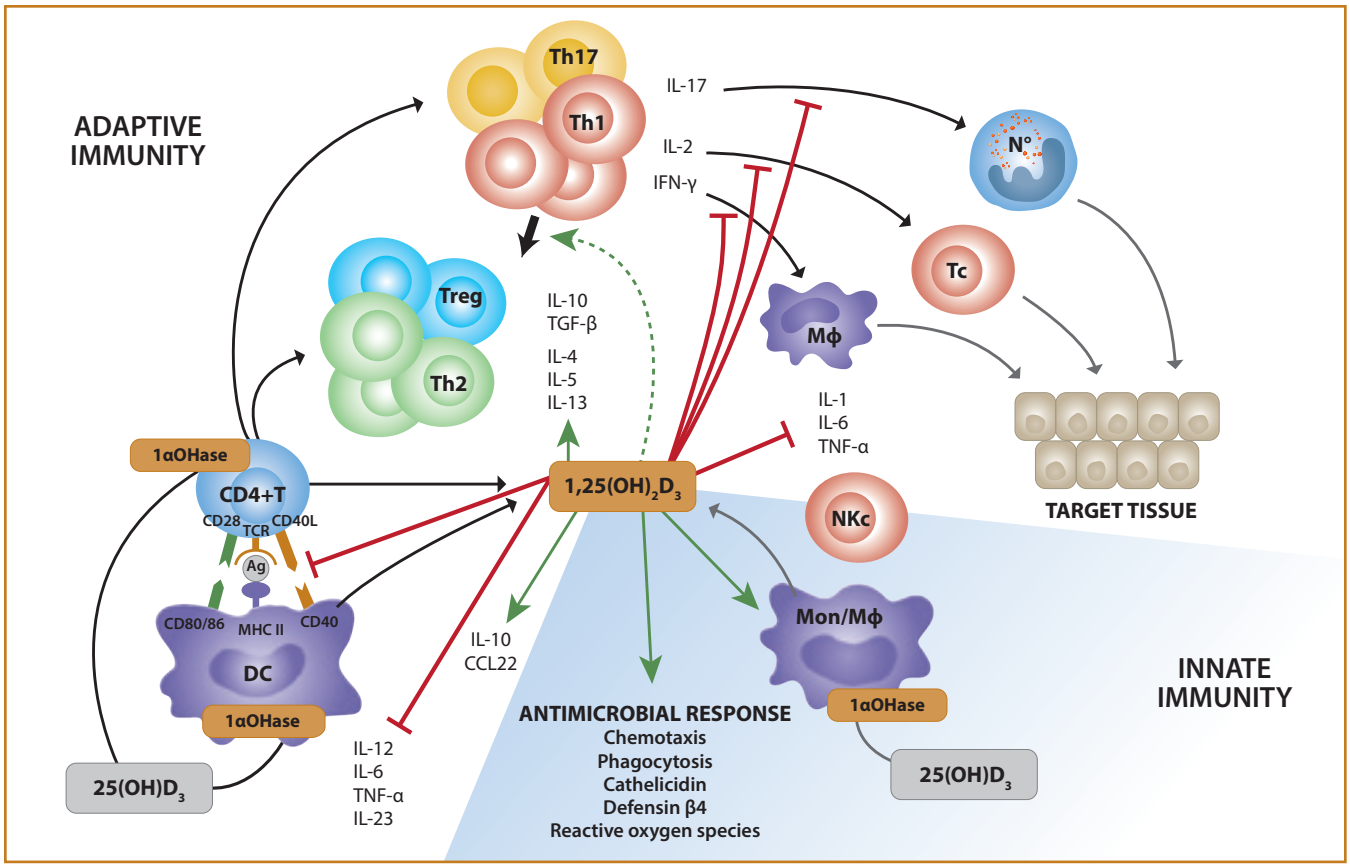

Figure 26: The Immunomodulatory Effects of Vitamin D3. 1,25(OH)2D3 targets different components of the innate and adaptive immune system. 1,25(OH)2D3 stimulates innate immune responses by enhancing the chemotactic and phagocytotic responses of macrophages as well as the production of antimicrobial proteins such as cathelicidin. On the other hand, 1,25(OH)2D3 also modulates adaptive immunity. At the level of the APC (like the DC), 1,25(OH)2D3 inhibits the surface expression of MHC-II-complexed antigen and of co-stimulatory molecules, in addition to production of the cytokines IL-12 and IL-23, shifting T-cells from a Th1 and Th17 phenotype towards a Th2 phenotype. In addition, 1,25(OH)2D3 directly affects T-cell responses, by inhibiting the production of Th1 cytokines (IL-2 and IFN-γ) and Th17 cytokines (IL-17 and IL-21), and by stimulating Th2 cytokine production (IL-4). 1,25(OH)2D3 favors Treg cell development via modulation of DCs and by directly targeting T-cells. Finally, 1,25(OH)2D3 blocks plasma cell differentiation, IgG and IgM production and B-cell proliferation. Adapted from *IBMS BoneKEy* (2011) 8, 178–186.

are many, though mostly as a modulator of proper gene expression through zinc-finger proteins.[64] Zinc deficiency suppresses thymic function, T lymphocyte development, T-cell dependent B-cell function, and macrophage activity.[65] Since there is no body store for zinc, constant intake through diet and supplementation is required to maintain adequate zinc levels.

Results from clinical trials using various doses and forms of zinc for the reduction of colds or related symptoms have been mixed.[66,67] Some reviews have suggested lozenges and nasal gels are able to directly inhibit rhinovirus attachment, although these studies have not always shown statistically significant results. As with other nutrients studied, supplementation of zinc alone is often inadequate to alter measurable clinical outcomes in otherwise healthy patients. However, when zinc status is compromised (inflammatory bowel disorders, anorexia nervosa, obesity) in the elderly[68,69] or in individuals with immune-related diseases such as HIV or chronic fatigue syndrome,[70,71] zinc supplementation has a more profound clinical effect. While clinical trial data is limited, many predict that zinc (status or intake) can influence outcomes in subjects with acute SARS-CoV-2 infections based on observational and mechanistic data.[72,73]

Antioxidants and Micronutrients for Mitochondrial Support

By virtue of their essential nature, all vitamins and minerals are needed to optimize immune cell functions. Therefore, any major micronutrient deficiency can lead to poor immune function and increase the risk for acute or chronic immune-related conditions. One common feature amongst the micronutrients with known immunomodulatory activity is their antioxidant and mitochondrial-supporting activities. Like vitamin C, zinc and carotenoids, many other antioxidant vitamins, minerals and nutrients have documented impact on the immune system and provide

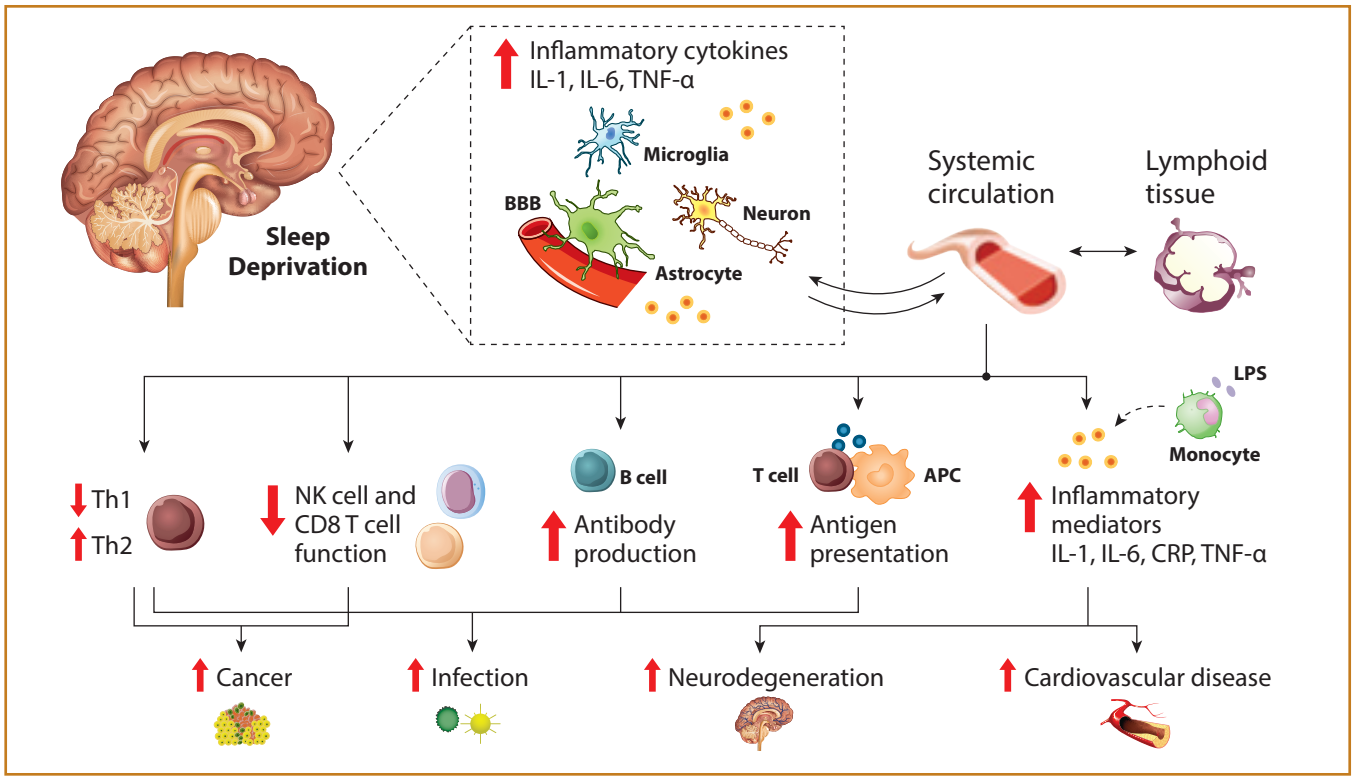

Figure 30: The Effects of Sleep Deprivation on Immune Dysfunction. Sleep deprivation, as induced experimentally or in the context of habitual short sleep, has been found to be associated with alterations in the circulating numbers and/or activity of total leukocytes and specific cell subsets, elevation of systemic and tissue (e.g., brain) pro-inflammatory markers including cytokines (e.g., interleukins [IL], tumor necrosis factor [TNF]-α), chemokines and acute phase proteins (such as C reactive Protein [CRP]), altered antigen presentation (reduced dendritic cells, altered pattern of activating cytokines, etc.), lowered Th1 response, higher Th2 response, and reduced antibody production. Furthermore, altered monocytes responsiveness to immunological challenges such as lipopolysaccharide (LPS) may contribute to sleep deprivation-associated immune modulation. Hypothesized links between immune dysregulation by sleep deprivation and the risk for immune-related diseases, such as infectious, cardiovascular, metabolic, and neurodegenerative and neoplastic diseases, are shown. Figure adapted from: Garbarino, S., Lanteri, P., Bragazzi, N.L. *et al.* Role of sleep deprivation in immune-related disease risk and outcomes. *Commun Biol* 4, 1304 (2021).

The immediate consequence of proinflammatory mediators is an increase in cortisol, a strong immune suppressor; however, chronic increases in inflammatory mediators lead to an adaptive downregulation of cortisol production, allowing for inflammatory-mediated progression of chronic disease (immune, metabolic, neurological, etc.).[125] Since sleep itself is a progressive process occurring in several stages and cycles, sleep disruptions or shortened sleep time can prevent the signals that reset metabolic processes, restore immune function, and improve memory consolidation.

Patients should be asked about their sleep habits, and their sleeping partner's habits, and whether they have had a past history of sleep loss (years of late-night studying, shift work, insomnia, etc.). Sleep studies to investigate sleep apnea may be needed.[126] Patients should be strongly encouraged to adjust their life and work habits to accommodate a minimum of seven hours of continuous sleep (in bed for 7.5 hours), especially when they have a chronic or immune-related disorder. Patients with autoimmune conditions should be particularly careful to ensure appropriate time and timing of sleep is maintained.

2. **Circadian disruptors** are those factors that create acute or chronic shifts in the body's circadian rhythm (circadian desynchronization). For today's patient, this usually comes in the form of acute jet lag, social jet lag, or shift work (second shift, third shift, changing shifts), all of which have been shown to have a range of negative physiological consequences, especially immune dysregulation.[127,128,129] While jetlag may be unavoidable, patients with jobs requiring frequent travel across multiple time zones should consider the impact of this travel on their overall health. The best remedies to resync the circadian cycle after jetlag, depending on the length of time spent in the new time zone, are exposure to sunlight and melatonin therapy (for an overview of the use of melatonin supplementation for immune-regulating and anti-inflammatory purposes, please see page 108).

Non-Pharmacological Immune-Modulating Agents

When most people think of non-pharmacological immune-enhancing or immune-modulating therapies, they most often have in mind some sort of product that is delivered in a capsule, tablet, or powder; or ingredients that can be added to boiling water to be made into a tea or soup. These can include vitamins, minerals, herbs, botanical extracts, fatty acids, mushrooms or other fugal products, and a variety of animal-derived products such as glandular extracts, colostrum and concentrated immunoglobulins. If we were to explore the many traditional medicinal practices around the world, our list of potential therapies would fill another volume as large as this entire Road map. Here, we overview the most common non-pharmacological agents used in the U.S., by those practicing an integrative/functional approach to Western medicine. Note that our discussion of diet, vitamins, minerals and fatty acids is discussed starting on page 80, mushroom and fungal products on page 120, and probiotics on page 114.

Immunomodulatory Herbs & Botanical Extracts

The use of herbs and botanical extracts for immune enhancement has ancient roots in nearly every culture across the globe. For some cultures, this is still the primary medicinal choice for prevention and treatment of common illnesses. Even in the West, where pharmaceutical drugs have dominated the medical landscape, the use of herbal therapies is still popular. Many of these herbs and botanical extracts have been studied using modern research techniques—methods that are not always suitable to describe the historical benefits seen with these compounds. Even so, we have learned surprising things about the mechanisms and clinical efficacy of many traditional herbal preparations, though some clinical trials have had less than favorable outcomes. Listed here are the herbs and botanical extracts most commonly used for immune-modulation in the United States.

Echinacea

Products containing various forms of Echinacea are among the top-selling herbal preparations every year in the United States. These products are consumed most often to prevent or treat common illnesses, especially for cold and flu prevention.[1] The general term Echinacea describes preparations of three species of purple coneflowers: *E. purpurea*, *E. angustifolia* and *E. pallida*. The roots and rhizomes of each species are used for medicinal purposes, while the whole plant (flower, leaf and root) is used in the case of *E. purpurea*. Dried roots, liquid extracts, tinctures, dried extracts and standardized extract preparations of each species are available as single-ingredient preparations or mixed with other herbs, vitamins or nutrients.

The constituents with potential immunomodulatory activity within Echinacea species are many, including arabinogalactan polysaccharides, alkamides, caffeic acid esters, echinacoside (not in *E. purpurea*), volatile oils, polyacetylenes and flavonoids.[2] Rather than a single active component, most researchers consider Echinacea's activities to be derived from a combination of these constituents. Various preparations and components of *E. purpurea* have been shown to stimulate macrophage activation, a key initiator of the immune response, as well as NK cell activity in both human and animal models.[3-7] These activities, in many cases, are linked directly to increased cytokine expression.[8,9] Preparations of *E. purpurea* root appear to modulate antigen presenting cells and T-reg cells.[10] Other Echinacea preparations also show limited antiviral,[11] antifungal[12,13] and antibacterial activities.[14]

Clinical trials involving preparations of Echinacea have been frequently performed and numerous reviews are available.[1] Comparing these trials with one another is difficult because most study designs differ in the type, dose and method of delivery of the Echinacea preparations; in addition to the length of the study and the primary outcome (prophylaxis vs. treatment). The most common studies are for the prevention or treatment of upper respiratory tract infections where Echinacea preparations have been shown to reduce the frequency, severity and/or duration of common cold symptoms in several trials, particularly in children.[15] One study showed *E. purpurea* attenuated

Probiotics and Related Therapeutics

Therapies designed to promote a healthy gastrointestinal microbiota are fundamental to promoting a healthy immune system, as we have already described early in this Road map (see page 39). In general, these therapies include dietary changes designed to promote a commensal-friendly environment, the avoidance of drugs that promote dysbiosis (i.e., PPIs, laxatives, antibiotics) and supplementation of probiotics, prebiotics or postbiotics. In this section we will outline the practical definitions and therapeutic uses of these supplement ingredients, while pointing to mechanisms by which probiotic supplementation might modulate immune functions.

Diet and the Microbiome

An individual's diet (historical and current) is likely the single greatest influence on the gut microbiome, as it serves as both a source of inoculation of microbes and provides the nutrients upon which the resident commensal organisms feed. For example, research looking at diverse dietary patterns has revealed significant differences in the gut microbiota from vegetarians compared to meat-eaters, Western urban children vs. rural African children, and a range of elderly subjects consuming different dietary patterns over time.[1,2] Not surprisingly, healthy dietary patterns like the Mediterranean diet have been shown to be associated with a more diverse and healthy gut microbiota, compared to standard unhealthy Western dietary patterns.[3]

To investigate the adaptability of the microbiota to changes in dietary patterns, researchers at Harvard University analyzed the fecal microbiota of individuals when shifted between an exclusively plant-based diet to an exclusively animal-based diet.[4] They found the microbiota pattern was noticeably shifted shortly after changing diets in a similar and predictable manner in multiple subjects (N = 11). This suggests the microbiota within the gut can adapt to changing nutrient availability and can do so quite rapidly (within days). Clinicians should be aware of this adaptability when they are using dietary interventions while also performing stool microbiota analysis to understand a patient's health.

There are several components of the diet that appear to have the greatest influence on the species diversity and abundance of the gut microbiota (at least as measured by fecal metagenomics).[5] Most of the population research has focused on macronutrient content (especially the diversity and complexity of the carbohydrate components), and phytonutrient diversity, though individuals consuming foods that radically alter bowel transit time or that cause a major inflammatory response will also experience an altered gut microbiota.

Carbohydrates, Fiber and Prebiotics

Overall, carbohydrates are the principal energy source for a majority of the gut microbiota. Individuals who consume a more diverse diet, including high amounts of dietary fiber and complex carbohydrates, typically have a more diverse (and healthy) gut microbiota.[6] An analysis of the data collected by the American Gut Project found that the self-reported number of unique plant species consumed by individuals was more predictive of microbial diversity compared to individuals self-identifying as vegan or omnivore.[7] This relationship is perhaps not surprising given the diverse array of fiber compounds (e.g., pectins, cellulose, hemicelluloses, gums, fructans, etc.) found in various plants. Fiber is a heterogeneous category of dietary compounds that vary greatly in their molecular structures (e.g., polymer chain length, branching, etc.); this heterogeneity in molecular structure gives rise to fiber's diverse properties (e.g., solubility, fermentability, digestibility, etc.) and consequent physiological effects.[8,9,10] The human host has a limited enzymatic capacity to hydrolyze fiber's chemical linkages; however, commensal bacteria within the gut microbiota have a wide variety of enzymes (e.g., glycoside hydrolases, glycosyltransferases, polysaccharide lyases, carbohydrate esterases, etc.) able to use different linkages within fiber molecules as substrates for metabolism and proliferation.[10] Therefore, consuming a diet diverse in plant species leads to an increase in the heterogeneity of fiber compounds available for the commensal gut microbiome to hydrolyze as substrates for growth, in turn supporting a more diverse gut microbiome.

The chaga mushroom produces a diverse range of secondary metabolites including lignins, phenolic compounds, melanins and lanostane-type triterpenoids; and because chaga is parasitic on birch trees, it contains large amounts of betulin or betulinic acid, a natural substance studied for its anticancer properties.[11] More recently, there has been discussion of utilizing the bioactive polysaccharides found in chaga mushroom in health products such as yogurt to enhance immunity.[12] Caterpillar mushroom, (*Cordyceps sinensis* [Berk.] Sacc) contains cordycepin, an adenosine-derivative with immunoregulatory activity.[13]

β-Glucans from Yeast Extracts

Like several mushroom species, certain yeasts produce complex carbohydrate moieties that can stimulate immune-cell function. Yeast β-glucans have a β (1,3) backbone with a β (1,6)-linked β (1,3) branches. The distribution and length of the various side chains differ depending on the growth conditions and method of isolation. Extraction and purification processes also drastically influence the glucan properties. These different extraction and purification procedures have led to the availability of several commercial preparations of yeast β-glucans with different applications. Like many mushroom β-glucans, yeast β-glucans have immunomodulating effects when taken up by immune cells or by cross-linking with dectin-1 receptors on innate immune cells.[14] Clinical trials on commercial preparation (250 mg/day) have been shown to alter cytokine profiles, reduce the incidence of upper-respiratory infections,[15,16] and improve immune function after strenuous exercise.[17] More recently, a 2021 systematic review and meta-analysis

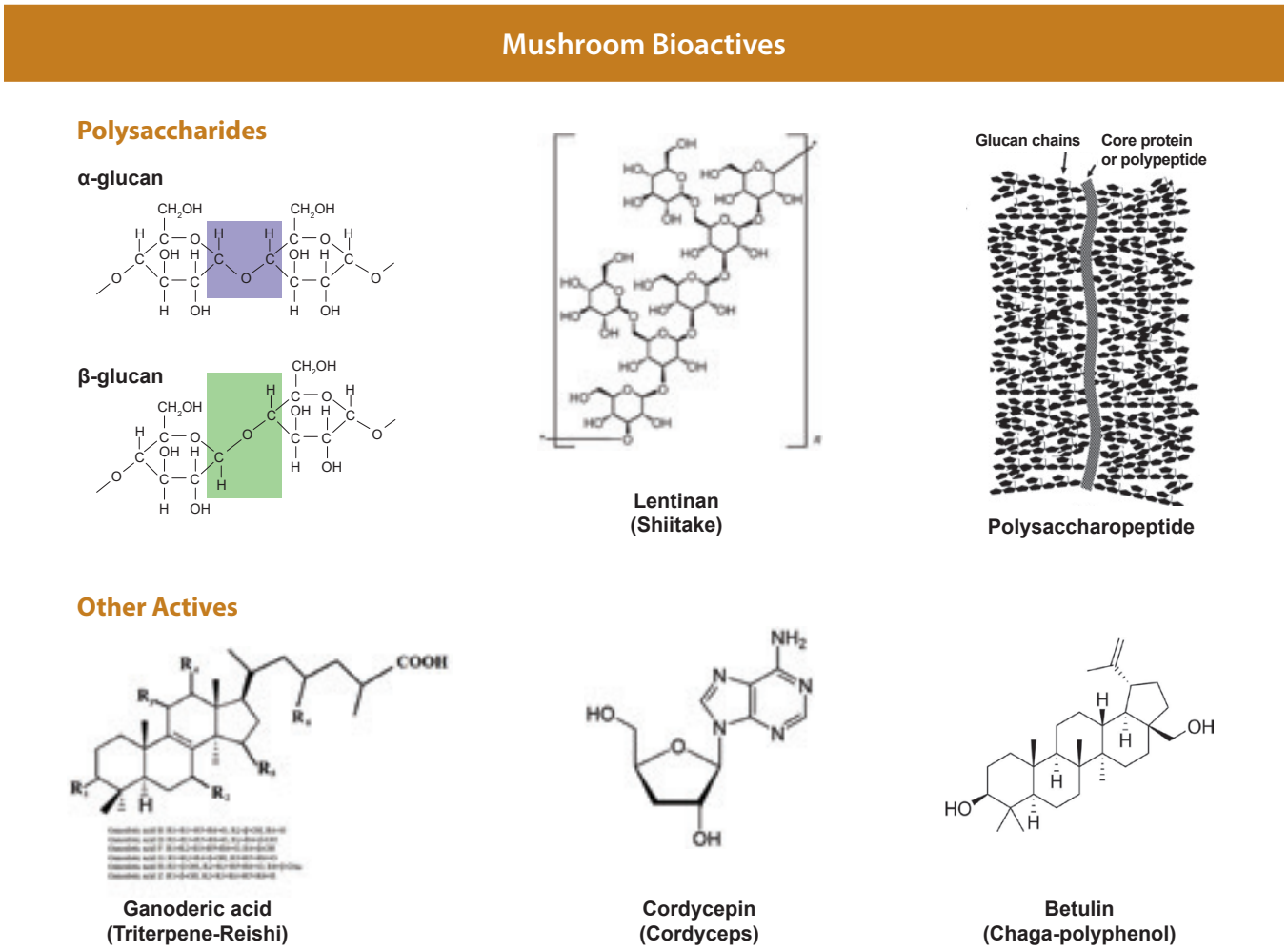

Figure 34: Mushroom Bioactive Compounds and Glucan Molecular Structures.

Candida Overgrowth in the GI Tract and Beyond

Candidiasis is the term used to describe an overgrowth of the yeast *Candida albicans* and similar species (*C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei*) in the GI tract or other mucosal tissues.[1,2] *Candida* is a normal inhabitant of the GI tract in humans, as well as the mucus membranes of other orifices, such as the mouth, nose and vagina, where it is often deemed a commensal organism.[3] In fact, *Candida* species are the dominant genera within the human mycobiome.[4,5,6]

When *Candida* grows as a single-celled "yeast" organism, it is generally not considered to be a pathogen. However, when *Candida* undergoes a phenotypic switch to its sessile, biofilm-forming hyphae form, it is considered a pathogen and difficult to remove.[7,8] Though these features are not necessary for invasive behavior, and *Candida* biofilm have not yet been demonstrated in the GI tract, agents that inhibit this phenotypic switch are considered important for inhibiting *Candida* overgrowth outside the GI tract (e.g., mouth, vagina) and especially on implanted devices.[9,10]

During times of immune suppression/compromise, critical illness or GI microbiota disruption (i.e., antibiotic use) *Candida* can become an opportunistic pathogen as the yeast alters its invasive characteristics and migrates from the GI tract to colonize other tissues.[11,12] In fact, a rise in candidiasis and other invasive fungal infections has even been reported during the outbreak of Covid-19.[13] The oldest description of a *Candida* infection is oral thrush, which is common in immune-compromised individuals.[14] Recurrent vulvovaginal candidiasis is experienced by millions of women worldwide, and along with thrush, is the most common form of extra-gastrointestinal complication seen by the clinician.[15] Candidemia, the invasion of live *Candida* in the blood or other tissue, is rare, severe and should result in immediate hospitalization (although the patient is likely to already be hospitalized as this is frequently a nosocomial infection).[16] Finally, *Candida* is often found on dental devices (e.g., dentures, implants) or other implants within the gastrointestinal, genitourinary tract or elsewhere, often resulting in continued re-infections in individuals treated for *Candida* overgrowth (some of these can be serious candidemia when involving cardiovascular implants).[17,18]

Candida overgrowth is commonly related to the following:

- Antibiotic use, either long-term use (acne, otitis media, sinusitis, etc.) or short-term, high-dose use (surgery, UTI, etc.).[19,20,21,22]
- High consumption of sugars, white flour, pastries, etc., are assumed to increase the growth of *Candida* in the GI tract and mouth. These assumptions are based on *Candida*'s use of simple sugars as an energy source, though studies examining the effect of *Candida* growth following increased sugar intake have had equivocal results.[23,24]
- Compromised immune system (HIV/AIDS, organ transplant, chemotherapy)[25]
- Chronic HPA axis activation/stress (which suppresses the immune system)[26,27]
- *Clostridium difficile* infection[28]
- Inflammatory bowel disease[29,30,31]

Diagnosing GI Overgrowth of *Candida*

While oral or vaginal *Candida* overgrowth is common and fairly easy to diagnose, *Candida* overgrowth within the GI tract often goes unrecognized or is attributed to other causes, some of which may be concomitant with *Candida* overgrowth, including dyspepsia (gas, bloating), bacterial dysbiosis, small intestinal bacterial overgrowth (SIBO) or

- Rheumatoid factor (RF): 70% specific and sensitive for rheumatoid arthritis; may also be found in other connective-tissue conditions such as SLE or scleroderma.[9]
- Anti-CCP (cyclic-citrullinated protein) antibodies: the presence of serum anti-CCP antibodies is approximately 95% specific for the diagnosis of RA, with a sensitivity similar to that of RF.[10]
- Antineutrophil cytoplasmic antibody (ANCA): react with cytoplasmic granules of neutrophils and is helpful to diagnose ANCA-associated vasculitis syndromes. Cytoplasmic ANCA (cANCA) is seen in patients with Wegener granulomatosis, Churg-Strauss syndrome and microscopic polyangiitis; while perinuclear ANCA (pANCA) is observed in patients with SLE and RA.[11]
- Anti-Nuclear Antibodies (ANA): describes a wide range of antibodies to nuclear components (see Table 5). These antibodies are most common for their association with SLE (where they show >95% sensitivity and 60% specificity), but they are also common in most other autoimmune conditions.[12]

Table 6: Summary of the Major Associations within the HLA Class II and Class I Region with Common Autoimmune Diseases

HLA Class II Effects		AUTOIMMUNE DISEASE	HLA Class I Effects	
Predisposing	Protective		Predisposing	Protective
?	?	Ankylosing Spondylitis	B*2701 B*2704 B*2705	B*2706 B*2709
DR3 DRB1*08	DR7	Graves' Disease	C*07 B*08	C*16 C*03 B*44
DR4 DR3	DR7	Hashimoto's Thyroiditis	?	?
DR3	?	Myasthenia Gravis	?	?
DR3	?	Addison's Disease	?	?
Shared epitope = DRB1*0101 DRB1*0102 DRB1*0401 DRB1*0404 DRB1*0405 DRB1*0408 DRB1*1001 DRB1*1402	DRB1*0103 DRB1*07 DRB1*1201 DRB1*1301 DRB1*1501	Rheumatoid Arthritis	?	?
DQ2 DQ8	?	Celiac Disease	?	?
DR15	DR14	Multiple Sclerosis	C*05 C*15	C*01
DR3 DR4 DQB1 position β57	DR15 DR14	Type 1 Diabetes	B*39 B*18 A*24	A*01 A*11 A*31
DR3 DR8 DR15	?	Systemic Lupus Erythematosus	?	?

Both allelic and haplotype associations have been shown. ? = Further studies needed to determine association. DR3 = DRB1*03-DQB1*02-DQA1*0501, DR4 = DRB1*04-DQB1*0302-DQA1*0301, DR7 = DRBI*07-DQB1*02-DQA1*02, DR14 = DRB1*14-DQB1*06-DQA1*0102, DR15 = DRB1*15-DQB1*06-DQA1*01, DQ8 = DQB1*0302 and DQ2 = DQB1*0201. Data summarized by Gough SC, Simmonds MJ. The HLA Region and Autoimmune Disease: Associations and Mechanisms of Action. *Curr Genomics*. 2007 Nov;8(7):453-65.

A Balanced and Evidence-Based Approach

The immune system is a sophisticated surveillance network which functions to protect us from a myriad of potentially harmful threats, often with an efficiency that goes unnoticed. However, if invading organisms or rogue cells get the upper hand, or the immune system begins to mistakenly target our own healthy tissues, signs and symptoms are soon to follow. It is these challenges to the immune system that result in a large number of hospital and physician visits, often resulting in a prescription designed to kill the invading organism or mitigate the damage to tissues caused by inflammation. Not surprisingly, assessing and supporting the functions of the immune system, or providing remedies to increase someone's ability to prevent or shorten an illness, are hallmarks of the art of medicine from ancient times to the present day. While often successful, these remedies were given with little knowledge of either the immune system or the disease processes driving the visible symptoms.

This Road map is not designed to replace the latest immunology textbooks; it would be much heavier (and expensive) if that were the case. Instead, our aim is to overview some of the important features and mechanisms within the immune system which are the best targets for lifestyle and non-pharmacological interventions- many of which have proven to reduce chronic disease through immune-related pathways. While Dr. Guilliams earned his Ph.D. in molecular immunology, he spent the past 25 years in the integrative medicine and natural products arenas. Here he merges these two disciplines in a way that can be leveraged by all healthcare providers regardless of their previous knowledge of immunology.

This Roadmap is intended to be an indispensable resource for anyone making nutrient-based or dietary supplement recommendations within a healthcare setting:

- **Clinicians**
- **Pharmacists**
- **Nutritionists**
- **Dietitians**
- **Nurses/Nurse Practitioners**
- **Medical Technicians**
- **Nutritional Researchers and Educators**
- **Health Coaches**
- **Medical/Health Journalists and Writers**
- **Students of Health Professions**
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Thomas G. Guilliams Ph.D. earned his doctorate from the Medical College of Wisconsin (Milwaukee), where he studied molecular immunology in the Microbiology Department. Since 1996, he has spent his time studying the mechanisms and actions of natural-based therapies, and is an expert in the therapeutic use of nutritional supplements. As the Vice President of Scientific Affairs at Ortho Molecular Products for 24 years, he worked with thousands of integrative and functional medicine clinicians, and developed a wide array of products and programs that allow clinicians to use nutritional supplements and lifestyle interventions as safe, evidence-based, and effective tools for a variety of patients. Tom teaches at the University of Wisconsin- Madison School of Pharmacy, where he holds an appointment as an Adjunct Asst. Professor, and at the University of Minnesota School of Pharmacy. He lives outside of Stevens Point, Wisconsin with his wife and children.

Dr. Guilliams' other writings can be found at The Point Institute www.pointinstitute.org

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