

Chapter 1
**Epigenetics and Immunosenescence Reversal:
An Evidence-Based Longevity Paradigm**

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ABSTRACT

Humankind has long thought of aging as a gradual, time-dependent, deterioration in one's well-being and quality of life, with an increased incidence and severity of debilitating chronic diseases. However, current medical opinion argues for a fresh, and more enlightened perspective on aging.

Indeed, until recently, clinical medicine has focused more upon mitigating the effects of aging rather than reversing the process itself. However, current developments in epigenetics and immunology mean that we are now ready to begin the greater challenge of halting or reversing the aging process.

There is a vast body of scientific literature indicating that immune dysregulation – specifically of the innate immune system – may be the determinative factor for the seemingly inevitable functional decline of advancing age. This dysregulation is characterized by a continual, low-grade, over-reactive state of systemic immune processes, which promote, in whole or in part, the pathognomonic signs of many of the chronic diseases that we associate with aging (e.g., cardiovascular disease, Alzheimer's disease, cancer, osteoarthritis, insulin-resistance, and diabetes).

INTRODUCTION – IMMUNITY AGAINST AGING

What is aging? Is aging inevitable? Is aging a scientific fact, a statistical tendency, or simply a widely-accepted belief? Is aging a natural function of human life and physiology, or is it a condition brought on by a disorder in human lifestyle and physiology?

If aging is truly a process that is primarily governed by genetics and the linear passage of time, then should it not be a common and prevalent occurrence for identical twins – humans of identical chronological age that are considered to possess identical genetics – to die on the same day, only minutes of hours apart?

What is termed 'aging' is typically defined as the gradual decline in one's well-being and quality of life, characterized by an increased incidence and severity of debilitating chronic diseases. However, the current scientific literature in immunity and aging, epigenetics, and neuropsychology have built a body of evidence which suggests that human immune system dysregulation – termed "immunosenescence" – to be the pathophysiologic common factor in the majority of the diseases and disorders that are deemed to be age-related. Our current laboratory and clinical research is in concordance with this literature, and has led us to glean the basis of a novel, evidence-based anti-aging paradigm:

1. Aging is a non-linear, experience-dependent process, not a linear time-dependent process.
2. Although genetics do play a role in aging, epigenetic dynamism and lifestyle are of greater importance.
3. Aging is a multifactorial clinical syndrome primarily resulting from progressive immunosenescence.
4. Persistent reversal of immunosenescence through use of Allotypic Immunomodulator (AIM) methods may be the simplest common factor to solve the healthful longevity equation.

Thus, by using safe, non-toxic, immunorestorative agents of a suitable mode of action, it should, in theory, be possible to effectively impact the aging process and its epigenetic errors. By restoring optimal immune function, we can positively impact upon human longevity by effectively immunizing ourselves against aging itself.

EPIGENETICS, IMMUNOSENESCENCE, AND DISEASE

Epigenetics

Epigenetics is the study of dynamic heredity beyond the traditional paradigm of DNA sequence-related characteristics established at conception. It has now become established at the epicenter of modern medicine due to its proven potential to explain the complex relationship between genetics, the environment, lifestyle, aging, and disease.¹

What can be termed “aging epigenetics” is an aspect of an emerging paradigmatic shift in how aging is being understood, and how it will be approached in the near future. Epigenetic modifications – including DNA methylation and histone modification – are effected by lifestyle factors (e.g., diet) and are found to be altered in the aging process, thus giving rise to diseases associated with aging. Epigenetic differences have been found in studies of monozygotic twins, and gene expression studies have shown that genetic variation between twin pairs increases as they age.^{2,3}

Epigenetic alterations of considerable functional and biological significance accumulate during the process of aging, and these alterations are important contributors in pathways of oncogenesis. DNA methylation global loss and the hypermethylation of promoter sequences in genes involved in both tumor suppression and progeria (Hutchinson-Gilford Progeria Syndrome) are of central importance in both aging and cancer.⁴

Immunosenescence

The condition of decline in immune function associated with increasing age is referred to as immunosenescence in the literature by many thought leaders.⁵ Immunosenescence is an insidious process which leads to: tissue damage secondary to chronic inflammation, impaired responses to antigen exposure, an increase in the rates of infectious disease morbidity and mortality (e.g., herpes zoster and *Mycobacterium tuberculosis*), and autoimmune disorders.⁵⁻⁸

The phenomenon of immunosenescence involves characteristic transformations in the immune system, mainly expressed as a decrease in cellular functions. Quite surprisingly, these changes are typically of early onset, progressing further as an adult advances in age. Individual immune status can be further depressed by the adverse effects of a number of lifestyle and environmental factors, including: stress, inadequate sleep, poor nutrition and gastrointestinal function, and toxic chemical and radiation exposure (including chemotherapy and radiation therapy).

Immunosenescence also appears to be directly associated with the phenomenon of age-related telomere shortening, which is known to reduce cellular proliferative capacity in the immune system in general, and of natural killer (NK and NKT) cells in particular.⁹

Natural Killer Cells

NK and NKT cells provide early defense against the propagation of cancer and viral infections, and are an important component of the innate immune system.^{10,11} Immunohistologically, NK cells are defined as cytotoxic immune cells expressing the CD16 Fc receptor site and the CD56 NK receptor, but lacking a CD3/T-cell receptor complex (i.e., CD3-CD16+CD56+). Functionally, they are immune cells that do not require major histocompatibility complex (MHC) recognition.

Human NK cells may be divided into two distinct subpopulations based on their respective CD56 cell surface receptor densities: CD56dim and CD56bright NK cells.¹² CD56dim cells make up roughly 90% of all CD56 positive NK cells, and effect cytotoxicity via the release of perforins and granzymes. CD56dim cells can also bind to target cells forming conjugates. CD56bright cells differ from CD56dim cells in that they are involved in cytokine secretion (interleukin-10 (IL-10), interleukin-13 (IL-13), interferon-gamma (IFN- γ), tumor necrosis factor-beta (TNF- β), and granulocyte-macrophage colony-stimulating factor (GM-CSF)) with the purpose of innate immune response regulation.¹³ During dormancy, CD56bright NK cells tend to be less cytotoxic than their CD56dim counterparts.

Immunosenescence affects NK cells, NKT cells, and phagocytic cells, in several ways, with the end result being intrinsic impairment and diminished cell counts. Studies show a comparatively weakened response to interleukin 2 (IL-2) in NK cells from adult donors of advanced age, as well as a shrunken NKT cell population displaying altered lymphokine production.^{14,15} Due to the essential immunoregulatory role of NK and NKT cells, their impairment and diminution has a profoundly negative effect on the aging adult immune response.

Anti-cancer immunity functional activity studies performed on adult donors of advanced age have further shown a diminished NK cell cytotoxicity against K562 tumor cells.¹⁶ Additionally, adults of advanced age with relative NK cell depression demonstrate a tripled 2-year mortality risk in comparison to subjects with adequate NK cell levels.¹⁷ Alternatively, studies of centenarians, postulated as exemplary models of healthy adult aging, reveal well preserved NK cell cytotoxic function.¹⁸ It is thus reasonable to consider that the clinical manifestations attributed to aging could result from the observed alterations in NK-cell number and function central to the immunosenescence model.

Coronary Heart Disease

Viral and bacterial infections have been indicated as a risk factor for coronary heart disease (CHD). This is of specific concern in the setting of the chronic inflammation induced by persistent, low-grade infection. In the particular case of elderly adults, NK cells are seen as being the primary pathway of antiviral defense.¹⁸ Thus, NK cells, as a first line of defense against those infections, might therefore play a role in offsetting CHD development.

A recent study has demonstrated a specific association between CHD and general NK cell impairment, showing lower NK cytotoxic activity in CHD patients as compared to age-matched healthy controls.¹⁹ Trial findings showed CHD patients to have a significantly lower total NK cell count and proportion, and particular reduction of the more cytotoxic CD56dim cell subpopulation. The percentage of NK cells identified as regulatory CD56bright cells was also lower in the CHD patients, although not at a statistically significant level. As a marker of the level of NK cell activation, the production of intracellular IFN- γ in CD3-CD56+ NK cells was found to be slightly lower in CHD patients as well.

Obesity/Metabolic Syndrome & Non-Insulin-Dependent Diabetes Mellitus

Obesity is a condition prodromal to CHD, metabolic syndrome, and non-insulin-dependent diabetes mellitus (NIDDM), and is characterized by a generalized pro-inflammatory state. Pathophysiologically, it is notable for: reduced levels of ghrelin (an appetite-stimulating peptide hormone with anti-inflammatory properties) and increased levels of leptin (an appetite-suppressing peptide hormone). This leads to leptin resistance, a heightened release of pro-inflammatory cytokines (including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α)) and of the inflammatory marker C-reactive protein (CRP).

The shift in the balance of ghrelin and leptin also disrupts their delicate positive and negative feedback control over neuropeptide Y (NPY) activity. NPY, ghrelin, and leptin all play a major role in the regulation of humoral and cellular immune activity, and their collective imbalance promotes an inhibition of apoptotic behavior in lymphocytes, suppression of NK cell activity inhibition, and oxidative stress in the form of superoxide anion production in macrophages.²⁰⁻²²

Cancer

Presently, there is a clear and urgent concern in the area of advanced adult oncology, given that the adult population is rapidly growing and advancing in age, concurrent with its meteoric rise in the frequency of obesity. The global incidence of cancer is trending strongly upward, and for many types of cancer there are still no reliably effective medical remedies. As the number of cancer patients grows ever more rapidly, there is evident a demand for the development of deeper insights into the basic mechanisms of oncogenesis in normal healthy adults, to yield specific new clinical strategies for the prevention, detection, and cure of cancer in the aging adult population.

At the leading edge of clinical and research oncology is the issue of new and growing risk factors for cancer which effect the general population. Given the aforementioned proinflammatory nature of obesity, it naturally follows that the current worldwide trend toward increasing obesity and diminished physical exertion also directly impacts upon cancer prevalence. Based upon studies performed by the International Agency for Research on Cancer, it is estimated that 25% of cancer cases worldwide may be directly attributed to obesity and sedentary lifestyle.

Despite the profound impact of obesity, the best of current scientific evidence indicates unequivocally that the single greatest risk factor for the development of cancer is that of advancing age. Specifically, the incidence of cancer increases in those adults of advanced age whom demonstrate age-dependent progressive immunosenescence.

INTERVENTION

Immunotherapy

Immunotherapy, or biologic therapy, employs substances called biological response modifiers (BRMs). The biologic therapies produced in the biotechnology and biopharmaceutical sectors –including monoclonal antibodies, interferons, interleukins, and several types of colony-stimulating factors – are primarily used in the treatment of cancer, rheumatoid arthritis, hepatitis C, and other diseases.

Side-effects caused by these types of biopharmaceutical therapies vary with the type of treatment, however common side effects include: chills, fever, loss of appetite, nausea, vomiting, and diarrhea. Depending on the severity of these problems, patients may find their health further compromised, frequently requiring hospitalization during, or as a result of their treatment.

One class of BRMs is referred to as immunomodulators. Pharmaceutical and biopharmaceutical immunomodulators typically function to either upregulate (i.e., immunostimulators) or downregulate (i.e., immunosuppressants) the human immune response. Examples of immunostimulators include: isoprinosine nucleoside, GM-CSF cytokine, vaccines, and vaccine adjuvants. Examples of immunosuppressants include: corticosteroids, certain monoclonal antibodies, and drugs such as cyclosporine, azathioprine, and 6-mercaptopurine. Because immunosuppressants tend to act non-selectively, they render the immune system less able to defend against infections and malignant metastasis. Additional serious side-effects include liver and kidney damage, peptic ulceration, hypertension, hyperglycemia, and dyslipidemia.

Allotypic Immunomodulators

Many natural products and their derived compounds also function medicinally as immunomodulators, and do so effectively without the toxicity and expense associated with the BRMs produced by biotechnology and biopharmaceutical platforms. An important feature among several of the natural product immunomodulators is their tendency to demonstrate a balancing, or true immunomodulation effect, as opposed to simply upregulating or downregulating the human immune response.

A great deal of interest has been focused upon a number of bioactive polysaccharides which have shown promising utility in modifying human immune responses.²³ Clinical and laboratory studies have demonstrated activity upon both innate and adaptive immune system functions, and polysaccharide receptors have been found on several types of immune and inflammatory cells, including NK cells, T- and B-lymphocytes, macrophages, and monocytes.²⁴

Advanced research in immunotherapy is now focusing primary attention on the investigation and clinical application of isolated polysaccharides of high-specificity, which can function reliably as AIMs. Bioactive polysaccharides come from many sources – higher plants, fungi, and bacteria – and produce a diversity of molecular classes, including arabinoxylans, β -D-glucans, and proteoglycans. Among these, oligo-arabinoxylans, polysaccharide-A (PSA) and polysaccharide-K (PSK) have been studied extensively in laboratory and clinical investigations, with the most promising recent results coming from studies on purified, high-specificity, rice bran oligo-arabinoxylan compounds.

AIM anti-cancer strategies can provide a significant therapeutic advantage in combating tumorigenesis at the pre-cancer, or initiation stage, as well as the pre-clinical and clinical stages of promotion and proliferation, via their activation of NK cell cytotoxicity.

OLIGO-ARABINOXYLAN COMPOUNDS

Previous *in vitro* and *in vivo* studies have demonstrated that a purified, high-specificity, oligo-arabinoxylan AIM derived from rice bran (Rice Bran Arabinoxylan Compound® (RBAC®) modulates NK, T- and B-cell immune cell functions in a dose-dependent manner.²⁵

Incubation of peripheral blood lymphocytes (PBLs) with RBAC induced increases in NK cell cytotoxicity in PBLs showing low baseline NK cytotoxic activity, and decreased activity in PBLs with high baseline NK cytotoxic activity. In a study of its potential as a cancer immunotherapy agent, RBAC was also found to effectively sensitize human T-cell leukemia cells (HUT 78) to CD95 death receptor-induced apoptosis.²⁶

RBAC has also been shown to possess antioxidant properties as a free-radical scavenger. Research has shown that it optimizes the production of the inflammatory cytokines IFN- γ , TNF- α , and IL-6, increases nitrous oxide release, and increases the overall phagocytic activity of macrophages.²⁷⁻²⁸

Published human trial data from a rheumatoid arthritis case series in Japan demonstrated anti-inflammatory activity of RBAC in close to 50% of subjects when administered over a 6-12 month period.³⁰

Together, these findings established RBAC as a broad-spectrum immunomodulator and anti-inflammatory agent worthy of clinical investigation. The most promising indications have been in application to the management of the several aging-related diseases and disorders that are proposed to occur via an immunosenescence mechanism.

Current Pharmacologic Investigations and Clinical Applications

Our research strategy is thus one of coordinated *in vitro* and clinical studies aimed at expanding the knowledge database of oligo-arabinoxylan immunomodulatory activity. It is a widely accepted hypothesis that the persistent generation of inflammatory mediators resulting from chronic, persistent antigenic challenge could potentially trigger the onset of associated inflammatory diseases. Present areas of application are focused upon the reversal of immunosenescence as a therapeutic strategy in the aging-related conditions of CHD, metabolic syndrome / NIDDM, and cancer.

Coronary Heart Disease

As mentioned above, pathogen burden and microbial infections are now a recognized risk factor for CHD. The general NK cell activity enhancement of RBAC established its potential for direct impact on bacterial infection, and was thus investigated.

RBAC was found to enhance oxidative bursts in neutrophils and monocytes, and phagocytosis of *Escherichia coli* in a dose-dependent manner. Incubation of RBAC alone with 31 types of bacteria showed no retardation of bacterial growth, and RBAC-treated phagocytic cells in the absence of bacteria showed no oxidative bursts. These findings indicate that RBAC does not have direct antibiotic activity, but rather acts as a modulator of phagocyte function.³¹

Obesity/Metabolic Syndrome & Non-Insulin-Dependent Diabetes Mellitus

To investigate the potential of RBAC for reducing cardiovascular risk markers (inflammation, lipids, and glucose) a single-blind, pilot trial was conducted in overweight subjects with elevated baseline inflammation levels. The primary objective was to assess the efficacy of this agent on the reduction in inflammation as indicated by high-sensitivity CRP (hs-CRP) levels, an inflammation biomarker which is produced in the liver corresponding generally to elevations in IL-6.

Endpoints were measured at baseline, 7 days, 30 days, and 60 days, and preliminary data analysis revealed no significant effect on hs-CRP in the study population. This again is indicative of a primary immunomodulatory effect without evidence of the immunosuppressive effect putatively requisite to impact hs-CRP levels.

Cancer

Chronic inflammation is also an occult source of premalignant conditions which, in the presence of depressed immunity, can progress unchecked into malignancies. Some examples of this are inflammation induced by *Helicobacter pylori* leading to gastric cancer, HPV infection and inflammation leading to cervical cancer, sunburn leading to skin cancer, Barrett's esophagitis leading to esophageal cancer, and hepatitis B or C leading to hepatocellular carcinoma.

Given the previously established apoptosis-sensitizing effect of RBAC on human leukemia cells, the chemotherapy-sensitizing activity of RBAC was evaluated with human breast cancer cells (MCF-7 and HCC70 cell lines) *in vitro*. MCF-7 and HCC70 cells were cultured with daunorubicin (DNR) in the presence of varying concentrations of RBAC (100-1000 µg/ml) for 3 days.

At a concentration of 500µg/ml, RBAC significantly enhanced the accumulation of DNR in MCF-7 cells and HCC70 cells over controls as determined by flow cytometry. Using 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) to assay cancer cell elimination, RBAC effectively decreased the DNR IC50 in MCF-7 cells compared to DNR alone by 3-, 5- and 5.5-fold, at concentrations of 100, 500, and 1000 µg/ml respectively. RBAC also enhanced the DNR sensitivity of HCC70 cells, decreasing the DNR IC50 of these cells by 2.5-fold.³²

At the molecular level, we have previously proposed molecular mechanisms by which AIMS could effectively combat tumorigenesis at the precancerous, or initiation stage, as well as the preclinical and clinical stages of promotion and proliferation, via their activation of NK cell cytotoxicity.³³ In a follow-up

trial to investigate the anti-tumor activity of RBAC *in vivo*, solid Ehrlich carcinoma (SEC) tumors were established in female Swiss albino mice via intramuscular inoculation with Ehrlich ascites carcinoma (EAC) cells. The mice were treated with RBAC (40 mg/kg body weight) via intraperitoneal injection 3 times per week from day 8 until day 35. Injection with RBAC caused a significant diminution in tumor volume (63.27%) and tumor weight (45.2%) as compared to controls ($p < 0.01$). More importantly, RBAC also induced a 1.8-fold increase in SEC cell apoptosis percentage. No adverse effects due to RBAC treatment were observed.³⁴

Pilot studies are presently in progress to evaluate the safety and toxicity of RBAC alone in healthy subjects, and also in combination with subcutaneous interleukin-2 (IL-2) therapy in patients with advanced malignancies. The patients must have advanced malignancy that has progressed and for which the primary treating physician believes standard and acceptable therapies have been exhausted. All patients will receive RBAC at 3 g/d orally for four weeks, at which point the dose of RBAC will be decreased to 1 g/d. At this time IL-2 will be added and administered subcutaneous (SQ) daily Mondays through Fridays for four weeks followed by a two-week respite (a six-week cycle overall). Subjects will be monitored for toxicity, and restaging will be conducted every 2 cycles post initiation of IL-2 dosing (12 weeks). Subjects will receive therapy until disease progression or undue toxicity. This study is currently entering the recruitment phase.

DISCUSSION

The immunosenescence literature and corresponding scientific literature indicate that the pathophysiologic state of functional decline characteristic of the condition that is termed aging arises from an immune system-based etiology. Further, our clinical and laboratory findings into the impact of AIM therapy on the amelioration of the diseases and disorders associated with what is termed aging are fully in accord with this tenet.

The studies reported above show a wide range of applications of the oligo-arabinoxylan AIM RBAC in contexts consistent with an immunosenescence-reversing effect. Summarized, the data demonstrate the potential of RBAC as:

- An AIM demonstrating a generalized balancing effect on proinflammatory cytokines and an enhancement of innate immune system function, with specific activity upon the pivotal NK cell compartment.
- A CHD risk-lowering modality via its enhancement of microbial pathogen phagocytosis.
- An effective chemotherapy-sensitizer, with potential as a novel adjuvant to the conventional treatment of breast cancer.
- An apoptosis promoter in solid tumors that is free of apparent side effects.

Further considerations could be extended to include two additional problem areas which face adults of advancing age: impaired wound healing and vaccination response. It has been proposed that in the case of impaired wound healing a possible underlying mechanism in the elderly may be a diminished local production of proinflammatory cytokines by macrophages.³⁵ When appropriately activated, these immunochemical messengers would serve to trigger the natural inflammatory processes that are essential to wound healing and recovery from various illnesses.

Adults of advancing age also tend to mount a weaker response to vaccination.³⁶ Given the activity of RBAC in enhancing B-cell proliferation and mitogen response, and the prevalent use of and reliance upon vaccines in this population, AIM therapy could significantly impact quality of life via restoration of generalized immunocompetence. Additionally, vaccine response studies represent a potential clinical tool for assessment of AIM therapy in the reversal of immunosenescence.

CONCLUDING REMARKS

Psychological stress and immune system dysregulation are inextricably intertwined, as has been well described in the psychoneuroimmunology literature, and both can exacerbate the signs and conditions we term as aging. The findings in the various disciplines suggest that stress and immunosenescence do not simply affect the aging process, but, that they may in fact create it.

The unfolding picture, from anecdotal experience to reproducible clinical evidence, is one which presents strategic AIM immunotherapy as a valid, broad-spectrum, anti-aging modality. In this regard, both as a clinical resource and personal health adjuvant, the long-term efficacy and non-toxic profile of

natural rice bran oligo-arabinoxylan AIMS are indeed most promising for adults of any age or state of health.

Applying AIM in the progressive management of the several major diseases associated with aging thus warrants further study, both in the interests of developing greater clinical acumen, and of expanding our existing knowledgebase towards a more comprehensive understanding of immunosenescence and its pathophysiologic consequences. We are highly motivated and guided towards this goal by the premise of immunosenescence as being the cause of aging, and we are continually diversifying our AIM research into novel areas, including Alzheimer's disease, inflammatory bowel disease (Crohn's), communicable viral diseases (e.g., HIV and influenza), vaccine optimization/potential, and impact upon telomere length *in vivo*.

Our ongoing work reveals that the strategic use of natural product-based AIM immunotherapy can play a central role as a valid, broad-spectrum, anti-aging modality. The resultant perspective suggests a novel and effective paradigm in the amelioration and treatment of aging and its related diseases and disorders. In the particular case of cancer, it is therefore clinically feasible to consider administration of RBAC in pursuit of optimization of anti-carcinogenesis immune function utilizing NK cell activity as a reference biomarker. Using our current clinical trial protocols as a basis, an evidence-based approach may reasonably be derived.³⁷

Taking AIM as a prevention and treatment for so many of the major chronic diseases of aging, and given the exploration of new areas for its application, we may someday soon find ourselves with a very different concept of what aging can truly mean – longevity. In this regard, as both a clinical tool and personal health agent, the long-term efficacy and non-toxic profile of natural rice bran oligo-arabinoxylan AIMS are indeed most promising for adults of any age or state of health.

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