# Age-related Disease: A Revolution Is Coming

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**Abstract**

We are starting to develop the analytical tools to examine damage to our DNA and screen for the presence of clonal hematopoiesis of indeterminate potential. This type of technology will soon support the personalization of approaches to both the prevention and treatment of age-related diseases, which have historically been characterized as beyond our control. We are at the start of an era that will one day be looked upon as the age of precision personalized lifestyle health care. This article is the first in a series in which I will be examining new tools and research that I believe is paving the path forward and leading to exciting times ahead.

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I just finished reading a groundbreaking book called *The Longevity Diet: Discover the New Science Behind Stem Cell Activation and Regeneration to Slow Aging, Fight Disease, and Optimize Weight,* which was written by Valter Longo, PhD,[1] who is director of the Longevity Institute at the University of Southern California and a principal scientist in the development and study of the fasting mimicking diet (FMD). I have followed Dr Longo's career for many years with great admiration. He has been published in top-tier journals and I consider his research to be brilliant work that ties together well-designed studies in cellular biology with animal studies and recent human clinical trials to provide a mechanistic explanation for the positive metabolic effects seen with FMD.[2,3] In his book, Dr Longo writes about some exciting findings regarding a FMD research group consisting of 16-month-old mice, which are described as being the equivalent of a 45-year-old human: "A stem cell-dependent process rejuvenated the immune system. Regeneration also occurred in the liver, muscle, and brain. Levels of several types of stem cells increased."[1] He went on to explain: "The fasting itself destroys many damaged cells, and damaged components inside the cells but it also activates stem cells."[1]

The concept that the body can regenerate organs that have been damaged due to age and faulty metabolism through activation of primordial stem cells is nothing short of revolutionary, and in the field of longevity research it would not be an exaggeration to describe it as the "Holy Grail." Intrigued by Dr Longo's discovery, I was inspired to review the work of other investigators to better understand the foundational research that I believe underpins the remarkable work Dr Longo and his team are pursuing. I began by looking at the basic and clinical science that connects age with altered immune system function and the increasing incidence of chronic disease. My investigation started with a review of the work of William Kannel, MD, who was a key figure in the Framingham Heart Study and an emeritus professor of medicine and public health at the Boston University School of Medicine. The famous and ongoing Framingham Study has been following a cohort of the population in Framingham, Massachusetts, since 1948, gathering data on age-related cardiovascular disease (CVD) incidence and life expectancy; this study was used to establish guidelines for cardiovascular risk factors. In a 2009 article published in the *American Journal of Cardiology*, Dr Kannel[4] wrote: "Examination of the risk of CVD in Framingham study participants who were designated as being at low risk due by current risk factor guidelines suggests that there is clearly an independent contribution of age to occurrence of atherosclerotic CVD."Subsequent studies of CVD risk confirmed that age itself emerges as the strongest predictor of cardiovascular risk. In a 2017 editorial published in the *New England Journal of Medicine*, John F. Keaney, Jr, MD,[5] stated, "Thus, the aging process itself must promote cardiovascular risk, although the mechanisms that are involved are poorly understood."

This lack of understanding about the relationship between age and CVD—and age and many other diseases—may be inching closer to resolution due to recent remarkable discoveries about the role that hematopoietic stem cells play in the immune system. This emerging research has the potential to validate Dr Longo's application of FMD as a therapeutic approach to reduce the impact of age as a determinate of health.

## Hematopoietic Stem Cells: Stand By for Breakthrough Discoveries

Hematopoietic stem cells are located in the red bone marrow and give rise to both myeloid (monocytes, macrophages, neutrophils, basophils, erythrocytes, dendritic cells, and platelets) and lymphoid (T cells, B cells, and natural killer cells) lineages of blood cells. The hematopoietic tissue contains hematopoietic stem cells (HSCs) with both short- and long-term regeneration capacity and constitutes approximately 1 in 10 000 cells in the myeloid tissue. As HSCs age, they can undergo mutational injury.[6] Renowned cancer research scientist Bert Vogelstein, PhD, from the Johns Hopkins Kimmel Cancer Center, has published several articles in the last 5 years that indicate some tissue types undergo spontaneous mutations millions of times more often than other tissue types as a result of their increased mitotic activity. His work has demonstrated a linear correlation between the number of stem cell divisions in various tissues and cancer incidence due to increased spontaneous mutational changes.[7,8]

Our HSCs—10 000 to 20 000 of them—divide continuously during our lifetimes to produce 100 billion new blood cells every day. As a consequence of this mitotic activity, stem cells pick up mutations (approximately 1 per cell per decade of life for most people).[9] Most of these mutated HSCs do not survive, but occasionally a mutation is beneficial for the survival of the cell. This situation can create a clonal expansion of the mutated cell, which can lead to this cell type becoming disproportionately abundant in the blood. It is possible that as much as 20% of blood cells may have this type of immortalized clone. These blood cells represent a phenomenon that has been termed *clonal hematopoiesis of indeterminate potential* (CHIP). A distinguishing—and significant—characteristic of these cells is the increased reactivity of the genes that control inflammation, and this important property has come to be identified as part of a system called the *inflammasome*. Although it has been known for some time that these cells exist in the blood of aged individuals, only recently have they also been found to be associated with altered function that is linked to the etiology of CVD and other chronic diseases of aging, including diabetes, dementia, blood and immune cancers, and inflammatory diseases.[10]

In 2014, Benjamin Ebert, MD, and his colleagues at Brigham and Women's Hospital, Harvard Medical School, reported that age-related clonal hematopoiesis is a common condition that is associated not only with increased risk of hematologic cancer, but all-cause mortality.[11] In 2017, Dr Ebert and his colleagues published findings from a follow-up study, and they reported that CHIP identified in peripheral blood cells was associated with nearly a doubling in the risk of CVD in humans and accelerated atherosclerosis in mice.[12] It was found that CHIP cells make up an increasing percentage of stem cells with age. CHIP is rarely found in people who are younger than 40 years, but it is found in up to 10% of people older than 70 years. Ebert et al found that the most common mutations associated with CHIP were in 4 genes: DNMT3A, TET2, ASXL1, and JAK2. Each of these mutated genes has been individually associated with CVD risk, with the JAK2 V617F polymorphism carrying 12 times the risk to CVD.[5] These mutated genes all influence the inflammatory potential of the myeloid blood cell through activation of the NLRP3 inflammasome function.[13] When the inflammasome is activated, the result is increasing inflammatory cytokine production (such as interleukin 1β [IL-1β]) and increasing levels of reactive oxygen species. Research indicates that the mutation of DMNT3A reduces the restraint of immune cell inflammatory response through alteration in the epigenetic silencing of genes associated with the inflammasome.[14] Mutation of TET2 has also been shown to be associated with accelerated atherosclerosis in mice due to increases in the inflammasome activity.[15]

## Inflammasome Activity as a Therapeutic Target for Age-related Disease

The association among CHIP, all-cause mortality in age-related studies, and activation of the inflammasome opens a new potential therapeutic opportunity for the prevention and treatment of disease. Paul Ridker, MD, director of the Center for Cardiovascular Disease Prevention at the Brigham and Women's Hospital and trial chairman of the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS), has recently published an important report with his colleagues on the results of a clinical trial involving heart disease patients who were treated with an anti-inflammatory monoclonal antibody against IL-1β that is approved for use in the treatment of rheumatologic disorders.[16] This drug has no effect on cholesterol levels but is effective in reducing the inflammasome activity of the proinflammatory cytokine IL-1β that is associated with promotion of monocyte and leukocyte adhesion to the vascular endothelial cells and the growth of vascular smooth-muscle cells. Recent studies have also shown that IL-1β is associated with CHIP, which—as already noted—is connected to the etiology of atherosclerosis. The expression of specific mutated inflammasome genes related to IL-1β production found in CHIP has been associated with increased atherosclerosis and death from any cause in older patients.[17]

As Ridker et al reported, the outcome of the randomized canakinumab intervention trial, which followed 10 061 patients who had previously had myocardial infarction and had initial serum hs-CRP > 2 mg/L, demonstrated a statistically significant reduction in reoccurrence of cardiovascular events versus placebo. It is important to point out that there was no significant change in serum cholesterol levels in the treatment group, indicating that the therapeutic benefit was a result of the influence on the inflammatory effect of the drug through the reduction in the activity of the inflammasome product

IL-1β. In the 2017 publication, the CANTOS investigators stated the following:

> Despite the fact that no significant reduction in cholesterol levels occurred in this trial, the magnitude of effect on cardiovascular events with canakinumab (given every 3 months) was similar to that associated with monoclonal antibodies targeting proprotein convertase subtilisin-kexin type 9 (PCSK9); given every 2-4 weeks.[16]

They continue: "Thus, our data suggest that other anti-inflammatory interventions, such as those that directly inhibit NLRP3 function or that alter downstream interleukin-6 signaling, may also be beneficial in reducing cardiovascular risk."[16] A secondary analysis—published in *The Lancet* in 2018—indicated that the clinical effect was related to the magnitude of reduction of both hs-CRP and IL-6 levels in the patients after treatment with canakinumab.[18]

Furthermore, the CANTOS team also found that cancer mortality was significantly lower among patients in the study who received canakinumab, a finding consistent with the influence of inflammasome activation and IL-1β release to the progression and invasiveness of certain tumors, particularly lung cancer, which has a high mutational rate. It is also known that canakinumab has a beneficial effect in rheumatoid arthritis, gout, and osteoarthritis, all of which are known to be associated with increased activity of the NLRP3 inflammasome.

### What Is the Connection Between the FMD and the Reduction of Age-related Chronic Diseases?

The understanding that CHIP is associated with activation of the NLRP3 inflammasome and that drugs that target the inhibition of the downstream inflammatory mediators produced by these myeloid cells may be effective is highly significant. These factors suggest that if a therapy could be found to reduce the presence of the CHIPs that activate the inflammasome, then a preventive approach to the family of age-related diseases could potentially be developed. There are reports that dietary restriction protects from age-associated alterations in DNA methylation and mutational injury, suggesting that diet may be an important variable influencing CHIP.[19] There is also evidence that specific plant-derived dietary principals such as flavonoids help to regulate the principal genes that are mutated in CHIP, including DNMT and TET.[20]

My interpretation of this research is that it may be possible to alter both the presence and function of CHIP as a contributing factor to inflammasome activation and metabolic inflammation that is associated with the etiology of many of the age-related chronic diseases. This effect may be realized by both lowering the rate of spontaneous DNA mutations in rapidly dividing hematopoietic cells (as described by Vogelstein), and increasing the replacement of CHIP by new hematopoietic cells that are free of the troublesome mutations.

Dr Longo and his colleagues at both the University of Southern California Longevity Institute and the Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research have published studies demonstrating that controlled fasting reduces cellular mitotic activity and promotes hematopoietic stem cell regeneration the result of which is to stabilize immune function.[21] They have demonstrated in both controlled animal studies and preliminary human intervention trials that a plant-based FMD promotes regeneration of the immune system by reducing autoimmunity and activation of the inflammasome. One study indicated that in an animal model of the inflammatory autoimmune disease multiple sclerosis, the FMD resulting in an amelioration of demyelination and neurological symptoms. Preliminary data from this study also suggested—according to the authors—that the FMD or a chronic, marginal ketogenic diet was safe, feasible, and potentially effective in the treatment of relapsing remitting multiple sclerosis in humans.[22]

Research related to the influence of diet quality and composition on immune system function has recently received additional support with the publication of an impressive collaborative study carried out by prominent research groups in the Netherlands, Norway, Germany, and—within the United States—teams at Harvard Medical School, the University of Massachusetts Medical School, and Texas A&M University. This study, which was described in an article published in *Cell* in January 2018 that was titled "Western Diet Triggers NLRP3-Dependent Innate Immune Reprogramming," is a very sophisticated animal study.[23] This work demonstrated that mice, when fed a diet comparable to the Western diet, were found to have induced systemic inflammation that was shifted back to normal immune function upon returning the animals to a standard chow diet. The researchers indicate that the Western diet induced changes in myeloid immune function due to epigenetic reprogramming that was associated with chronic inflammation and metabolic disease. The effects of the Western diet on the myeloid immune system were mediated through activation of the inflammasome through NLRP3 gene expression that resulted in a portfolio of downstream inflammatory mediators being produced.

The studies I have discussed in this article reflect revolutionary research. In closing, I will return to Dr Longo's book, *The Longevity Diet*, and a statement I would like to highlight that appears on page 39: "Among the longevity factors within your control, what you eat is the primary choice you can make that will affect whether you live to 60, 80, 100, or 110—and more important, whether you will get there in good health." We have much more to learn about the connection of CHIP to diseases of aging and how modifiable the production of CHIP is through diet, lifestyle, or pharmacological interventions. We recognize that protecting our genome—what I like to call our "book of life"—against mutational injury is very

important, particularly as it relates to our precious stem cell population. We are starting to develop the analytical tools to examine damage to our DNA and screen for the presence of CHIP. This type of technology will soon support the personalization of approaches to both the prevention and treatment of age-related diseases, which have historically been characterized as beyond our control. We are at the start of an era that will one day be looked upon as the age of precision personalized lifestyle health care. This article is the first in a series in which I will be examining new tools and research that I believe is paving the path forward and leading to exciting times ahead.

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