

Misha Blagosklonny: a life of ideas

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Keywords: hyperfunction, programmatic theory, disposable soma 2, quasi-program, biogerontology, evolutionary physiology, Mikhail Blagosklonny

Received: July 22, 2026

Accepted: August 1, 2026

Published: August 6, 2026

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Aging was founded in 2009 by the oncologist and biogerontologist Misha Blagosklonny who, sadly, died in September 2024 in Boston MA, of cancer. He was 63. By way of introduction to this Commemorative Collection, we describe here some details of his life and work, with emphasis in the latter on his original and provocative ideas about the fundamental nature of the aging process.

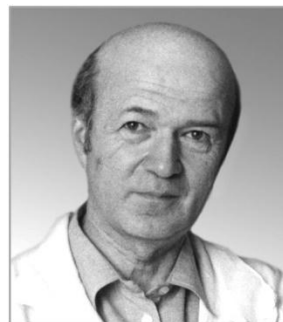
His life

Mikhail Vladimirovich Blagosklonny (to give him his full name) was born in Leningrad (now Saint Petersburg) in the U.S.S.R. His parents, Yanina Blagosklonnaya and Vladimir Dilman met as medical school graduates in Leningrad. His father was also a gerontologist, and is regarded as one of the most significant medical researchers of the Soviet era [1, 2] (Figure 1). Dilman worked for many years at one of the leading Russian research centers, the N.N. Petrov National Medical Research Center of Oncology in Leningrad, and was founder and director the Laboratory of Endocrinology there. He moved to the West in 1990, where he joined the New York University Medical Center. Dilman died in 1994 at the age of 68.

As a young man, Misha followed in his father's footsteps. Keen to continue Dilman's work, particularly relating to the role of the hypothalamus in aging [3], he secured a degree in internal medicine and then a doctorate in experimental medicine and cardiology. In 1991, shortly prior to the dissolution of the Soviet Union, he too moved to the U.S., initially finding work in the field of cancer cell biology and therapeutics, but

then reverting to research on aging, eventually at the Roswell Park Cancer Institute in Buffalo, NY where he was Professor of Oncology.

Biogerontology in the U.S. benefitted considerably from an extended brain drain of talented scientists from Russia, whose research blossomed in their new milieu. By comparison with such contemporaries, Misha initially fared less well. Success as a research scientist requires considerable stamina and a thick skin in the face of many disappointments, including rejection of research papers and grant applications. By nature temperamental and highly sensitive, he was at times so stricken by such reversals that he eventually shifted to purely theoretical investigations, and work as a journal editor. One of the original motivations for establishing his own journals was to provide a bearable means to



Vladimir Dilman



Misha Blagosklonny

Figure 1. Father and son. Vladimir Dilman was a renowned gerontologist in the Soviet Union. Misha Blagosklonny at the Second International Conference "Genetics of Aging and Longevity" in Moscow, April 2012.

publish his prolific output of highly novel theoretical ideas.

Misha Blagosklonny's main scientific contributions were in the domain of general theories of aging. His particular approach to developing theory was what he called conceptual research [4]. An increasing challenge for scientists is the ever growing volume of research papers being published, such that keeping abreast of one's field is ever more difficult. Misha argued that it is possible to achieve major scientific advances by exploring the vast archives of published work. By means of conceptual research one can not only develop new hypotheses but also test them by repurposing existing findings to draw new conclusions, sometimes in ways very different from those intended by the original researchers. Importantly, conceptual research is an evidence-based approach.

He initially used this approach for his oncological research, with a particular focus on anti-cancer drug action. This led him to the protein mTOR (mechanistic target of rapamycin). An interest in the mTOR-inhibitory drug rapamycin as a possible anti-cancer agent led him to the deduction that it may inhibit aging, particularly by blocking cellular senescence [5, 6]. This reignited his earlier interest in theories about the causes of aging, both evolutionary (e.g. antagonistic pleiotropy, disposable soma) and mechanistic (e.g. molecular damage accumulation, telomere shortening).

This conceptual research, along with some experimental work on cellular senescence, led to remarkable outpouring of essays about aging, of which there are more than 70; for a summary and detailed overview of their contents, see [7]. In them he developed an elaborate conceptual framework of ideas about aging as an evolved, programmatic process, and related it to new scientific discoveries as they appeared. He frequently presented arguments describing how his new framework better explained experimental research findings than more standard explanations, that were often based on the view of aging as a process of molecular damage accumulation [7].

Misha's theoretical world view: a thumbnail sketch

Biogerontological research from the 1980s-2000s took place in the context of a framework of interrelated guiding theories of aging, including the evolutionary theory, the oxidative damage theory and, linking the two, the disposable soma theory [8–11]. However, during the course of the 2000s doubts increasingly emerged about several key concepts in aging, including the oxidative damage theory [12–14], along with difficulties with the evolutionary physiology of aging (i.e. with integrating

evolutionary and proximate accounts) [15]. Perhaps as a consequence of this, the 2010s saw a distinct shift in emphasis away from understanding the causes of aging, and towards applied approaches to discover anti-aging interventions. This was marked particularly with the growing popularity of the hallmarks of aging account [16], and the emergence of the geroscience agenda [17].

Moving in the opposite direction, Misha conceived of a new, broad synthesis of evolutionary and mechanistic theory, that he first started to publish in 2006 [5, 18, 19]. At around the same time João Pedro de Magalhães, another biogerontologist with an interest in general theories, arrived at a similar synthesis [20, 21].

One way to understand the Blagosklonny framework is as an alternative to the disposable soma theory, proposed by Tom Kirkwood in 1977 [11, 22]. This important and influential theory provided a means to integrate the evolutionary theory of aging with the claim that molecular damage accumulation is the main, primary cause of aging. It is evident from the wide range of lifespans across animal species that aging is to a large extent genetically determined, and therefore the product of evolution. The evolutionary theory argues that aging evolves not because it confers any adaptive benefit, but due to reduced natural selection against deleterious effects of genes at later ages (the late-life selection shadow) [10, 23].

The disposable soma theory argues that different animal species age at different rates due to differences in the relative effort made in terms of somatic maintenance: better maintenance leads to a slower aging rate. Key to the theory is the assumption that somatic maintenance is a resource-costly process, such that competition for limited resources between maintenance and reproduction leads to trade-offs between longevity and reproductive output. Consequently, natural selection favors genotypes leading to inadequate somatic maintenance, dooming the soma to life-limiting damage accumulation [11, 22].

The Blagosklonny framework argues that the belief that molecular damage accumulation is the chief cause of aging is unfounded and, consequently, that the disposable soma theory is incorrect [6, 18, 19]. Instead, Misha proposed that a major driver of aging is non-adaptive and pathogenic action in later life of programs and processes that in early life are beneficial. An example of this is the process of acute inflammation, that is critical for tissue repair (e.g. wound healing) throughout life, but which becomes chronically activated in later life, and contributes to many diseases of aging [24].

The germ of these ideas was his experimental observation that growth stimulation in conditions of cell

cycle arrest leads to cellular senescence without any involvement of molecular damage [25]. Instead, the driver of progression of arrested cells into cellular senescence (or geroconversion [26]) was hyperactivation of mTOR. From this Misha explored with conceptual research the wider principle that a major driver of aging was not progressive damage accumulation and breakdown, but rather the opposite: too much of certain functions - what he referred to as hyperfunction [5]. Due to this term, his ideas are sometimes referred to as the hyperfunction theory.

According to this view, the aging process is actively genetically determined. Is this, then, saying that aging is a programmed process? Here he points out a problem with the word “programmed”, that has historically been a source of confusion, namely that it has two distinct meanings. The first is programmed in the sense of genetically determined; the second, programmed as in a programme for something, implying an adaptation. According to Blagosklonny’s framework aging is programmed in the first but not the second sense, or - to use his terminology - it is quasi-programmed [5].

Returning to the evolutionary physiology perspective, Misha’s framework argues that natural selection favors

gene variants that promote growth and reproduction, but in later life promote development of diseases of aging. According to this view, evolved growth control systems such as the mTOR pathway, growth hormone and IGF-1 (insulin-like growth factor 1) signaling are often set at levels that are too high, and cause as a result diverse pathologies that contribute to aging. Misha referred to this as disposable soma theory 2, given that the soma is disposable as the result of mTOR/quasi-program action (rather than resource allocation etc.), due to antagonistic pleiotropy and the late-life selection shadow [27]. The basic Blagosklonny framework is depicted schematically in Figure 2.

Though Misha published many essays, for the first decade after they first started to appear they drew little attention at all, much to his chagrin. This may to some extent reflect a general lack of consensus with respect to theories of aging, and a falling away of interest in evolutionary physiology. Misha’s somewhat quirky writing style may also have contributed to their neglect. Their main initial influence was on the work of one of the authors of this article (D.G.), starting from 2013, which demonstrated the utility of the quasi-program model for explaining the origins of senescent pathology in the nematode *Caenorhabditis elegans* [28–31].

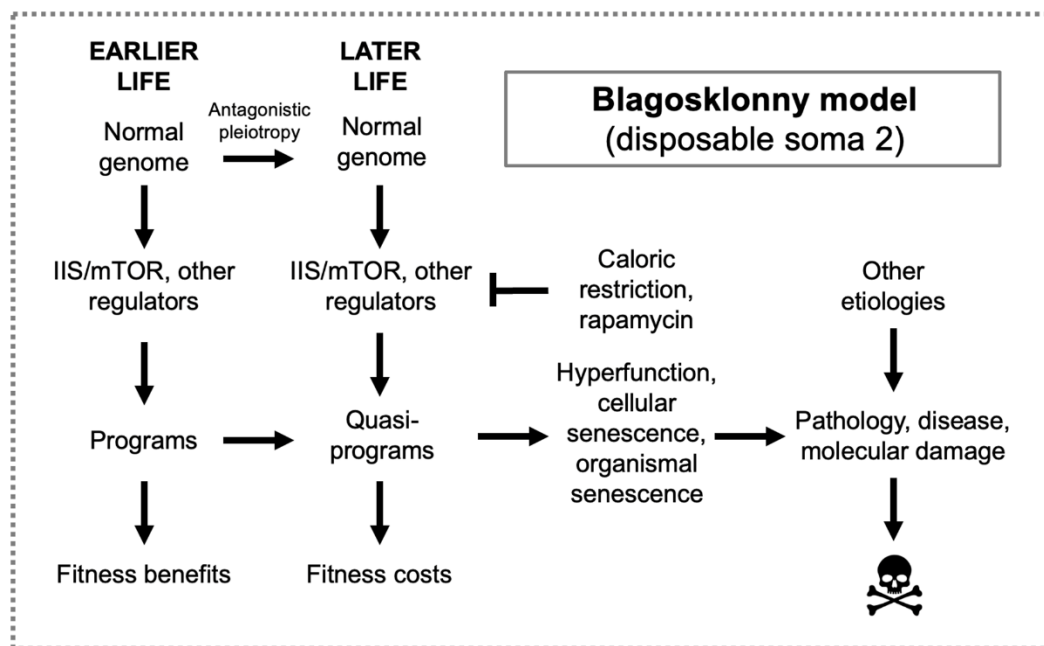


Figure 2. The basic framework of Misha Blagosklonny’s view of aging, or disposable soma 2. Here natural selection favors a genotype that optimises early life fitness. The resulting regulatory settings are too high to be optimal for later life health and survival. This results in quasi-programmed hyperfunction in life (i.e. hyperfunction is genetically determined, but not adaptive). This is consistent with Williams’ understanding of the nature of antagonistic pleiotropy, where genes are beneficial early in life, but actively pathogenic later [10, 32]. Such hyperfunction can be inhibited, e.g. by rapamycin and caloric restriction. Molecular damage, as commonly associated with advanced aging, is here viewed as largely a consequence of late-life pathology, rather than a cause of it (with the exception of cancer). This framework shares many features with João Pedro de Magalhães’ developmental theory of aging [20, 21]. Arrows indicate activation, T bars inhibition.

More recently, they have been receiving somewhat more attention, and Blagosklonny's theories have been extended to incorporate a number of topics and new concepts in a wider framework of programmatic theory. These include hypofunction [32], reproductive death (semelparity) and costly programs [33–35], biological constraint and bad spandrels [36], evolutionary medicine [37], cellular senescence [38], biological clocks [39], among other things [40, 41]. The Blagosklonny framework has also been integrated with Dilman's earlier four models theory [42] into a broader multifactorial model, with promise as a possible general model for late-life disease etiology [7, 43]. Nonetheless, Misha's theories remain far from the mainstream of the biology of aging, although the field is currently notably lacking in any mainstream as far as aging theories are concerned - with the possible exception of evolutionary theory. The hallmarks of aging, though a point of reference for the field, is not a theory as such [44].

An original mind

Whether or not Misha Blagosklonny's ideas will enter the mainstream of biogerontological thought only time will tell. Either way, there is no doubt that he was a highly original and insightful thinker. A commentary on Vladimir Dilman describes the creative and integrative thinking style that he was noted for [1]; evidently this was a characteristic passed from father to son.

This special commemorative collection of *Aging* includes several other new articles, each offering further insight into Misha Blagosklonny's contributions to the theoretical understanding of the aging process. Alexey Golubev summarizes the ideas and work of Vladimir Dilman from the unique perspective of someone who worked with him in the U.S.S.R. in the 1980s [2]. This provides insights into Misha's intellectual background and influences, and also the work of a thinker whose contributions to research on aging are under-appreciated. João Pedro de Magalhães provides a perspective on Misha's influences on him, and the importance of his ideas in the emerging theoretical framework that is programmatic theory [45]. One of the authors of the present article (D.G.) offers an account of some additional new theory building on the Blagosklonny framework, illustrating how the doors opened by Misha's innovations continue to lead on to new ideas [46]. Finally, several other articles relating to Misha's legacy have also appeared recently [47, 48].

CONFLICTS OF INTEREST

M.D. is founder and shareholder of Cleara Biotech and a consultant for Rubedo Life Sciences and dsm Firmenich.

FUNDING

D.G. acknowledges funding support from a Wellcome Trust Investigator Award (215574/Z/19/Z). M.D. acknowledges funding support from Hevolution Foundation (HF-GRO).

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