Priority Review

Mikhail 'Misha' Blagosklonny's enduring legacy in geroscience: the hyperfunction theory and the therapeutic potential of rapamycin

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Keywords: rapamycin, longevity medicine, healthspan, geroscience, hyperfunction
Received: October 31, 2024 **Accepted:** January 8, 2025 **Published:** January 12, 2025

ABSTRACT

The untimely passing of Dr. Mikhail "Misha" Blagosklonny has left a lasting void in geroscience and oncology. This review examines his profound contributions, focusing on his pioneering the Hyperfunction Theory and his advocacy for rapamycin, an mTOR inhibitor, as a therapeutic agent for lifespan extension. Contrary to traditional damage-centric models, the Hyperfunction Theory rejects damage accumulation as the primary driver of aging. Instead, it redefines aging as a quasi-programmed process driven by the persistent, excessive activity of growth-promoting pathways beyond their developmental roles, leading to age-related pathologies. We explore how Blagosklonny's insights predict rapamycin's ability to decelerate aging by modulating excessive mTOR signaling, supported by empirical evidence across multiple physiological systems, including immune, cardiovascular, cognitive, and oncologic health. His forward-thinking approach, advocating for the cautious clinical use of rapamycin and suggesting personalized, preventive, and combination therapy strategies, has catalyzed interest in translational geroscience. This review synthesizes Blagosklonny's legacy, presenting rapamycin as a foundational pharmacological intervention with potential in managing age-related decline and extending healthspan, and underlines his impact in shifting aging research from theoretical frameworks to actionable interventions. Blagosklonny's work remains an enduring inspiration, paving the way toward treating aging as a modifiable condition.

INTRODUCTION

The untimely passing of Dr. Mikhail 'Misha' Blagosklonny marked the loss of a pioneering scientist—and a valued colleague and friend—who reshaped oncology and geroscience [1–4]. Throughout his career, Blagosklonny authored over 270 publications, served as an editor for Cell Cycle, Oncotarget and Aging (Albany NY), and advanced a more integrated view of cancer, cellular biology, and aging [1]. By bridging these fields, he reframed aging as a quasi-programmed process in which growth-promoting pathways persist beyond their developmental purpose, thereby contributing to age-related diseases. His legacy rests on two major contributions: the Hyperfunction Theory of aging and his pioneering advocacy for rapamycin, an mTOR (mechanistic target of rapamycin) inhibitor, as a therapeutic intervention for extending lifespan. The Hyperfunction Theory represents a fundamental departure from traditional damage-based theories of aging. By framing aging as a quasi-programmatic process driven by the overactivity of growth-promoting pathways such as mTOR, Blagosklonny positioned his work as an alternative to damage accumulation models, which he critiqued as inadequate for explaining the underlying biology of aging.

Blagosklonny's 2006 proposal that rapamycin might serve as a "longevity drug" anticipated the 2009 Interventions Testing Program (ITP) findings, which confirmed rapamycin's capacity to extend lifespan in

genetically diverse mice, even when administered late in life. This manuscript reviews Blagosklonny's Hyperfunction Theory, focusing on its implications for rapamycin's mechanism of action, potential in longevity, and his proposed framework for clinical application.

Redefining aging: the Hyperfunction Theory

Hyperfunction versus damage models

Before Blagosklonny's contributions, aging research was primarily guided by damage-centric theories, which propose that aging is driven by cumulative damage from stressors such as oxidative stress, protein aggregation, DNA degradation, and other factors [5–19]. These theories positioned aging as a process of gradual deterioration over time.

Blagosklonny's Hyperfunction Theory introduced a complementary perspective, proposing that aging is not only due to accumulated damage but also to the persistent activity of growth-promoting pathways, such as mTOR, beyond their developmental roles [20–22]. The Hyperfunction Theory posits that these growth pathways, which drive development and reproduction in early life, become deleterious when they remain active in later life, leading to cellular hypertrophy, hyperfunction, and senescence [21, 23–27]. Unlike damage-based theories, which attribute aging to the gradual accumulation of molecular and cellular damage, the Hyperfunction Theory explicitly rejects this perspective as the primary explanation for aging [28, 29]. Instead, it proposes that persistent growth-promoting signals, such as mTOR, drive cellular and tissue dysfunction. Blagosklonny likened this to a "runaway car without brakes," where damage occurs as a secondary consequence of unchecked growth signaling rather than as the root cause [25, 30].

Blagosklonny's Hyperfunction Theory aligns with the concept of antagonistic pleiotropy, originally proposed by George C. Williams in 1957, which posits that genes beneficial in youth can contribute to aging later in life [31, 32]. Hyperfunctional pathways such as mTOR reflect this concept by supporting survival and reproductive success early on, while driving pathology as organisms age. By expanding on this idea, Blagosklonny integrated damage models with hyperfunction, suggesting that prolonged mTOR signaling exacerbates both cellular overactivity and the accumulation of molecular damage [22, 33]. This alignment underscores the evolutionary roots of aging, where pathways beneficial for growth and reproduction become maladaptive in later life. For instance, David Gems, a key contributor to theoretical and experimental studies of aging, has highlighted the role of mTOR signaling in promoting hypertrophy and fibrosis [34], which contribute to diseases such as atherosclerosis and cancer, and in aging *C. elegans* hermaphrodites, run-on physiological apoptosis becomes a pathogenic with time [35]. His perspective aligns with the Hyperfunction Theory, suggesting that these mechanisms represent a significant aspect of aging biology [20].

The Hyperfunction Theory vs. damage models: exchange with aubrey de grey

While de Grey emphasizes that cellular damage is the principal driver of aging, Blagosklonny suggests that hyperfunction may underlie much of this damage, establishing a cycle where excessive growth signaling promotes metabolic byproducts that accumulate and cause cellular decline [6, 30].

Blagosklonny directly engaged with Aubrey de Grey, a proponent of damage-based theories, in a 2021 exchange published in Rejuvenation Research. Blagosklonny emphasized that hyperfunction, not damage accumulation, underpins aging, arguing that Hyperfunction Theory explains why damage accumulates—not from aging but as a downstream byproduct of hyperactive signaling:

> "Hyperfunction of signaling pathways can occur without progressive changes of their activity. For example, when the same activity of growth-promoting pathways remains unchanged in postdevelopment, it is a hyperfunction. By analogy, a car driving 65 mph on highway is not speeding (hyperfunction) but driving 65 mph on the driveway is. In the latter case, the car certainly will be damaged, but not by rusting (molecular damage), but by damage of its macroparts. Similarly, hyperfunction does not cause molecular damage, but causes organ damage. Thus, the brain is damaged by stroke, which can be a result of hypertension, which, in turn, is developed by hyperfunctional cells of multiple tissues. There is no place for molecular damage in this sequence of events…"

In his rebuttal, de Grey argued that while the Hyperfunction Theory offers valuable insights, damage repair remains essential for addressing aging:

> "While hyperfunction undoubtedly contributes to aging, it cannot fully explain the accumulation of oxidative and genetic damage that impairs cellular function [30]."

Blagosklonny further posited that while molecular damage accumulates, it does not necessarily constrain

lifespan under typical conditions; however, if interventions extend lifespan significantly, such damage may become more limiting [36]. This dialogue highlights the contrasting paradigms while reinforcing Blagosklonny's central assertion that aging interventions should prioritize targeting hyperfunction at its source.

Building on the Hyperfunction Theory, Blagosklonny proposed that targeting overactive growth pathways could mitigate aging and its associated diseases. This theoretical framework directly informs the exploration of rapamycin, an mTOR inhibitor, as a potential therapeutic agent. The Hyperfunction Theory, together with João Pedro de Magalhães' related developmental model [37, 38] has inspired the emergence of an expanding suite of programmatic theories, encompassing hypofunction, costly programs, constraint theory, and adaptive death [39–44].

Predictive health benefits of rapamycin based on the Hyperfunction Theory

Blagosklonny's insights on cellular aging center around the concept that the transition from a quiescent (non-dividing) state to a senescent one—termed geroconversion—is driven by growth-promoting mediators, notably the mTOR (mechanistic target of rapamycin) pathway, particularly when cells encounter a block in the cell cycle [45]. Under normal circumstances, cells in quiescence remain inactive without progressing to senescence. However, when growth signals such as those from the mTOR pathway remain active in cells that can no longer divide, it results in an overactive cellular state that fosters aging and senescence via continued, maladaptive activity of growth-related pathways beyond their developmental roles [22]. This theory suggests that key molecular mechanisms, including the mTOR pathway, remain chronically overactive, thereby promoting cellular processes that, while beneficial in early life, contribute to age-related diseases as they persist.

Rapamycin, an mTOR inhibitor, offers a promising therapeutic intervention by selectively modulating this excessive signaling, potentially decelerating the aging process. Blagosklonny proposed that if hyperfunction drives aging, then inhibiting these pathways with rapamycin should delay or mitigate multiple age-related conditions [22]. His predictions, derived from the Hyperfunction Theory, have been corroborated by numerous studies exploring rapamycin's effects across several biological systems [22, 24, 25, 46, 47]. The following sections explore the health benefits of rapamycin as predicted by Blagosklonny and supported by empirical research.

- Immune Function: According to the Hyperfunction Theory, mTOR hyperactivity contributes to immune dysfunction by promoting chronic inflammation. Blagosklonny hypothesized that mTOR inhibition would alleviate immune hyperfunction and rejuvenate immune responses. This prediction was confirmed in animal models [48–52], and subsequently by Joan Mannick and colleagues, who found that elderly patients treated with low-dose everolimus (a rapamycin analog) demonstrated improved vaccine efficacy and reduced infection rates [53–55]. Foundational work by Chen et al. (2009) demonstrated that rapamycin can restore hematopoietic stem cell (HSC) function in aged mice, enhancing adaptive immunity and effective responses to viral challenges [56]. More recently, Ando et al. (2023) showed that mTOR signaling plays a crucial role in regulating T cell exhaustion and the efficacy of PD-1-targeted immunotherapy, revealing the nuanced outcomes of mTOR inhibition depending on the phase of immune activation [57]. While not all findings have been consistent, initial evidence shows promising potential, marking this approach as an area of significant scientific interest [55, 58]. These results support Blagosklonny's hypothesis that rapamycin can enhance immune function by moderating age-associated immune hyperactivity without compromising essential immune defenses.

- Cardiovascular Health: Persistent mTOR activation is thought to contribute to hypertrophy and fibrosis in cardiovascular tissues, accelerating age-related arterial plaque buildup [59–61]. Blagosklonny proposed that mTOR inhibition could have protective cardiovascular effects [22, 62]. Research on companion dogs, including studies led by Matt Kaeberlein, has yielded promising evidence that rapamycin may reduce markers of cardiac aging and improve heart function [63]. These preliminary findings align with Blagosklonny's theoretical predictions, though some variability in results suggests that further investigation is necessary to validate and deepen our understanding of these effects [63, 64]. These findings underscore rapamycin's potential to support cardiovascular health, reducing the impact of age-related pathology and positioning mTOR inhibition as a therapeutic avenue in cardiology [60, 61, 65].

- Cognitive Function: Blagosklonny suggested that by reducing hyperfunction in neural cells, rapamycin could prevent neuroinflammation associated with neurodegenerative diseases [47, 62, 66]. He proposed that rapamycin might help mitigate the buildup of amyloid and tau proteins, hallmarks of Alzheimer's disease. Studies in rodent models of

neurodegeneration have supported this prediction, showing that rapamycin delays cognitive decline, reduces neuroinflammation, and slows the accumulation of amyloid plaques [67–75]. Similarly, in Parkinson's disease (PD) models, rapamycin mitigates neurodegeneration by inhibiting mTORC1 activity, rescuing dopaminergic neuron loss and behavioral deficits [76]. King et al. (2008) demonstrated that rapamycin also inhibits the aggregation of misfolded proteins, such as polyglutamine and huntingtin, via a reduction in protein synthesis, independent of its effects on autophagy [77]. These findings validate the notion that mTOR inhibition protects cognitive function by reducing cellular hyperfunction and preserving neural health.

- Cancer Prevention: A cornerstone of Blagosklonny's Hyperfunction Theory is the overlap between aging and cancer, both driven by hyperactive growth pathways [22, 23, 46, 78–84]. Blagosklonny hypothesized that mTOR inhibition would reduce cancer risk by suppressing the excessive cellular signaling that fuels tumor development. Research has confirmed that rapamycin reduces tumor progression and pre-cancerous lesion growth, affirming his view that hyperfunction contributes to both aging and cancer [12, 78, 79, 85–92]. This reinforces rapamycin's potential as a dual-action therapeutic, addressing cellular pathways that drive both age-related decline and carcinogenesis.

Rapamycin has shown considerable potential for lifespan extension across diverse animal models, from invertebrates such as *C. elegans* [93] and *D. melanogaster* [93] to mammals, including mice, where it mitigates various aging-related phenotypes [80, 85, 87, 88, 94–110]. In mammalian models, rapamycin has been associated with improvements in body composition, metabolic and physical function, and reduced incidence of aging-related pathologies such as sarcopenia, osteoarthritis, ovarian decline, and tendon stiffness. These effects extend across multiple physiological systems—circulatory, respiratory, digestive, musculoskeletal, endocrine, integumentary, reproductive, and oral health—as well as in the management of benign neoplasms and other age-associated conditions [55, 64, 67, 97, 102, 103, 106, 111–125]. Preliminary findings, presented by Adam Salmon at the American Aging Association 52nd Annual Conference (2024), further suggest rapamycin's potential for lifespan extension in primates. Studies consistently report that rapamycin administration increases median and maximum lifespan [89, 95, 99, 101, 102, 123, 126–128]. These findings have sparked considerable interest in rapamycin's translatability to human aging, with preliminary data from human studies and clinical trials suggesting beneficial effects on age-related biomarkers and immune function. Such results underscore rapamycin's emerging role as a pharmacological intervention with broad potential in mitigating age-associated decline in humans. As research continues, there is increasing optimism that rapamycin may hold practical applications for human life extension and age-related disease prevention, validating Blagosklonny's predictions within the framework of the Hyperfunction Theory.

Clinical translation and future directions

Pragmatic use: a balanced approach to rapamycin's clinical application

Blagosklonny was a strong advocate for rapamycin's cautious use in clinical settings, arguing that extensive animal safety data and emerging human studies supported its potential benefits in promoting healthy aging. In his 2019 article, "Rapamycin for Longevity," he proposed that delaying treatment until human lifespan studies are complete would defer possible benefits for individuals who could benefit today [126]. Blagosklonny's view remains controversial, as many researchers, including those working in the field of geroscience, emphasize the importance of validating efficacy and safety in humans before recommending rapamycin for longevity purposes [129]. Nevertheless, Blagosklonny's advocacy has catalyzed significant interest and momentum in aging research, sparking increased funding and studies into rapamycin's applications [32, 58, 64, 71, 72, 95, 110, 120, 130–144]. By championing a "pragmatic use" approach, Blagosklonny has opened pathways for informed, personalized decision-making between patients and healthcare providers. This framework allows patients to weigh the potential benefits and risks of off-label rapamycin use, guided by ongoing research and medical supervision, while awaiting definitive evidence on lifespan extension effects in humans.

While Blagosklonny advocated for rapamycin's use based on its established safety profile when administered appropriately, he acknowledged discussions in the scientific community about potential side effects and the exploration of alternatives. Some researchers have proposed that developing TORC1-specific inhibitors or utilizing alternative rapalogs like everolimus could mitigate rapamycin's side effects, such as glucose intolerance and immunosuppression [119]. Studies by Lamming et al. (2013) suggest that these rapalogs may offer similar therapeutic benefits with reduced adverse effects due to their different pharmacokinetic properties [119]. Additionally,

intermittent dosing regimens have been investigated as a strategy to minimize side effects while maintaining efficacy. For instance, Arriola Apelo et al. (2016) demonstrated that alternative rapamycin treatment schedules could mitigate impacts on glucose homeostasis and the immune system in mice [145]. However, Blagosklonny remained skeptical about the necessity of developing new rapalogs solely to overcome side effects he considered manageable with proper dosing of rapamycin [126, 146]. He emphasized that rapamycin, as a well-studied and FDA-approved drug, could be effectively utilized in anti-aging therapies through personalized dosing strategies without waiting for new drug developments. This perspective underscores the ongoing debate within the geroscience community regarding the optimal approach to mTOR inhibition in aging interventions.

Blagosklonny's framework for clinical application includes several principles designed to optimize the therapeutic potential of rapamycin:

1. Personalized Dosing: Blagosklonny emphasized individualized dosing regimens, suggesting that optimal results can be achieved through low-dose or intermittent administration tailored to the patient's tolerance and specific health profile. This approach aims to maximize rapamycin's benefits while minimizing adverse effects [126, 127, 133, 147–150].

2. Preventive Application: Blagosklonny advocated for the initiation of rapamycin treatment before the onset of age-related diseases, proposing that early intervention could maximize mTOR inhibition's protective effects against age-associated decline [22, 46, 66, 84, 126, 127, 133, 147, 151–153].

3. Combination Therapy: To further enhance therapeutic outcomes, Blagosklonny proposed combining rapamycin with other agents, such as possibly metformin or ACE inhibitors, that may work synergistically with mTOR inhibition. This approach anticipated the current interest in multi-targeted geroprotective strategies that address multiple aging pathways, reinforcing his forward-looking vision for personalized anti-aging interventions [46, 62, 126, 154]. This approach is gaining traction [101, 142, 155–160].

Blagosklonny's proposal for "longevity clinics" where patients could receive individualized anti-aging therapies reflects an innovative approach that is garnering significant interest in translational gero-science and longevity medicine [126, 127, 133, 161–170]. These clinics offer a potential framework for Blagosklonny's vision, where cutting-edge gero-protective treatments can be administered under specialized supervision, translating geroscience insights into practical healthcare solutions.

CONCLUSION

Mikhail Blagosklonny's enduring legacy in geroscience

Dr. Mikhail Blagosklonny's contributions have fundamentally reshaped geroscience and oncology, offering a pioneering framework for understanding aging not merely as an accumulation of damage but as a quasi-programmed process. His Hyperfunction Theory, centered on the persistent activation of biological growth pathways like mTOR, presents aging as an extension of early-life growth signals that drive cellular and tissue decline over time. By advocating for rapamycin to mitigate these effects, Blagosklonny established a new paradigm that combines theoretical insights with actionable interventions.

Ongoing clinical research into mTOR inhibitors for healthspan and lifespan extension reflects Blagosklonny's impact, marking a shift in gero-science towards treating aging as a modifiable condition. His vision has inspired a new wave of research focused on interventions that aim not only to extend life but to enhance its quality, underscoring his belief in the potential of translational geroscience.

Blagosklonny's Hyperfunction Theory offers a compelling alternative to traditional damage-based theories, presenting a novel framework for under-standing the causes of aging. This contribution will undoubtedly be remembered in the coming decades and beyond as an innovative contribution to our theoretical grasp of the aging process and a foundation for exploring effective therapeutic approaches. Blagosklonny's work leaves an enduring legacy, embodying the shift from viewing aging as an inevitable decline to treating it as a condition that science and medicine can manage. As a colleague and friend, Misha's commitment to advancing geroscience remains a personal and professional inspiration.

ACKNOWLEDGMENTS

The author acknowledges the lifestyle medicine, geroscience, aging biotechnology, and longevity medicine communities, including those on social media (@agingdoc1) and professional platforms (LinkedIn) for fostering insightful discussions that contribute to advancements in this field.

CONFLICTS OF INTEREST

The author declares no conflicts of interest related to this study.

FUNDING

No funding was used for this paper.

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