Research Perspective

# A brief history of the hyperfunction theory of aging and future directions

**João Pedro de Magalhães**[1]

[1]Genomics of Ageing and Rejuvenation Lab, Department of Inflammation and Ageing, College of Medicine and Health, University of Birmingham, Edgbaston, Birmingham B15 2WB, UK

**Correspondence to:** João Pedro de Magalhães; **email:** jp@senescence.info
**Keywords:** antagonistic pleiotropy, longevity, programmatic aging, quasi-program
**Received:** December 29, 2025 **Accepted:** June 19, 2026 **Published:** July 24, 2026



## ABSTRACT

**Aging remains a mystery of biology, and debate regarding why we age has been ongoing for centuries. Many theories of aging have been proposed, most of which focus on errors and the gradual accumulation of molecular damage. By contrast, aging may be primarily a programmatic process, arising from developmental programs that continue to run later in life and, as a form of antagonistic pleiotropy, become detrimental. Here, I review the history of programmatic theories of aging, from early caloric restriction experiments to more recent conceptual frameworks to which Mikhail Blagosklonny made key contributions, particularly the hyperfunction theory. The discovery that single-gene manipulations can modulate aging in animal models, together with evidence that rapamycin extends lifespan, provides empirical support for the hyperfunction theory. Finally, I discuss the prospects of the hyperfunction theory and its implications for the future of aging biology.**

## INTRODUCTION

Understanding the mechanisms underlying aging processes is crucial for biogerontology and for developing translational approaches [1]. There is much debate, however, regarding the fundamental nature and drivers of aging [2]. The prevailing view is that aging results from the gradual accumulation of errors throughout life. This includes different types of errors and damage in the DNA, epigenome, mitochondria, telomeres, proteins, and other molecular and cellular components [1, 3].

By contrast, the idea that aging arises from genetically encoded processes has gained traction in recent years, the so-called "programmatic theories". It is important not to conflate programmatic and programmed theories, as the latter view aging itself as an evolved adaptation serving a function, while in programmatic theories late-life decline is driven by developmental programs that run-on without aging being adaptive. In this context, Mikhail Blagosklonny was instrumental in reviving programmatic theories of aging, particularly the hyperfunction theory. Here, I review the historical background of programmatic theories, including Blagosklonny's influential contribution and my own personal perspective, and discuss recent developments in the field as well as future prospects.

### Weismann, McCay, and early aging programs

Scientific discussion of the causes of aging dates back at least to the time of Aristotle in ancient Greece, and the first proposal that aging may be linked to development appeared in the 19th century [4]. August Weismann initially put forward the idea that aging may have evolved for a purpose (i.e., is programmed), though he later abandoned this view. In the early 20th century, however, the programmatic hypothesis that growth, development, and aging were interconnected was under scrutiny. Interestingly, Clive McCay's breakthrough caloric-restriction experiments were

designed to test the hypothesis that growth restriction could influence aging [5].

Over the following decades, however, the idea that aging results from a program or from continued developmental processes became less popular. The evolutionary theory of aging argued against a programmed (i.e., adaptive) aging process, predicting that such a program would be selected against [6]. The dominant view was that aging arises from the declining force of natural selection with age, the so-called "selection shadow" [7, 8]. In this model, both genetic variants with detrimental late-life effects, or variants beneficial early in life but harmful later, can become fixed in populations, contributing to aging; here, aging is not an adaptation and, in that sense, not programmed.

Although classical evolutionary theory explains why we age, it offers little mechanistic detail regarding how we age. In the 1970s, Kirkwood proposed the disposable soma theory, suggesting a trade-off between reproduction and somatic maintenance as a driver of species differences in aging [9]. An underlying assumption of the disposable soma theory was that aging is largely the result of damage accumulation [7]. It is noteworthy that Blagosklonny was at times critical of the disposable soma theory [10], and offered his hyperfunction theory as an alternative to it, given that it too combines evolutionary and mechanistic explanations [11].

The increasing emphasis on molecular damage in aging research was likely driven, at least in part, by advances in molecular biology and biochemistry. The explosion of molecular discoveries in the second half of the 20$^{th}$ century revealed a vast and intricate number of cellular components and biological processes, which in turn led to a proliferation of theories linking aging to defects in each of these many processes. Because virtually any important biochemical or molecular process can malfunction and become harmful to cells, it is easy to conceive new damage-based theories of aging. Indeed, I speculate that almost any biological process can be shown to change with age if studied well enough.

This abundance of molecular detail reinforced the perception that aging is driven by stochastic damage and led to many theories and frameworks positing damage accumulation as the root cause of aging [3, 12]. It was against this trend that a new wave of programmatic theories emerged at the start of the 21st century.

**From free radicals to the genetic regulation of aging**

Like many scientists entering the field at the end of the 20$^{th}$ century, I encountered the free radical theory of aging as the prevailing theory when I started studying biogerontology. Its central idea that oxidative damage gradually accumulates in multiple cell components and drives the process of aging is beautifully attractive in its simplicity and elegance [13]. It also explained species differences in aging by linking metabolic rate to mitochondrial reactive oxygen species (ROS) production [14].

During my PhD (2004), and assuming these processes were drivers of aging, I studied oxidative stress, DNA damage, telomeres, telomerase, and cellular senescence in human cells [15]. However, the groundbreaking work by Van Remmen et al. in 2003, showing that mice heterozygous for mitochondrial superoxide dismutase (SOD2) – despite higher levels of oxidative damage – do not have a shorter lifespan, was a major hit on the free radical theory [16]. My work and that of others showing that metabolic rate does not correlate with mammalian longevity further disproved the rate-of-living theory and, by extension, questioned free-radical-based explanations for species differences in aging [17]. If aging were simply passive damage accumulation from metabolic by-products, then this is not supported by these comparative analyses, at least for current measures of metabolic rate. Other studies, such as the observation that rats kept at lower temperatures eat 44% more food than controls and yet do not have shorter lifespans [18], provided further evidence against simplistic metabolic explanations for aging. Taken together, these results challenged the free radical theory of aging and made me question the idea that inevitable molecular damage is the driver of mammalian aging.

One observation that shaped my interest in genetic and programmatic mechanisms came from my PhD work with telomerase-immortalized cells. I found it striking that human cells can proliferate indefinitely *in vitro* as long as they express telomerase [19], despite the various forms of damage that they supposedly sustain. If unavoidable, cumulative intrinsic damage determines cellular aging, indefinite proliferation should not be possible. Moreover, unlike mouse cells, human cells do not spontaneously transform [20]. Therefore, at the fundamental level, human cells can overcome intrinsic damage and can remain functional indefinitely when key genetic programs allow it. Interestingly, Blagosklonny's observation that growth stimulation can induce cellular senescence even in the absence of molecular damage was also an important inspiration for his programmatic theories [21–23].

Developmental biology also provides clues. Most physiological functions improve from zygote to adult, and cell transplantation experiments in mice suggest that some cell populations possess intrinsic longevity

beyond that of the organism [24]. If aging is due to inevitable damage accumulation, why does such damage not accumulate during early embryonic stages? Perhaps repair mechanisms are progressively downregulated throughout development, but in that case age-related damage is no longer simply a product of passive deterioration but rather a consequence of genetic programs that regulate repair and maintenance mechanisms during development.

Similarly, strong correlations across mammals between developmental time, growth rate, and lifespan shaped my views – detailed below – on the developmental theory of aging [17]. In other words, how long it takes animals of a given species to develop is a very strong predictor of how long they will live afterwards – and presumably how fast they will degenerate. Furthermore, a mouse ages much faster than a human, regardless of environment; clearly, the genome encodes species-specific rates of aging, even between closely related species like humans and chimpanzees.

The fact that aging can be genetically manipulated in animal models further demonstrates that it is, at least in part, under genetic regulation. From my early days in the field, I found this fascinating, to the point of publishing – against the advice of more senior colleagues – a short opinion piece [25]. The significant impact of single gene manipulations on aging and longevity further supports the view that aging is not merely a process of passive deterioration. Instead, it points to coordinated biological processes in – at least to some degree – determining and regulating our longevity and aging rates. In mice, the growth hormone (GH) and insulin-like growth factor 1 (IGF-1) pathway, in particular, is a major regulator of aging [26]. Intriguingly, the wild-type alleles that promote normal levels of these signals appear to reduce lifespan, suggesting a quasi-program (non-adaptive program) that promotes aging [27].

By the early 21st century, the field was ripe for a revival of programmatic theories. Although some forms of damage – such as DNA damage, which is clearly important in cancer and similar mutation-driven diseases – contribute to aging, the idea that aging primarily emerges from genetic programs, namely the same developmental programs that build an organism, became a powerful one.

**Hyperfunction, quasi-programs, and software design flaws**

Blagosklonny and I developed our ideas independently. As I completed my PhD, and unconvinced that oxidative damage, telomeres, or cell senescence were drivers of aging, I became increasingly interested in genetic programs. Early proposals focusing solely on neuroendocrine mechanisms did not convince me [28], and did not convince Blagosklonny either, though his father was a proponent of neuroendocrine aging processes [29]. Developmental regulation clearly extends beyond hormones, implying deeper programmatic mechanisms.

George Williams's antagonistic pleiotropy theory was a major influence on both my work and Blagosklonny's. Williams proposed that processes beneficial early in life but harmful later would be favored by evolution, an observation that set the stage for programmatic theories [30]. After reviewing the literature on antagonistic pleiotropy, developmental theories of aging, and programmatic mechanisms [28, 31, 32], I formulated my first model proposing aging as a continuation of a subset of developmental programs. Published in 2005, it focused largely on physiological processes that may represent cases of antagonistic pleiotropy due to a continuation or cessation of developmental processes whose "run-on" becomes detrimental later in life [33]. I worked in collaboration with my postdoctoral mentor, George Church, whose zoological background complemented my comparative perspective. We also conceived the relation between development and aging in the context of oxidative signaling, which plays key roles during development [34].

In 2006, Blagosklonny published his seminal conceptual paper proposing the quasi-programmed theory of aging, introducing the term hyperfunction [35]. Blagosklonny proposed "a quasi-program for aging, a continuation of the developmental program that is not turned off, is constantly on, becoming hyper-functional and damaging, causing diseases of aging." While acknowledging that damage occurs with age, including damage caused by ROS, he argued that such damage plays a negligible role in determining lifespan. Instead, quasi-programs are the principal drivers of aging and limiting human lifespan [35].

A central component of Blagosklonny's model is the target of rapamycin (TOR) pathway as a major driver of growth and, later, aging. From his first publication in 2006, he argued that TOR activation promotes hyperfunction, aging, and age-related diseases – a concept he expanded upon in later work [36]. He also proposed rapamycin as a promising therapy against aging and age-related diseases.

Blagosklonny was a prolific author, publishing many influential conceptual papers, including several on the hyperfunction theory, as reviewed by others in this special issue [23]. The fact that rapamycin is the most

effective lifespan-extending drug discovered so far supports programmatic theories and Blagosklonny's ideas [37, 38]. I believe, however, that there must be more to growth and developmental regulation than mTOR alone. Species differences – for example, why mice grow, develop, and age so much faster than humans – must involve additional pathways. Therefore, while mTOR may underpin programmatic processes at a high regulatory level, from my comparative biology perspective, I cannot see how mTOR alone could account for species differences in aging.

I first became aware of Blagosklonny's work through his 2006 review. He first emailed me in June 2006 to compliment senescence.info, my website on aging. After his 2006 quasi-program paper was published, I requested a PDF from him later that year. We corresponded only occasionally. In 2008, he sent me a manuscript on TOR-driven program of aging, and I replied that although I agreed with much of it, I felt he placed too much emphasis on the mTOR pathway. His medical background meant that his hyperfunction theory had a strong human-pathophysiological focus, whereas my approach has emphasized cellular, molecular, genetic, and comparative perspectives. I believe we first met in person at the 3rd International Conference on Genetics of Aging in Sochi, Russia, in April 2014, and had a cordial discussion about our respective theories.

My recent work on programmatic theories, including the software design flaw hypothesis, emphasizes the genome and epigenome as master regulators of an informational architecture producing late-life dysfunction [39, 40]. Meanwhile, Blagosklonny's framework focused more on pathology as a manifestation of hyperfunction. In retrospect, it is unfortunate that we never collaborated, as our perspectives are highly complementary.

More recently, I have also proposed that processes that reduce cancer risk early in life may represent adaptive processes that later contribute to aging. Declines in cell proliferation, growth, and plasticity from early development until adulthood may protect against cancer, but later impair regeneration, cell proliferation, and tissue homeostasis [41]. Like me, Blagosklonny also argued that, while molecular damage drives cancer, it does not drive aging [42].

**The future of the hyperfunction theory**

Although programmatic theories, such as hyperfunction and software design flaw, provide powerful conceptual frameworks for understanding the aging process, much work remains to be done. They are still outside the dominant geroscience paradigms, such as the "hallmarks" and "pillars" of aging, which has drawn criticism from me and others [43, 44]. The unfortunate consequence – I would argue – is that most aging studies focus exclusively on adult life, hindering efforts to connect aging to developmental processes. If aging processes follow trajectories set early in life, then studying the whole life course is imperative to elucidate aging mechanisms. Besides, if repair and maintenance mechanisms are downregulated during development, then studying early development may prove valuable for identifying rejuvenation therapies, as already demonstrated in partial reprogramming.

In addition, most attempts to develop interventions and translate findings from the biology of aging to the clinic have been grounded on damage-based paradigms, such as antioxidants and senolytics [45, 46], which have so far shown limited ability to broadly retard organismal aging. While such interventions might still prove effective for specific conditions, I would argue that developing effective interventions for aging will ultimately require a greater mechanistic understanding of its underlying causes, including programmatic theories.

At present, programmatic theories remain largely underappreciated and overlooked. Blagosklonny did not seem deterred by this; he was confident he was on the right track to develop a conceptual model that explains aging and most age-related diseases. He also noted the importance of conceptual and theoretical understanding in biology [47], something often overlooked in an era dominated by high-throughput approaches.

Programmatic theories still face many challenges. They remain somewhat abstract, despite attempts (including mine and Blagosklonny's) to outline specific mechanisms, such as TOR and epigenetic regulation. Their direct relevance to human pathology is also far from established. A few aging changes, such as presbyopia and thymic involution, could reflect hyperfunction or programmatic design flaws [39, 48]; David Gems has also suggested that osteoarthritis may fit this category [49]. However, such cases are exceptions rather than the rule.

The majority of age-related degenerative changes lack clear mechanistic explanations. Except for cancer, which I view as the opposite side of aging and is driven largely by DNA damage and somatic mutations [41], I suspect most degenerative changes arise from programmatic mechanisms: the continuation or misregulation of developmental pathways that early in life change an embryo from a highly plastic and resilient organism to an adult with more limited cell plasticity

and resilience, whose run-on later results in loss of plasticity, resilience, and the major features of what we call aging. How much of the aging phenotype is programmatic? I speculate that, apart from cancer and a few other mutation-driven pathologies, most degenerative changes are due to gene regulatory programs set during development that persist into later life and become maladaptive. In other words, the loss of function and repair observed across most organs with age is the product of growth and signaling networks operating beyond their adaptive window. These quasi-programmatic processes may, in turn, result in downstream damage to cells and tissues.

Testing programmatic theories remains challenging. If aging is encoded in human biology, it will be difficult to modify with current technology. The fact that GH and IGF-1 inhibition can slow aging in mice is remarkable and supports the hyperfunction theory [27]. Likewise, the life-extending effects of caloric restriction and rapamycin further support this notion [25, 33, 39]. These interventions have systemic effects, which explains their impact on broader aspects of the aging phenotype, yet presumably more specific processes exist and remain unknown. As such, I speculate that reactivating developmental mechanisms in aged tissues could restore plasticity and function, albeit at the possible cost of increased cancer risk [41]. Several growth and signaling pathways, such as hedgehog, hippo, and wnt signaling, decline from early development and merit further study. Their complex regulation complicates therapeutic manipulation, however.

It is important to mention that programmatic theories are falsifiable. For example, if mice genetically engineered to greatly reduce molecular errors (e.g., somatic mutations) were shown to live substantially (e.g., 2-3x) longer, and aging is slowed across organs, this would strongly challenge the hyperfunction theory. Likewise, robust life-extension and multi-organ aging retardation from interventions that reduce molecular damage without altering developmental signaling would also challenge the theory. A central challenge in geroscience, however, is that life-extending interventions remain modest, making it difficult to test mechanistic theories.

Partial reprogramming using Yamanaka factors to rejuvenate cells and reset the epigenome demonstrates that biological time can be reversed, at least in cells [50]. Indeed, many companies are currently pursuing rejuvenation technologies [51]. If partial reprogramming or other genetic interventions can reverse biological age in tissues or organisms, it would strongly support a programmatic model of aging. While I believe this is possible, Yamanaka factors are perhaps too blunt for organ rejuvenation and may increase cancer risk; tissue-specific factors that revert cells to young rather than embryonic states will, I assume, be needed. Elucidating tissue-specific rejuvenation factors and demonstrating that these are not only effective in retarding aging *in vivo* but also require regulatory resetting rather than damage repair alone would provide strong evidence for the hyperfunction theory.

## CONCLUSIONS

Reflecting on the development of programmatic theories from the 19th century to the present, the core concepts emerged early and progressively evolved, shaped by Williams's antagonistic pleiotropy [30], and more recently by integrating mechanisms, such as TOR – as argued by Blagosklonny [36] – and epigenetics – as I have discussed [39]. A strength of the more recent programmatic theories is that they are evolutionary physiology theories, linking evolutionary and proximate mechanisms [27]. Much remains unknown, however.

The hyperfunction framework developed by Blagosklonny, and the elegant term hyperfunction itself, provide a powerful and underappreciated lens through which to understand aging. It is tempting to speculate that Blagosklonny will be proven increasingly correct in the decades ahead. He was a scientist ahead of his time, a bold thinker unafraid to challenge prevailing views. While current life-extending interventions support the hyperfunction theory, further empirical evidence is needed. Mapping the relationship between developmental and regenerative gene regulatory programs and age-related dysfunction may help determine the extent to which programmatic processes drive aging. Moreover, identifying and decoding rejuvenation programs within development processes may reveal targets for selectively modulating these pathways in late life.

Overall, programmatic mechanisms offer a coherent conceptual framework that fits the current empirical data, including species differences in aging and longevity manipulations in animal models. Aging is likely a hybrid phenotype, however, made up of different processes involving damage- and program-based mechanisms, and elucidating their contributions is now essential. Blagosklonny's contributions to hyperfunction theory and to programmatic perspectives more broadly have been immense, laying the foundation for future progress in understanding why we age.

## ACKNOWLEDGMENTS

I am thankful to David Gems and Idalio Viegas for comments on previous drafts. Work in my lab is

supported by grants from LongeCity and the Biotechnology and Biological Sciences Research Council. During the preparation of this work, the author used AI-assisted tools, Grammarly, Quillbot and ChatGPT, to improve readability and language. After using these tools, he reviewed and edited the text as needed and he takes full responsibility for the content of the publication.

## CONFLICTS OF INTEREST

JPM is CSO of YouthBio Therapeutics, a company developing rejuvenation gene therapies based on partial reprogramming, an advisor/consultant for the BOLD Longevity Growth Fund and NOVOS, and the founder of Magellan Science Ltd, a company providing consulting services in longevity science.

## REFERENCES

1. de Magalhães JP. An overview of contemporary theories of ageing. Nat Cell Biol. 2025; 27:1074–82. https://doi.org/10.1038/s41556-025-01698-7 PMID:40595368

2. de Magalhães JP. Distinguishing between driver and passenger mechanisms of aging. Nat Genet. 2024; 56:204–11. https://doi.org/10.1038/s41588-023-01627-0 PMID:38242993

3. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell. 2013; 153:1194–217. https://doi.org/10.1016/j.cell.2013.05.039 PMID:23746838

4. Comfort A. Ageing: The Biology of Senescence. (London: Routledge & Kegan Paul). 1964.

5. McCay CM, Crowell MF, Maynard LA. The effect of retarded growth upon the length of life span and upon the ultimate body size. Nutrition. 1935; 5:155–71. PMID:2520283

6. Kowald A, Kirkwood TB. Can aging be programmed? A critical literature review. Aging Cell. 2016; 15:986–98. https://doi.org/10.1111/acel.12510 PMID:27534524

7. Kirkwood TB, Austad SN. Why do we age? Nature. 2000; 408:233–8. https://doi.org/10.1038/35041682 PMID:11089980

8. Rose MR. Evolutionary Biology of Aging. (New York: Oxford University Press). 1991. https://doi.org/10.1093/oso/9780195061338.001.0001

9. Kirkwood TB. Evolution of ageing. Nature. 1977; 270:301–4. https://doi.org/10.1038/270301a0 PMID:593350

10. Blagosklonny MV. Why the disposable soma theory cannot explain why women live longer and why we age. Aging (Albany NY). 2010; 2:884–7. https://doi.org/10.18632/aging.100253 PMID:21191147

11. Blagosklonny MV. MTOR-driven quasi-programmed aging as a disposable soma theory: blind watchmaker vs. intelligent designer. Cell Cycle. 2013; 12:1842–7. https://doi.org/10.4161/cc.25062 PMID:23708516

12. Kennedy BK, Berger SL, Brunet A, Campisi J, Cuervo AM, Epel ES, Franceschi C, Lithgow GJ, Morimoto RI, Pessin JE, Rando TA, Richardson A, Schadt EE, et al. Geroscience: linking aging to chronic disease. Cell. 2014; 159:709–13. https://doi.org/10.1016/j.cell.2014.10.039 PMID:25417146

13. Harman D. Aging: a theory based on free radical and radiation chemistry. J Gerontol. 1956; 11:298–300. https://doi.org/10.1093/geronj/11.3.298 PMID:13332224

14. Harman D. The aging process. Proc Natl Acad Sci USA. 1981; 78:7124–8. https://doi.org/10.1073/pnas.78.11.7124 PMID:6947277

15. de Magalhães JP. Modelling human ageing: role of telomeres in stress-induced premature senescence and design of anti-ageing strategies. Doctoral dissertation. (Namur, Belgium: University of Namur). 2004.

16. Van Remmen H, Ikeno Y, Hamilton M, Pahlavani M, Wolf N, Thorpe SR, Alderson NL, Baynes JW, Epstein CJ, Huang TT, Nelson J, Strong R, Richardson A. Life-long reduction in MnSOD activity results in increased DNA damage and higher incidence of cancer but does not accelerate aging. Physiol Genomics. 2003; 16:29–37. https://doi.org/10.1152/physiolgenomics.00122.2003 PMID:14679299

17. de Magalhães JP, Costa J, Church GM. An analysis of the relationship between metabolism, developmental schedules, and longevity using phylogenetic independent contrasts. J Gerontol A Biol Sci Med Sci. 2007; 62:149–60. https://doi.org/10.1093/gerona/62.2.149 PMID:17339640

18. Holloszy JO, Smith EK. Longevity of cold-exposed rats: a reevaluation of the "rate-of-living theory". J Appl Physiol (1985). 1986; 61:1656–60. https://doi.org/10.1152/jappl.1986.61.5.1656 PMID:3781978

19. Bodnar AG, Ouellette M, Frolkis M, Holt SE, Chiu CP, Morin GB, Harley CB, Shay JW, Lichtsteiner S, Wright WE. Extension of life-span by introduction of

telomerase into normal human cells. Science. 1998; 279:349–52.
https://doi.org/10.1126/science.279.5349.349
PMID:9454332

20. Rangarajan A, Hong SJ, Gifford A, Weinberg RA. Species- and cell type-specific requirements for cellular transformation. Cancer Cell. 2004; 6:171–83.
https://doi.org/10.1016/j.ccr.2004.07.009
PMID:15324700

21. Blagosklonny MV. Cell senescence and hypermitogenic arrest. EMBO Rep. 2003; 4:358–62.
https://doi.org/10.1038/sj.embor.embor806
PMID:12671679

22. Demidenko ZN, Blagosklonny MV. Growth stimulation leads to cellular senescence when the cell cycle is blocked. Cell Cycle. 2008; 7:3355–61.
https://doi.org/10.4161/cc.7.21.6919
PMID:18948731

23. Gems D, Demaria M. Misha Blagosklonny: A life of ideas. Aging (US). in press.

24. Magrassi L, Leto K, Rossi F. Lifespan of neurons is uncoupled from organismal lifespan. Proc Natl Acad Sci USA. 2013; 110:4374–9.
https://doi.org/10.1073/pnas.1217505110
PMID:23440189

25. de Magalhães JP. Is mammalian aging genetically controlled? Biogerontology. 2003; 4:119–20.
https://doi.org/10.1023/a:1023356005749
PMID:12766537

26. Junnila RK, List EO, Berryman DE, Murrey JW, Kopchick JJ. The GH/IGF-1 axis in ageing and longevity. Nat Rev Endocrinol. 2013; 9:366–76.
https://doi.org/10.1038/nrendo.2013.67
PMID:23591370

27. Gems D. The hyperfunction theory: An emerging paradigm for the biology of aging. Ageing Res Rev. 2022; 74:101557.
https://doi.org/10.1016/j.arr.2021.101557
PMID:34990845

28. Bowen RL, Atwood CS. Living and dying for sex. A theory of aging based on the modulation of cell cycle signaling by reproductive hormones. Gerontology. 2004; 50:265–90.
https://doi.org/10.1159/000079125
PMID:15331856

29. Golubev AG. On the intergenerational transfer of ideas in aging and cancer research: from the hypothalamus according to V.M. Dilman to the mTOR protein complex according to M.V. Blagosklonny. Aging (Albany NY). 2025; 17:2655–63.
https://doi.org/10.18632/aging.206338
PMID:41269205

30. Williams GC. Pleiotropy, natural selection, and the evolution of senescence. Evolution. 1957; 11:398–411.
https://doi.org/10.1111/j.1558-5646.1957.tb02911.x

31. Rollo CD. Growth negatively impacts the life span of mammals. Evol Dev. 2002; 4:55–61.
https://doi.org/10.1046/j.1525-142x.2002.01053.x
PMID:11868658

32. Zwaan BJ. Linking development and aging. Sci Aging Knowledge Environ. 2003; 2003:pe32.
https://doi.org/10.1126/sageke.2003.47.pe32
PMID:14645858

33. de Magalhães JP, Church GM. Genomes optimize reproduction: aging as a consequence of the developmental program. Physiology (Bethesda). 2005; 20:252–9.
https://doi.org/10.1152/physiol.00010.2005
PMID:16024513

34. de Magalhães JP, Church GM. Cells discover fire: employing reactive oxygen species in development and consequences for aging. Exp Gerontol. 2006; 41:1–10.
https://doi.org/10.1016/j.exger.2005.09.002
PMID:16226003

35. Blagosklonny MV. Aging and immortality: quasi-programmed senescence and its pharmacologic inhibition. Cell Cycle. 2006; 5:2087–102.
https://doi.org/10.4161/cc.5.18.3288 PMID:17012837

36. Blagosklonny MV. TOR-driven aging: speeding car without brakes. Cell Cycle. 2009; 8:4055–9.
https://doi.org/10.4161/cc.8.24.10310
PMID:19923900

37. Moskalev A, Guvatova Z, Lopes IA, Beckett CW, Kennedy BK, De Magalhaes JP, Makarov AA. Targeting aging mechanisms: pharmacological perspectives. Trends Endocrinol Metab. 2022; 33:266–80.
https://doi.org/10.1016/j.tem.2022.01.007
PMID:35183431

38. Harrison DE, Strong R, Sharp ZD, Nelson JF, Astle CM, Flurkey K, Nadon NL, Wilkinson JE, Frenkel K, Carter CS, Pahor M, Javors MA, Fernandez E, Miller RA. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. Nature. 2009; 460:392–5.
https://doi.org/10.1038/nature08221 PMID:19587680

39. de Magalhães JP. Ageing as a software design flaw. Genome Biol. 2023; 24:51.
https://doi.org/10.1186/s13059-023-02888-y
PMID:36973715

40. de Magalhães JP. Programmatic features of aging originating in development: aging mechanisms beyond molecular damage? FASEB J. 2012; 26:4821–6.
https://doi.org/10.1096/fj.12-210872 PMID:22964300

41. de Magalhães JP. The evolution of cancer and ageing: a history of constraint. Nat Rev Cancer. 2025; 25:873–80. https://doi.org/10.1038/s41568-025-00861-4 PMID:40859047

42. Blagosklonny MV. Molecular damage in cancer: an argument for mTOR-driven aging. Aging (Albany NY). 2011; 3:1130–41. https://doi.org/10.18632/aging.100422 PMID:22246147

43. Gems D, de Magalhães JP. The hoverfly and the wasp: A critique of the hallmarks of aging as a paradigm. Ageing Res Rev. 2021; 70:101407. https://doi.org/10.1016/j.arr.2021.101407 PMID:34271186

44. Keshavarz M, Xie K, Schaaf K, Bano D, Ehninger D. Targeting the "hallmarks of aging" to slow aging and treat age-related disease: fact or fiction? Mol Psychiatry. 2023; 28:242–55. https://doi.org/10.1038/s41380-022-01680-x PMID:35840801

45. de Magalhães JP. Longevity pharmacology comes of age. Drug Discov Today. 2021; 26:1559–62. https://doi.org/10.1016/j.drudis.2021.02.015 PMID:33617794

46. Partridge L, Fuentealba M, Kennedy BK. The quest to slow ageing through drug discovery. Nat Rev Drug Discov. 2020; 19:513–32. https://doi.org/10.1038/s41573-020-0067-7 PMID:32467649

47. Blagosklonny MV, Pardee AB. Conceptual biology: unearthing the gems. Nature. 2002; 416:373. https://doi.org/10.1038/416373a PMID:11919607

48. Skulachev MV, Skulachev VP. New data on programmed aging - slow phenoptosis. Biochemistry (Mosc). 2014; 79:977–93. https://doi.org/10.1134/S0006297914100010 PMID:25519058

49. Gems D. How aging causes osteoarthritis: An evolutionary physiology perspective. Osteoarthritis Cartilage. 2025; 33:921–32. https://doi.org/10.1016/j.joca.2025.05.001 PMID:40381687

50. Ocampo A, Reddy P, Martinez-Redondo P, Platero-Luengo A, Hatanaka F, Hishida T, Li M, Lam D, Kurita M, Beyret E, Araoka T, Vazquez-Ferrer E, Donoso D, et al. *In Vivo* Amelioration of Age-Associated Hallmarks by Partial Reprogramming. Cell. 2016; 167:1719–33.e12. https://doi.org/10.1016/j.cell.2016.11.052 PMID:27984723

51. de Magalhães JP, Ocampo A. Cellular reprogramming and the rise of rejuvenation biotech. Trends Biotechnol. 2022; 40:639–42. https://doi.org/10.1016/j.tibtech.2022.01.011 PMID:35190201