***Note**: This is a preprint of a book chapter in the forthcoming edited volume Frontiers of Longevity Science (Springer Nature), expected in hardback in 2026. This preprint is shared for scholarly discussion and feedback; the final published version may differ.*

The Strong Epigenetic Theory: Aging as a Suicide Program

Yuri Deigin [1*]

[1] YouthBio Therapeutics Inc.; ORCID 0000-0002-3397-5811
* Correspondence to: ydeigin@gmail.com

Abstract

Mainstream gerontology largely remains tethered to the "wear and tear" paradigm, viewing aging as the stochastic accumulation of damage driven by the Second Law of Thermodynamics. This chapter challenges that consensus by proposing the Strong Epigenetic Theory of Aging: the hypothesis that mammalian aging is not the result of inevitable entropy, but of an evolved, centrally coordinated life-history program that actively downregulates maintenance. Drawing on comparative biology, the chapter delineates four evolutionary control modes for lifespan — stop, slow, pause, and rewind — demonstrating that longevity is a tunable parameter rather than a material constraint. A hierarchical control stack is proposed that implements this program: a central scheduler (the hypothalamic-pituitary axis) that dictates organismal tempo and orchestrates distinct life-history transitions such as menopause; an epigenetic operating system (DNA methylation and chromatin landscape) that converts transient endocrine signals into durable cellular states; and peripheral execution modules that drive systemic decline through mechanisms like thymic involution, retroelement derepression, and mesenchymal drift, among others. Finally, the chapter argues that the reversibility of biological age via partial cellular reprogramming serves as the ultimate existence proof that aging is a software problem. If senescence is a driven trajectory rather than a random accumulation of errors, it is amenable to comprehensive therapeutic rewinding.

1. Prologue: Rust, or a Script?

To this day gerontology is dominated by the metaphor of the machine: the body is a car, and aging is wear and tear — stochastic damage driven by the Second Law of Thermodynamics. This paradigm has guided decades of research, yet failed to produce a single intervention that extends rodent lifespan more than caloric restriction, discovered almost a century ago (McCay et al., 1935).

Adherents invoke the Second Law to claim aging is inevitable, but they confuse damage creation with damage accumulation. While damage creation is indeed chemically unavoidable, whether that damage

accumulates in an open system like our body is strictly a function of the ratio between injury and repair. If repair, clearance, and regeneration capacity exceed the rate of damage creation, net accumulation is zero.

Biology offers definitive existence proofs that tissue is not materially destined to fail. The germline has avoided net damage accumulation for billions of years. Vertebrates like Bowhead whales and Greenland sharks maintain massive physiology and complex tissues for centuries (George et al., 1999; Nielsen et al., 2016). If a whale can sustain mammalian organ function for over 200 years, the failure of human organs at 80 is not a material limit imposed by physics, but a regulatory limit imposed by biology.

This is the core of my Strong Epigenetic Theory: aging is not the result of inevitable entropy, but of an evolved life-history structure — a programmed gradual downregulation of maintenance.

A distinction is vital here. The “weak” epigenetic view propagated by theories like the Information Theory of Aging (Lu et al., 2023b) claims that the epigenetic changes causal to aging are the result of random damage. It frames aging as the loss of epigenetic information, and describes rejuvenation via cellular reprogramming as restoring that information from a protected backup copy (Yang et al., 2023). I disagree. Reprogramming is not a "System Restore" of a cell type’s youthful settings. Epigenetically, an old fibroblast is much closer to a young fibroblast than to a pluripotent stem cell, yet reprogramming drives past any potential “young fibroblast” state and into a radically different developmental attractor, pluripotency. The logical reading is that youth is not a hidden archive file but a reachable coordinate on the epigenetic life history landscape. Reprogramming rejuvenates old cells because genomes already contain machinery for traversing that landscape — machinery routinely exercised in development and reproduction — so cells can be pushed back toward earlier, lower-age configurations without invoking an unproven backup copy. The “strong” view argued here follows: the epigenetic changes driving aging are the result of policy, not randomness. Aging is not a scratched DVD, but a movie player reaching its tragic third act.

To be clear: “program” here does not mean a dedicated pro-damage module evolved solely to sabotage the body. Rather, it means a regulated, clock-like life-history schedule. Just as development coordinates growth, conserved endocrine and epigenetic control layers coordinate the acceleration, deceleration, or withdrawal of maintenance. The Strong Epigenetic Theory does not deny stochastic damage; it is a claim about control — why damage accumulation is tightly contained in some phases and permissively amplified in others, and why those shifts occur in a stereotyped, synchronized, species-specific way.

This chapter assembles the empirical case that aging behaves like a regulated, time-structured trajectory. I will propose the control stack that implements it — from hypothalamic scheduling to cellular execution — and suggest where in that stack we can intervene.

2. The Natural History Zoo: Lifespan as a Tunable Parameter

We begin where the "wear and tear" metaphor is weakest: natural history. When we look across the tree of life, we see a wild divergence that defies thermodynamic explanations: closely related species with near-identical physiology can dramatically differ in their lifespans. Lifespan looks much more like a trait — something evolution can tune over wide ranges — than a physical constraint.

My favorite illustration comes from rockfish. The Rougheye rockfish (*Sebastes aleutianus*) can live for over 205 years, while its cousin the Calico rockfish (*Sebastes dalli*) lives for just 12 (Cailliet et al., 2001; Love et al., 2002). Both swim in the same ocean, have similar metabolic rates, and share the same basic body plan. Yet one lineage appears to sustain functional maintenance for over two human lifespans, while another collapses on a decade-long schedule.

We see the same dramatic elasticity within Salmonidae. Pacific pink salmon mature after ~18 months at sea and return to spawn as two-year-old adults, completing their entire life cycle in just 2 years (NOAA). Yet within the same family, the lake trout (*Salvelinus namaycush*) — sharing the same basic physiology — has been reported to live up to 70 years (USFWS).

Decapod crustaceans also show lifespan elasticity: from 3–4-year blue crabs to ~100-year American lobsters (Vogt, 2012, 2019; NOAA); and Bigmouth buffalo can reach century-scale ages with minimal apparent decline — older fish showing lower stress markers, stronger innate immunity, and longer telomeres than younger conspecifics (Sauer et al., 2021).

The fossil record echoes this within the mammalian lineage. Jurassic mammaliaforms like Krusatodon and Morganucodon — despite shrew-like body sizes — show dental evidence of slow life histories, with lifespans estimated at 9–14 years (Panciroli et al., 2024; Newham et al., 2020). Contrast this with a modern mouse, which matures in weeks and dies in two years.

Hydra offers the most philosophically clarifying case, because it compresses the contrast into a single genus. Long-term follow-up suggests that *Hydra vulgaris* can maintain negligible senescence under laboratory conditions, consistent with an adult body plan built around continuous self-renewal. Yet a closely related species, *Hydra oligactis*, can be pushed into rapid, stereotyped decline specifically after sexual reproduction is induced (Martínez & Bridge, 2012). Mechanistically, Hydra also blurs the soma-germline narrative: its interstitial stem cell lineage supports both somatic lineages and gametogenesis. The implication is that "immortality versus aging" is not a hard architectural constraint imposed by physics, but a mode that can be toggled by regulation.

3. The Control Panel: Stop, Slow, Pause and Rewind

Across the biosphere we see four recurring control modes for lifespan regulation: abrupt stop, slowed aging, paused aging, and even partial rewind. Each provides a different kind of existence proof that aging is not an untimed, unavoidable decay process, but something biology can start, stop, and reconfigure.

3.1. The “Stop” Button

The most dramatic evidence for phenoptosis comes from semelparous organisms, whose rapid post-reproductive death used to be dismissed as metabolic “exhaustion” — a hypothesis that collapses under comparative scrutiny. The death of Pacific salmon is not a caloric bankruptcy but a chemical execution, a fact made clear by two natural controls. First, closely related but iteroparous species like Steelhead and Atlantic salmon undertake similarly punishing migrations yet survive to spawn again, proving the upstream journey is not intrinsically fatal. Second, landlocked “kokanee” sockeye complete their life cycle in a closed freshwater loop; yet, despite never enduring the exhausting ocean marathon, they remain semelparous, executing the fatal program on the same strict schedule.

The mechanism of this execution is a programmed “corticosteroid storm.” Upon reaching the spawning grounds, the salmon’s hypothalamic-pituitary-adrenal (HPA) axis initiates a massive release of stress hormones, triggering immune system collapse, kidney failure, and rapid tissue necrosis (Robertson & Wexler, 1960). Crucially, this death is optional. If the gonads are removed prior to maturation, the corticosteroid storm never arrives, and the fish do not die. In fact, they thrive: castrated salmon not only extend their lifespans by up to 74% but continue to grow, eventually reaching massive sizes — up to three times the weight of normal males and six times the weight of normal females (Robertson, 1961).

Anguillid eels follow similar logic. They spend decades in a growth-focused “yellow eel” phase before flipping into “silvering” — a puberty-like transition preparing them for a terminal migration. They stop feeding and regress their digestive tracts as the gonadotropic axis ramps up (Palstra & van den Thillart, 2010; Aroua et al., 2005). This switch is accompanied by rising cortisol, suggesting that, here too, the reproductive mission is coupled to corticosteroid activation (van Ginneken et al., 2007).

Semelparity also appears in several mammalian species. The male Antechinus, a small marsupial mouse, dies abruptly at 11 months after frenzied mating. As with salmon, the cause is a programmed overdose of stress hormones. Castration prevents this by blocking the androgen-dependent drop in corticosteroid-binding globulin. Castrated males can survive well beyond the natural time of mortality, even in the wild (Moore, 1974; McDonald et al., 1981), with one captive specimen recorded at 5.4 years — nearly six times its natural lifespan (Weigl, 2005).

Other cases — sea lampreys rescued from post-spawning death by hypophysectomy, female octopuses rescued by optic gland removal, and monocarpic plants (e.g., agave or Puya) and bamboo that can persist in good health for a century yet then undergo a synchronized, clocked post-reproductive die-off (e.g., ~120 years in Phyllostachys reticulata) — follow the same template: reproduction triggers a timed, regulated self-dismantling program, and interrupting the trigger can prevent it.

Once we recognize that evolution has repeatedly written hard “stop” programs into its creations, it is natural to ask whether our gradual decline is a sophisticated variation of the same pattern. A plausible stabilizing feature — suggested by the examples above — is that these programs are entangled with developmental and reproductive control: by coupling phenoptosis to the same core circuitry that governs maturation and fertility, evolution prevents “hacking”, as variants that would break the program would also compromise their development, puberty, and ultimately reproductive success.

3.2. The "Slow" Button

If the preceding examples show that nature can program a "Stop" button, social insects show that it can program a "Slow" button. In ant, bee, and termite colonies, queens and workers share identical genomes. Yet their lifespans differ by orders of magnitude.

A honey bee worker lives for just 5–6 weeks in the summer. Her sister, the queen, can live for 8 years — an 80-fold difference. In black garden ants, the disparity in absolute numbers is even starker: queens have been recorded living up to 29 years while workers live 1–2 years (Hölldobler & Wilson, 1990).

Critics often argue that queens live longer because they are "pampered" and do not forage. But the case of the Indian jumping ant (*Harpegnathos saltator*) refutes this explanation. In this species, if the queen dies, ordinary workers can fight for dominance and transition into "gamergates" (pseudo-queens). The worker's ovaries expand, her brain rewires, and her lifespan extends from 7 months to 4–5 years. Crucially, the effect is reversible: when gamergates are forced back into a worker-like state, their lifespan contracts back toward worker-like survival (Yan et al., 2022). This is a sophisticated, genetically encoded "longevity mode" that dissociates reproduction from senescence — a software patch that the worker genome always possesses but only activates upon promotion.

And this "slow mode" appears hackable: in the ant *Temnothorax nylanderi*, workers infected by the tapeworm *Anomotaenia brevis* show dramatically prolonged survival relative to uninfected nest-mates — lifespan extension on a scale that looks like a forced shift into a queen-adjacent life-history state (Beros et al., 2021). A close parallel has now been documented in social wasps: in *Polistes dominula*, workers parasitized by a female strepsipteran (*Xenos vesparum*) often survive to overwinter like future queens (Beani et al., 2021). A vertebrate analogue has also been reported: freshwater pearl mussel glochidia (*Margaritifera margaritifera*) parasitizing on Atlantic salmon gills can suppress an accelerated post-reproductive senescence trajectory and thereby extend host survival (Ziuganov, 2005).

3.3. The "Pause" Button

Some organisms can even pause aging entirely for extended periods. Larvae of the nudibranch *Phestilla sibogae* can delay metamorphosis for weeks while waiting for a specific environmental cue (a coral host). During this delay, they remain metabolically active — swimming, feeding, and burning oxygen — yet they do not age. Their subsequent adult lifespan remains completely undiminished by this period of extended activity (Miller & Hadfield, 1990).

The same uncoupling is present in the dauer larvae of *C. elegans* (Klass & Hirsh, 1976). Triggered by overcrowding or starvation, these larvae enter a state of developmental arrest that can last for months — six times their normal lifespan. Crucially, when they exit this state, their subsequent adult lifespan is unchanged; time spent in dauer does not "count" against their total allotment.

We also see this in the seasonal aging differences of the monarch butterfly. The summer generations live only a few weeks, driven by a frantic reproductive schedule. But the generation born in late summer enters reproductive diapause. These "Methuselah" monarchs migrate thousands of miles to Mexico and

live for 9 months — almost ten times longer than their parents — before re-activating their reproductive systems to head north in the spring (Herman, 1981; Herman & Tatar, 2001).

This phenomenon is not limited to insects. A remarkably similar seasonal life-history split was documented in classic Soviet research on small mammals. In a series of long-term field studies, Shvarts and colleagues analyzed the "alternation of generations" in voles and shrews. Spring-born generations followed a "live fast, die young" trajectory: they grew fast, reached sexual maturity within 2–3 months, and typically died within 4–6 months. By contrast, autumn-born animals delayed their sexual maturation, entering winter in a physiologically juvenile state. As a result, these overwintering animals only bred the following spring, at 8–10 months of age, and could survive one or even two winters (Shvarts et al., 1964; Olenev et al., 1980; Ivanter et al., 1985). A similar dichotomy is observed in the American Montane vole (*Microtus montanus*), which delays puberty by nearly 5 months if born in the fall, effectively hitting "pause" on its life history until spring arrives (van Dalum et al., 2020).

3.4. The "Benjamin Button" Button

The best example of aging in reverse comes from dermestid beetles. When starved, these larvae do not merely arrest development; they undergo "retrogressive ecdysis," literally growing smaller and biologically younger (Fahy, 2010; Shivananjappa et al., 2023).

In classic experiments, Beck and Bharadwaj (1972) demonstrated that *Trogoderma glabrum* beetles could be toggled between "childhood" and "near-maturity" repeatedly. By alternating feeding and starvation, they extended the insect's lifespan from the standard 8 weeks to over 2 years.

An even more extreme example was documented in *Trogoderma tarsale* (Wodsedalek, 1917). In a famous accidental experiment, larvae forgotten in a drawer survived 5 years of starvation — not by hibernating, but by consuming their own tissues, shrinking to approximately 1/600th of their original mass. When finally re-fed, they regrew and could be cycled through "childhood" multiple times.

Crucially, rewinding is not confined to larval bodies or metamorphic transitions. In honeybees, adult workers can reverse their "career" from high-mortality foraging back to nurse-like hive tasks when colony demography demands it. This is accompanied by a physiological rollback: foragers forced to revert show reversal of immunosenescence, alongside a nurse-like drop in juvenile hormone and rise in vitellogenin (Amdam et al., 2005). And at the molecular level, the brain methylation patterns that distinguish nurses and foragers also shift back toward the nurse-associated configuration in reverted nurses (Herb et al., 2012).

3.5. The Verdict: Existence Proofs

Taken together, these four buttons — stop, slow, pause, and rewind — are existence proofs that biology can regulate lifespan using discrete, switch-like control logic. Across phyla, reproduction, caste, season and starvation trigger specific programmes that terminate the organism, extend lifespan by orders of magnitude, suspend the clock, or reverse developmental state.

Humans, of course, do not execute a single catastrophic endocrine switch at maturity, nor can we shrink back into childhood. Yet our decline follows a highly conserved pattern. To understand that structure, we now look for the mammalian signature: endogenous timers.

4. Central Scheduling: From Biological Timers to the Hypothalamus–Pituitary Axis

4.1. Timers Everywhere: From Circadian Rhythms to Decadal Transitions

Mammalian biology is saturated with timers — we are clockwork organisms. Biological processes are initiated, maintained, and terminated on precise schedules that range from hours to decades. Aging must be interpreted against this backdrop. If evolution has repeatedly solved the problem of long-horizon timing, it would be extraordinary if senescence alone were exempt — left to drift as an untimed accident of entropy.

At short scales, circadian clocks coordinate daily rhythms of gene expression, hormone release, and metabolism. At intermediate scales, many mammals run seasonal and circannual programs: hibernation, molting, migration, and breeding, which remain calendar-locked even when food and temperature are held stable, implying internal interval-keeping.

At longer scales still, mammals execute decadal transitions. Puberty is the clearest example: a long juvenile phase of enforced reproductive quiescence, followed by a coordinated, species-typical reactivation of the hypothalamic-pituitary-gonadal axis. This delay is clearly programmed — maintained as a regulated state and then released in a discrete transition that remodels growth, metabolism, immune function, and behaviour.

Reproductive cessation provides the complementary endpoint. True human-like menopause is rare, but age-associated reproductive senescence — the durable shutdown of ovulation and fertility, whether or not a species menstruates — appears widely across mammals and is accompanied by predictable shifts in metabolism, immune tone, and disease risk (Cohen, 2004; Winkler & Gonçalves, 2023).

Classic ovarian transplantation work in rodents already hinted that long-horizon transitions are imposed from above rather than emerging from ovarian "wear." The same ovary can behave "young" or "old" depending on the age of the host's hypothalamic environment: old hosts can silence young ovaries, while young hosts can restore cyclicity to old ovaries (Aschheim, 1976).

Together, puberty and reproductive cessation make a simple point: mammals possess machinery that can track internal time over decades and trigger coordinated, organism-wide state changes at specific positions along that timeline.

Recent multi-omics studies reinforce the notion that human aging is punctuated rather than smoothly stochastic. Longitudinal profiling identified two major molecular "transition periods" around ~44 and ~60 years, with distinct functional domains shifting at each wave (Shen et al., 2024). Cross-sectional plasma

proteomics similarly found waves of change around ~34, ~60, and ~78 (Lehallier et al., 2019). Viewed alongside endocrine-driven developmental transitions across childhood and puberty, these patterns support aging as a regulated, stage-like organismal re-tuning (Mäkinen et al., 2025).

I posit that these transitions are consequences of a centrally imposed state.

4.2. When Does Aging Begin? Puberty as the On-Switch

In my view, the question "when does aging begin?" has a clear operational answer in mammals: it is the inflection point in the mortality curve that signals the beginning of an exponential rise. Across a wide range of animals, age-specific mortality is characteristically U-shaped: high after birth, declining toward a minimum around the approach to sexual maturity, then rising through adulthood — sometimes after a delay, sometimes with substantial post-reproductive survival, but with a recognizably conserved geometry (Gage, 1998; Chu et al., 2008). This isn't exclusive to humans: similar patterns appear in wild mammals with good life tables (Barlow & Boveng, 1991; Levitis et al., 2013). The Strong Epigenetic reading is straightforward: the pre-reproductive interval is a "construction and calibration" phase, during which the organism is actively driven toward lower risk. The onset of adulthood is where the long-horizon schedule we call aging actually begins (Kinzina et al., 2019; Gladyshev et al., 2024).

In semelparous systems, reproductive maturation is a discrete switch that repurposes and then decommissions the soma. As noted with anguillid eels, decades of "yellow eel" growth flip into "silvering" — a puberty-like transition preparing for a terminal migration with systemic remodeling and rising stress markers. Since a hard stop exists there, it is plausible mammals implement a softened homolog: not a cliff, but a ramp — puberty as the trigger for a centrally paced scaling back of maintenance.

The logic holds in reverse: evolution extends life by delaying the switch. As monarch "Methuselahs" and autumn-born vole/shrew cohorts illustrate, large lifespan differences are produced by holding the reproductive axis down. This is fully aligned with the Strong Epigenetic Theory: delay the policy switch, and you delay the onset of rising hazard.

Neoteny thus looks like a general evolutionary life-extension method: retain juvenile programs and keep more effective maintenance. Humans are classically described as neotenic apes (Gould, 1977; Penin et al., 2002) with "transcriptional neoteny" in the brain (Somel et al., 2009). Long-lived mammals like the naked mole-rat also appear neotenic: prolonged "youth-like" physiology and flattened hazard curves (Buffenstein, 2005; Skulachev, 2017).

A kind of "induced neoteny" is seen in classic long-lived dwarf mice — Ames (PROP1), Snell (PIT1/POU1F1), and "little" (GHRHR) — where the hypothalamus-pituitary-peripheral axes are chronically set to low growth and low reproduction: delayed or even disrupted sexual maturation, reduced GH/IGF signalling, and a somatic tempo that stays closer to juvenile settings. These animals mature slowly yet show striking lifespan extension and protection from age-linked pathologies (Brown-Borg et al., 1996; Flurkey et al., 2001; Bartke, 2008). Again, re-tuning a few endocrine setpoints that coordinate growth and puberty can shift the adult hazard regime.

This makes puberty a parsimonious marker for the "aging begins" boundary. It is the canonical decadal transition evolution already uses to re-tune endocrine setpoints and couple reproduction to an altered mortality policy. The next subsection names the switchboard: the hypothalamus-pituitary axis.

4.3. The Hypothalamus-Pituitary Axis as the Tempo-Setter

Vertebrate aging appears coordinated: systems shift together and biological clocks advance in synchrony across tissues. The Strong Epigenetic reading is that aging is not only local chemistry but is also a system-level control problem. And if it is controlled, there must be a controller.

The hypothalamus-pituitary axis is the obvious candidate. It is the hub that integrates internal state and external context, broadcasting instructions to reset peripheral setpoints. This architecture already runs physiology: the machinery that locks daily rhythms and times developmental transitions is exactly what one would expect to sit upstream of a multi-decade trajectory.

From this vantage point, puberty and reproductive cessation are canonical scheduler actions: holding the HPG axis in suppression, releasing it, and shutting it down on species-typical schedules. Aschheim's classic ovary swaps expose this hierarchy: gonads largely read out a hypothalamic–pituitary state rather than an autonomous age (Aschheim, 1976). A scheduler exists, and its levers are endocrine.

This framing also suggests a falsifiable prediction: if the scheduler sits in the head, then swapping the scheduler should swap the schedule. Parabiosis already points in this direction — old tissues partially "act young" in a young systemic milieu, and young tissues partially "act old" in an aged milieu — but shared circulation still leaves ambiguity about which signals are doing the causal work and whether the brain remains upstream of the effect. The limiting-case experiment is heterochronic "command transplantation": transplanting a young head onto an old body should drive a coordinated rejuvenation of peripheral physiology, while an old head placed on a young body should impose an aged systemic tempo.

Historically, the "central control" framing has deep roots. Long before methylation clocks, neuroendocrinologists argued that aging reflects an upstream shift in hypothalamic regulation and endocrine feedback — less a random breakdown than a directional re-setting of control thresholds. Dilman framed aging as progressive, centrally mediated shifts in homeostatic setpoints (Dilman, 1971). Everitt emphasized hypothalamic-pituitary responsiveness (Everitt, 1973), and Frolkis described a transformation of regulatory systems (Frolkis, 1976). Blagosklonny's hyperfunction theory can be read as a molecular-era continuation of this logic: late-life pathology as the inertia of developmental growth programs failing to shut down on time and thereby pushing tissues into pro-pathology states (Blagosklonny, 2021). In this case, the continuity is literally intergenerational: Blagosklonny was Dilman's son, and Golubev uses that genealogy to trace a direct conceptual line from Dilman's "elevation" framework to Blagosklonny's growth-signalling interpretations (Golubev, 2025).

Modern work turned this intuition into a mechanism. Researchers showed that activating IKKβ/NF-κB in the hypothalamus accelerates aging, whereas inhibiting it extends lifespan (Zhang et al., 2013). NF-κB

suppressed hypothalamic GnRH output, and peripheral GnRH partially restored neurogenesis — directly linking a reproductive signal to systemic aging control.

A 2017 follow-up moved from inflammation to cellular infrastructure. Ablating hypothalamic neural stem cells accelerated aging, while transplanting young hypothalamic stem cells — or delivering their secreted exosomes — extended lifespan (Zhang et al., 2017). The exosomal cargo included miRNAs capable of shifting gene expression, suggesting the hypothalamus exports regulatory "state packets" to enforce body-wide tempo. Altering this central module alters the trajectory for the entire organism.

In their heyday, classical neuroendocrine theories were limited by the tools of their time: they could describe control logic without naming its implementation. But their core intuition fits cleanly into the modern epigenetic frame. A central scheduler is exactly what you would expect if aging is a program that must be coordinated across organs. The hypothalamus can set organism-wide tempo through endocrine axes (HPA, HPT, HPG, GH/IGF) that inform peripheral gene-regulatory states. The periphery then executes those instructions locally through stable epigenetic state changes, translating systemic policy into tissue-specific chromatin and transcriptional outcomes.

The key point is not that the hypothalamus ages first and drags the body down with it, but that it is where evolution places long-horizon control. Once we accept endocrine "self-destruct subroutines" in nature, the mammalian situation is not metaphysically different. The difference is tempo: semelparous species execute a catastrophic cascade; iteroparous mammals implement a slow schedule.

5. Epigenetic Clocks: Readouts of a Conserved Trajectory

Against this background, the discovery of epigenetic clocks was confirmatory. DNA methylation clocks track biological age with striking precision across tissues, individuals, and species, despite vast differences in turnover and exposure. This is deeply problematic for stochastic damage models: neurons and leukocytes experience different wear-and-tear histories, yet age in epigenetic synchrony.

These clocks are genuine biomarkers: they correlate tightly with mortality and respond to interventions. Individuals with accelerated methylation age face elevated risks of death and disease; those with younger clocks enjoy reduced hazard. Each year of "epigenetic lead" quantifiably increases mortality risk, and multi-year leads can raise death odds by 40–50% over follow-up periods (Horvath, 2013; Chen et al., 2016).

A particularly direct demonstration of bidirectionality of these clocks comes from allogeneic hematopoietic stem-cell transplantation, which functions as a natural heterochronic experiment in humans. Researchers measured DNA methylation age in donor-recipient pairs and found that donor-derived blood cells transplanted into older recipients show accelerated epigenetic aging, whereas cells transplanted into younger recipients show deceleration (Holland et al., 2024).

Crucially, methylation clocks are highly conserved in mammals. Researchers built pan-mammalian clocks from 11,754 profiles across 185 species (Lu et al., 2023a). When normalized to life history, trajectories collapse onto a shared shape: rapid ticking during development, then exponentially slower progression

through adulthood. This “broken-stick” geometry suggests that aging is the asymptotic tail of a developmental timing program, not a separate process that begins after development ends.

That said, it is essential to interpret these clocks correctly. The CpG sites that constitute a clock are not the engine of aging. The canonical Horvath clock uses 353 CpGs out of millions; mutating them would no more stop aging than smashing a speedometer would halt a car. These sites are readouts — high-fidelity witnesses to a deeper process. Their value is diagnostic: they reveal that the organism is moving along a conserved, regulated trajectory.

One objection stemming from recent simulation work is that methylation clocks might arise solely from accumulating stochastic variation (Meyer & Schumacher, 2024), but this is a category mistake: showing that random drift is sufficient to generate a clock-like signal *in silico* does not mean that real biological clocks are nothing but noise. Moreover, the simulated clocks in such models do not recapitulate key empirical features of methylation aging — most notably the rapid, exponential ticking during development followed by a slower, linear post-pubertal phase. Finally, the authors themselves acknowledge that their simulations do not rule out programmed, non-stochastic contributions to aging.

6. The Epigenetic Operating System: How Transient Signals Become Durable State

If aging is a timed trajectory, something must store it. The epigenome provides this memory, converting transient hypothalamic signals into durable reality. Endocrine signals are pulsatile, yet aging is persistent. That persistence requires an operating system.

6.1. Writability: why the “operating system” is not just a metaphor

Before unpacking how that memory works, it’s worth establishing the key point that makes the operating system framing legitimate: the epigenome is writable, and state is reversible. When researchers used a modular CRISPR-based platform to install specific chromatin marks at chosen loci in living cells, they showed that writing a mark such as H3K4me3 can initiate gene expression *de novo* (Policarpi et al., 2024).

This extends to *in vivo* methylation. Pan et al. (2025) used inducible dCas9–DNMT3A and dCas9–TET1 mice to show that targeted editing drives physiological outcomes: methylating the Pcsk9 promoter lowered serum cholesterol, while demethylating Mecp2 reactivated expression from the inactive X chromosome.

Reversibility makes the converse argument: resetting the regulatory state restores youthful function. Reprogramming fibroblasts from very old human subjects, including centenarians, restores mitochondrial respiration (Lapasset et al., 2011; Hashizume et al., 2015) and reverses all cellular hallmarks of aging (Sarkar & Sebastiano, 2016).

This is the conceptual license for what follows: if the regulatory state can be written and rewritten, then it can serve as the organism’s long-term memory and execution layer.

6.2. Rejuvenation Is Real: The Germline And Embryonic Reset

Biology has solved the "entropy problem" in at least one context. The germline has persisted for ~3.5 billion years — an unbroken lineage of continuous division. A common intuition is that germ cells are intrinsically privileged, born with a special anti-aging shield. But developmental biology argues against this exceptionalism. In Drosophila, germline identity can be specified by localizing polar granules within a shared embryonic cytoplasm: "germness" is a positional instruction that can be assigned, not a magically protected lineage with unique anti-aging hardware. Hydra makes the same point from the opposite direction: it blurs the soma-germline boundary, with a single interstitial stem-cell lineage supporting both somatic renewal and gametogenesis (Martínez & Bridge, 2012). Even unicellular lineages implement a version of this logic: they can execute programmatic rejuvenation during sporulation, restoring replicative potential even from aged mothers (Stewart et al., 2005; Ünal et al., 2011; Coelho et al., 2013).

If germ cells are not inherently immune, then the absence of transgenerational aging demands another explanation: periodic resetting must occur.

We now have data pointing to when this happens. Using methylation clocks, Gladyshev and colleagues reported that biological age is not simply wiped clean at fertilization; it declines through early development and reaches a minimum during early post-implantation stages corresponding to gastrulation — an inferred "ground zero" from which epigenetic age then begins to rise (Kerepesi et al., 2021). Single-cell analyses reproduce the same pattern and associate the nadir with *de novo* methylation dynamics, consistent with an active reset rather than passive averaging (Trapp et al., 2021). A similar minimum around gastrulation has been reported in Xenopus, suggesting that this rejuvenation logic is conserved beyond mammals (Zhang et al., 2023a).

Importantly, the reset is not only epigenetic. At the proteome level, early development includes an explicit clearance of damaged proteins: undifferentiated mouse ES cells carry high levels of carbonylated and AGE-modified proteins, yet these lesions are eliminated upon differentiation *in vitro* and are enriched specifically in the inner cell mass *in vivo*, with differentiating lineages showing markedly reduced damage (Hernebring et al., 2006). This clearance coincides with elevated proteasome activity and induction of proteasome-activating machinery, and follow-up work argues directly against "dilution by faster growth" as an explanation (Hernebring et al., 2013). This provides more evidence that rejuvenation is staged — damage removal ramps with early differentiation, dovetailing with the timing of the methylation clock nadir.

This also offers a mechanistic clue for why OSKM is such a potent rejuvenation lever: reprogramming may be forcing adult cells back onto elements of an early-embryo reset corridor that begins with the maternal-to-zygotic transition (MZT) and zygotic genome activation (ZGA) — when transcriptional control is handed over to the embryo and chromatin competence is rebuilt — and culminates later near the gastrulation-associated nadir (Kojima et al., 2025). In mice, ZGA unfolds in waves, consistent with a staged, system-level reconfiguration (Schultz, 1993; Svoboda, 2018). Notably, iPSC reprogramming can transiently activate early-embryonic ZGA-like modules such as the MERVL/Zscan4 network, and brief early Zscan4 expression measurably boosts iPSC formation (Eckersley-Maslin et al., 2016; Hirata et al., 2012). Likewise, transient activation of Dux — an upstream driver of ZGA-like transcription — can

improve reprogramming efficiency and has been linked to coordinated epigenetic and metabolic remodeling in early reprogramming (Yang et al., 2020; Hu et al., 2024). In that framing, OSKM does not invent rejuvenation but reactivates the machinery evolution built to ensure the next generation starts at zero.

6.3. From Fast Switches To Deep Storage: Evolution Of The Epigenetic Operating System

In short-lived invertebrates, life-history transitions can be implemented by fast, reversible regulatory controls, with epigenetic chromatin marks providing one route. Labbadia and Morimoto (2015) showed that the C. elegans heat shock response is actively epigenetically shut down at reproductive maturity: stress-response loci acquire repressive H3K27me3 histone marks, blocking inducibility even under stress. The same organism also shows an analogous implementation of boundary-coupled decline: a post-reproductive loss of food-odor chemotaxis is driven by an active transcriptional switch in which the nuclear hormone receptor nhr-76 represses the odorant receptor odr-10 in sensory neurons (Yokosawa & Noma, 2025).

The same boundary-coupled logic appears in other short-lived taxa. In the rotifer Brachionus manjavacas, transcriptomics show that proteostasis is not eroded by slow damage but re-parameterized at a life-history transition: proteasome-related genes rise through early life and then, at the shift into reproductive senescence, expression flips — 31 of 38 structural proteasome subunits and catalytic co-factors drop (Gribble et al., 2017).

Mammals face a different control problem. When the life history spans decades, histone marks alone are too labile. Evolution layered in a more stable form of epigenetic memory: DNA methylation. This layer does not replace histone regulation but sits on top of it.

Epigenetic control did not start with CpG methylation. All eukaryotes, including unicellular yeast, use histone-based chromatin marks to encode regulatory state, whereas DNA methylation is patchily distributed and in some lineages is greatly reduced or apparently non-regulatory. From an evolutionary perspective, histone regulation looks like the older, universal mechanism, while vertebrate-style DNA methylation is better seen as a younger overlay that provides longer-term memory.

In mammals these layers are tightly coupled and form an integrated network: repressed DNA methylation tracks with repressive histones (H3K9me3), while gene-body methylation tracks with active transcription (H3K36). Mechanistically, they reinforce each other: hypermethylated regions accrue repressive histones, locking the state (Rose & Klose, 2014).

A decisive test of entropy-versus-program debate comes from the Gladyshev group's comprehensive profiling of the mouse methylome (Sziráki et al., 2018). Across ~800,000 CpG sites over the lifespan, global entropy rises — but the landscape shifts in a structured, non-random way. The asymmetry is the tell: methylation gains concentrate in promoters and CpG islands (silencing expression), while losses occur in repetitive elements (loosening genomic parasites). Pathway analysis shows 1,162 pathways gaining methylation versus only 102 losing it. The gaining (silencing) group is dominated by

developmental and growth-factor modules (IGF, TGF-β, WNT) and stem-cell maintenance programs, and even includes parts of the methylation machinery itself (Dnmt1).

This pattern is hard to reconcile with simple wear and tear. Passive failure could explain loss of repression but it does not explain widespread, targeted hypermethylation, which is an active, energy-consuming operation. The organism is not merely running out of order; it is spending ATP to silence networks that built it. Even the authors' own modeling distinguishes between a subset of sites driven by entropic drift and those driving these specific developmental shifts. Stochastic noise clearly exists, but it is layered on top of a coordinated rewrite of the operating system.

6.4. Pathway-Level Themes: A Conserved Mode Switch Written Into Expression And Methylation

If methylome remodeling is real, it should show up as coherent shifts in gene expression rather than random scatter. That is exactly what multi-tissue atlases report. Shavlakadze et al. (2019) defined an "Age-Related Gene Expression Signature" (AGES) across rat tissues that looks like a systemic mode switch: coordinated upregulation of innate immune, inflammatory, and apoptotic pathways coupled with downregulation of mitochondrial and oxidative phosphorylation genes, especially in liver, kidney, and muscle.

Importantly, age-linked hypermethylation often looks targeted rather than noisy. In human leukocytes, hypomethylation behaves more like drift, while hypermethylation disproportionately targets specific immune-regulatory genes, consistent with a distinct non-stochastic component (Marttila et al., 2015). This targeted silencing is visible in $CD4^+$ T cells, where the BACH2 locus shows increased DNA methylation accompanied by reduced BACH2 expression with age (Zhao et al., 2016). Similarly, in the intestine, aging involves targeted promoter hypermethylation of Wnt and homeostatic genes — an epigenetic shift leading to degrading function and increased cancer risk (Thalheim et al., 2018; Krepelova et al., 2025).

The proof of causality lies in breaking the "writer." Jeong et al. (2018) showed that deleting Dnmt3a in hematopoietic stem cells effectively immortalized them, allowing serial transplantation for twelve generations. Molecular profiling showed that this blocked the methylation process that normally restricts self-renewal.

Speaking of *in vitro* immortalization, it is worth making the lineage-level implication explicit: once cells are removed from organismal constraint, "entropy" does not enforce a fixed terminal timer. A single defined intervention — restoring telomerase activity — can bypass telomere-driven senescence and extend the proliferative lifespan of otherwise normal human cells, showing that the usual limit is an enforced checkpoint, not inevitable chemical exhaustion (Bodnar et al., 1998).

The same point is visible at extreme scale in continuous cell lineages: HeLa cells, derived in 1951, have been propagated for decades, multiplying into an effectively unbounded lineage under permissive conditions. Other workhorse lines (e.g., CHO, Vero, HEK293) tell the same story: cell populations can persist and expand long after they have been severed from the organism. None of this implies these cells remain "pristine" — genomic instability and culture adaptation are real — but it does show that what

terminates lineages *in vivo* is typically not passive wear-out but active constraint via epigenetic control layers that progressively throttle self-renewal and maintenance.

7. Slow phenoptosis implementation: withdrawal of maintenance

If evolution learned how to maintain the germline indefinitely and can reset biological age in embryos, then our aging looks more like a choice than an inevitability. The question is: why would the adult program withhold maintenance when during the early stages of organismal development the body appears to have more than enough maintenance capacity?

A common compromise position — Blagosklonny's hyperfunction theory — tries to have it both ways: yes, aging is an epigenetic continuation of development, but late-life decline is an accident, a byproduct of youth-optimized programs that keep running (Blagosklonny, 2021). The problem is that "inertia" predicts the wrong direction. If aging were merely development overshooting, the default should be continued refinement: stabilization of function, perhaps even improvement with age.

This is exactly what we observe in species where mortality risk does not explode exponentially — turtles and lobsters continue to grow and reproduce without "breaking." In contrast, the mammalian pattern requires a highly specific, convergent explanation: across independent subsystems, the body begins to drift in the same direction after sexual maturation — toward reduced repair, reduced resilience, and increased vulnerability.

The Strong Epigenetic Theory offers a simpler interpretation: the post-pubertal organism is not merely failing to maintain itself; it is being managed toward shutdown. The withdrawal of maintenance is not an unavoidable side effect of running out of evolutionary cleverness, as if evolution just forgot to turn off the development program, or couldn't figure out how to do so. It is the implementation layer of a protracted phenoptosis program — the slow analog of the cliff-edge stop button we see in semelparous species.

Mechanistically, a gradual self-destruction program does not need to break the machine, it only needs to nudge setpoints: downshift genome surveillance, loosen transposon suppression, relax proteostasis, throttle autophagy and self-renewal, bias immune tone toward chronic inflammation, tilt wound healing toward fibrosis. None of these changes has to be fatal in isolation. The signature is directionality and coordination: many small dial turns across tissues, executed over decades, producing a predictable macroscopic endpoint — exponentially rising hazard.

Some of the cleanest withdrawal examples are not subtle degradations but explicit permissioning rules in the genome-maintenance stack. The PIWI–piRNA system — one of the most potent transposon-defense layers — is classically concentrated in the germline in mammals, effectively reserving a high-grade genome policing apparatus for the lineage that must persist indefinitely (Houwing et al., 2007; Juliano et al., 2011). A superorganism version of the same logic appears in social insects: in *Macrotermes bellicosus*, piRNA-pathway genes are down-regulated in old major workers but not in long-lived reproductives, consistent with caste-specific retention of germline-like transposon defense (Elsner et al., 2018). Meanwhile, in high-regeneration animals, PIWI homologs are redeployed in long-lived somatic

stem-cell compartments (e.g. planarian neoblasts), consistent with the idea that "immortality tools" can be allocated to whichever cell lineages the organism chooses to keep perpetually young (Kim et al., 2019).

The DREAM complex represents a similar case. It is a master repressor that curbs essentially all major DNA-repair systems in somatic tissues. Disabling DREAM de-represses broad repair programs (a "germline-like" state in the soma) and produces striking resistance to diverse DNA-damage stresses (Bujarrabal-Dueso et al., 2023). Moreover, lower DREAM activity has been linked to reduced mutation rates and longer mammalian lifespan, as well as later-onset or less severe neurodegenerative pathology in humans (Koch et al., 2025).

Finally, consider regeneration — often invoked as something mammals must turn off to avoid cancer. In reality, mammals do not gradually lose regeneration because they run out of a metaphysical repair budget; they often turn it off at a boundary. The neonatal mouse heart can regenerate substantial injury, yet this capacity collapses within the first postnatal week — an abrupt developmental switch (Porrello et al., 2011). The same architecture appears in skin repair: early-gestation fetal mammals heal cutaneous wounds in a regenerative, scarless mode, but later in development this flips to the adult default — fibrotic scarring (Larson et al., 2010). That looks like a programmed policy change: a permissive repair mode is allowed early, then revoked on a schedule.

And the common intuition that regeneration is throttled to prevent cancer has the causality backwards. Standard laboratory mouse strains — despite curtailed adult regeneration — still exhibit a heavy late-life neoplastic burden, with tumors among the most common contributors to morbidity and mortality in aging cohorts (Brayton, 2012; Pettan-Brewer & Treuting, 2011). Conversely, classic high-regeneration species (planaria and axolotls) demonstrate that regeneration and tumor control can coexist: these animals regenerate aggressively without rampant cancer (Oviedo & Beane, 2009). The inference is that regeneration is one dial among many, and its throttling is better seen as part of a broader mode shift in maintenance permissions.

The common theme here is that the soma is not limited by an inability to build robust maintenance machinery, but instead is kept on a lower-permission setting by regulation.

8. Where the Buck Stops: Cells as Effectors of Systemic Policy

Even in a centrally coordinated model, the buck stops at individual cells. The hypothalamus can change hormone pulses and circadian timing, but what we call "youthful" or "aged" physiology is the aggregate result of what cells do locally.

The causal chain runs from hypothalamus to blood, to transcription networks, to stable gene-expression programs. The endocrine milieu constrains what is possible; the epigenome determines what is realized. Age-related changes — loss of regeneration, fibrosis, metabolic inflexibility — arise when large numbers of cells adopt new, coordinated expression states.

A popular “damage-first” retort to this gene-expression view is that cells are merely reacting to an externally deteriorating scaffold: the extracellular matrix (ECM) stiffens with age (via crosslinking, altered proteoglycans, scarring), and mechanosensing then forces otherwise competent cells into an “old” state. In the CNS, the flagship example is Segel et al. (2019), who show that the oligodendrocyte progenitor cell (OPC) niche stiffens with age and that soft substrates, or interference with mechanotransduction via Piezo1, restore OPC proliferation, differentiation, and youthful transcriptional signatures.

The missing backdrop is development. Brain mechanics do not sit still from neonatal life to adulthood; they change systematically as myelination, ECM composition, and cellular packing evolve. AFM studies show large, region-specific shifts in stiffness across development, and experimental perturbations of major ECM components can move local stiffness and reshape how neural stem-cell niches behave (Ryu et al., 2021; Viji Babu & Radmacher, 2019). In that light, it is unsurprising that OPCs treat “stiff” as a maturity cue — that aggressive expansion is no longer appropriate. Segel et al. themselves place Piezo1 in this developmental logic by showing it regulates OPC number during CNS development. What gets labeled as “aging via stiffness” is more plausibly a conserved developmental circuit being engaged in an aged context.

And even if stiffening is part of the causal picture, the causal buck still does not stop at the ECM — because you can override the context by editing the decoding layer. Segel et al.’s strongest result is precisely that inhibiting Piezo1 boosts proliferation, differentiation, and remyelination in aged animals despite the surrounding environment remaining “old”. The shift is fast and transcriptomic — consistent with a context-dependent state switch, not the slow reversal of random molecular lesions.

Finally, the ECM itself is not an autonomous actor. Its composition is largely an output of cellular programs — secretion, enzymatic processing, inflammatory state, developmental gene regulation. During corticogenesis, for example, epigenetic regulators such as PRC2/H3K27me3 tune ECM gene expression and thereby reshape local mechanics; PRC2 inhibition shifts proliferation versus differentiation and alters production of ECM-associated proteoglycans (Ditzer et al., 2025). The natural causal reading is layered: epigenetic state shapes ECM composition, which shapes mechanics, which biases cell behaviour — not the reverse. In a control stack, mechanics is a potent intermediate signal, but the epigenetic operating system and its transcriptional outputs remain where systemic policy is compiled into durable cellular phenotype.

This has direct implications for intervention. If aging is implemented as a shift in cellular gene-expression state, then that is where we can intercept it. Partial reprogramming is the cleanest example: impose a subset of youthful epigenetic settings onto old cells and they behave young again.

Strictly speaking, the Strong Epigenetic Theory is ultimately a gene expression theory of aging. Epigenetic mechanisms — DNA methylation, histone marks, chromatin architecture — matter because they provide long-term storage and permissions for gene expression, enforcing patterns over time rather than merely reflecting them. On shorter timescales, the same architecture already runs daily life: circadian programs, stress responses, metabolic switches. The Strong Epigenetic Theory simply extends that control logic from hours and days to decades: aging is what you get when the scheduler installs a more conservative gene expression regime across the organism.

With this control stack in hand — scheduler, operating system, cellular execution — we can now ask what it looks like in practice when a mammal transitions into a new life-history mode.

9. Case Study A: Menopause as a Neuroendocrine–Epigenetic Mode Switch

Reproductive aging provides the clearest mammalian example of a programmed transition. It culminates in a categorical outcome — fertility on, fertility off — arriving on a stereotyped timeline and accompanied by coordinated systemic changes in metabolism, immune tone, and disease risk. For decades, the dominant framing treated menopause as an exhaustion problem: the ovary "runs out" of follicles and the downstream endocrine consequences ripple outward. That story has an intuitive simplicity but it is wrong.

Classical neuroendocrinology already contained the correct intuition: the ovary is the victim, not the perpetrator. Aschheim's transplantation experiments yielded outcomes difficult to reconcile with a purely peripheral failure model: senile ovaries can resume cyclic function when grafted into young hosts, while young ovaries placed into an old host fail to cycle (Aschheim, 1976). Later cross-transplantation work in mice reproduced this logic in a cleaner, quantitative form: aged ovaries placed into young hosts could still support robust reproductive function, including pregnancies, whereas young ovaries placed into aged hosts showed sharply reduced reproductive success (Parkening & Collins, 1985).

The hypothalamus provides the bridge for this control. Reproductive aging is not just estrogen loss; it is a change in interpretation. Age-associated shifts in ERα expression in hypothalamic neurons reshape metabolic responses to hormones (Xu et al., 2011; Correa et al., 2015). The resulting phenotype (visceral fat, reduced expenditure) is best viewed not as deficiency, but as a centrally imposed re-specification of metabolic setpoints. And critically, there is evidence that the timing of this transition is not merely correlated with hypothalamic change, but is epigenetically tunable: in a rat model, pharmacologic interference with DNA methylation maintenance accelerates entry into reproductive senescence, while methyl-donor support delays it, consistent with a brain-level epigenetic timer that helps set the pace of reproductive shutdown (Bacon et al., 2019).

Recent imaging and molecular data reveal how this central policy is executed peripherally. The ovary is an actively regulated ecosystem, not a passive depleting reserve. Gaylord et al. (2025) used 3D imaging to show that oocyte density declines in structured spatial pockets, accompanied by an unexpectedly rich neural component: ovarian sympathetic axon density increases in aged ovaries, and manipulating these nerves alters follicle dynamics. Simultaneously, Li et al. (2025) report that human oocytes undergo a coordinated shift in the mid-30s: chromatin pivots toward ribosome biogenesis and translation while closing down lysosomal and proteasomal maintenance. Critically, this state is modifiable. Short-course rapamycin pushes the system back toward a maintenance-permissive regime, restoring proteostasis and nearly doubling IVF success rates.

Menopause therefore looks like a centrally scheduled transition imposed on peripheral tissue, stabilized by durable molecular state changes, and partially reversible when the relevant signalling regime is perturbed. In miniature, it recapitulates the full control stack described in this chapter — central

scheduling, epigenetic state enforcement, and cellular-level execution. This lends credibility to the broader claim: if evolution can deliberately shut down reproduction through a timed neuroendocrine-epigenetic mode switch, it is entirely plausible that somatic aging is implemented through analogous, slower, distributed switches across tissues.

10. Case Study B: Somatic Execution Modules in Slow Phenoptosis

In iteroparous mammals, gradual phenoptosis would need to be distributed: small, coordinated biases across subsystems, each tolerable on its own, but together enough to generate a reliable, exponentially rising hazard. And mammalian aging does look like a synchronized state shift: in humans, multi-tissue transcriptome analyses reveal correlated, system-wide aging trajectories across organs (Yang et al., 2015). Two domains reflect this logic well: an immune setpoint shift (endogenous inflammatory drive plus loss of immune renewal), and a structural remodeling shift (gradual replacement of functional tissue with scar).

10.1. Immune Setpoint: Retroelements And Thymic Involution

A large fraction of the mammalian genome consists of ancient viral elements. In youth, these sequences are held in check by heterochromatin and methylation; with age, that repression relaxes in a non-random, biologically meaningful way — and one consequence is a direct, mechanistically grounded bridge from the "retrobiome" to cancer.

Beyond general derepression in tumors (Burns, 2017), somatic retrotransposition is a common driver of structural genomic variation. LINE-1 insertions can seed large deletions, transductions, and rearrangements (Helman et al., 2014; Tubio et al., 2014; Rodriguez-Martin et al., 2020). Additionally, a recent study identified a non-mutational mechanism where reactivated LINE-1 RNAs nucleate 3D chromatin contacts that sustain oncogenic expression (Lee et al., 2026). This mirrors developmental roles where LINE-1 RNA guides chromatin transitions in early embryos (Jachowicz et al., 2017) and scaffolds the exit from the 2-cell state (Percharde et al., 2018). Thus, late-life relaxation of retroelement control likely drives cancer via multiple axes: genomic instability, regulatory rewiring, and oncogenic reactivation of embryo-like chromatin dynamics (Karttunen et al., 2023; Burns, 2017).

Retrobiome derepression can also kindle the inflammatory background in which tumors arise. As repetitive elements become transcriptionally active, they generate cytoplasmic intermediates that mimic viral infection. Innate sensors detect these signals and trigger type I interferon pathways and a chronic inflammatory tone — the core of inflammaging (De Cecco et al., 2013). Importantly, reverse-transcriptase inhibitors can dampen this sterile antiviral signaling (De Cecco et al., 2019; Simon et al., 2019; Mehmood et al., 2025).

Now pair that endogenous inflammatory engine with a second, complementary move: thymic involution — a controlled reduction in immune "freshness." Across mammals, the thymus undergoes a stereotyped age-linked decline that reduces thymopoiesis and naïve T-cell export (Lynch et al., 2009). What's

program-diagnostic is not only that it happens, but that it shows timing structure, accelerating around developmental transitions — most conspicuously puberty — when endocrine state is being retimed.

Even more diagnostic is rewritability. In mice, sex-steroid ablation can drive thymic regeneration; and in elderly men receiving androgen blockade, investigators reported increased circulating T cells with evidence consistent with increased naïve (TREC+) output (Sutherland et al., 2005).

At the identity layer, thymic involution also behaves like a compilable program. In aged mice, forcing TEC-specific FOXN1 upregulation was sufficient to regenerate thymic structure and increase thymopoiesis (Bredenkamp et al., 2014). Reviews of sex-steroid ablation make the broader point explicitly: endocrine inputs can be used as "upstream knobs" for immune regeneration (Velardi et al., 2015).

Recent work bolsters the "upstream knobs" concept. Friedrich et al. (2025) identified a small set of thymus-support signals that decline with age. Briefly restoring them in old mice reboots thymic output, replenishing naïve T cells and restoring vaccine and antitumor responses, including synergy with checkpoint blockade. Crucially, effects are reversible when dosing stops.

And this systemic control framing is not thymus-specific. Heterochronic parabiosis shows that old animals can be durably shifted toward youthful epigenetic and transcriptomic states across multiple organs by a young systemic environment, consistent with the existence of circulating, upstream regulators that can reset broad aging modules rather than merely patch local damage (Zhang et al., 2023b).

Together, these modules converge: derepressed repeats can both rewrite oncogenic regulation and raise innate alarm, while thymic involution shrinks adaptive renewal.

10.2. Mesenchymal Drift: A Slow Architectural Demolition Loop

Running in parallel is a broad shift toward mesenchymal programs and fibrotic remodeling. Across tissues, epithelial and endothelial cells show age-associated movement along a shared gene expression trajectory toward mesenchymal-like identity, and stromal composition shifts in the same direction (Lu et al., 2025; de Lima Camillo et al., 2025).

That process looks like half-hearted wound-healing activated in normal tissues. The same machinery that closes a wound — myofibroblast activation, EMT-like plasticity, ECM deposition — becomes chronically engaged, generating scars where none are needed (Wynn, 2008; Rockey et al., 2015). This is also where the immune module bleeds into the structural one: inflammaging keeps issuing pro-repair cues that bias stromal cells toward persistent activation.

A clean example of this immune-fibrosis coupling is IL-11. In fibroblasts, IL-11 signalling drives myofibroblast activation and fibrogenic protein synthesis, promoting ECM deposition (Schafer et al., 2017). In mouse pulmonary fibrosis, therapeutic anti-IL-11 treatment diminishes inflammation and reverses established lung fibrosis (Ng et al., 2019). And importantly for aging, anti-IL-11 treatment in old mice reduced EMT gene-set enrichment across adipose, liver, and muscle, and extended median lifespan by over 22% (Widjaja et al., 2024).

The circuitry is also self-reinforcing. Mesenchymalization promotes fibrosis, fibrosis stiffens the ECM, and stiffness feeds back through mechanotransduction to stabilize myofibroblast identity. Importantly, this module has levers: selectively inhibiting fibroblast YAP/TAZ activity can shift fibroblasts toward a fibrosis-resolving state and reverse experimental fibrosis in mice — consistent with a programmable state rather than one-way deterioration (Haak et al., 2019).

The slow architectural demolition loop is also coupled to a third, quieter module: maintenance throttling. Across organs, multi-omic profiling shows coordinated downshifts in proteostasis and metabolic machinery alongside rises in inflammatory and fibrotic programs — exactly the kind of "permission change" that makes scar replacement and immune drift more likely to compound over time (Takasugi et al., 2024).

The most program-like feature of mesenchymal drift is reversibility along a trajectory. Partial reprogramming can coherently shift aged transcriptomes away from mesenchymal drift and back toward more youthful identity programs, alongside clock rollback (Lu et al., 2025).

Together, the retrobiome and mesenchymal drift illustrate how gradual phenoptosis can be implemented without a kill switch. A long-lived mammal simply adjusts the dials: loosen transposon repression (driving cancer and internal inflammation), tilt wound healing toward EMT (scarring), and throttle cleanup (proteostatic dysfunction). This yields a tuned, iteroparous death: not a guillotine, but a slow demise by a thousand cuts.

11. Intervention: Partial Reprogramming as Program Reset

The decisive proof that age and identity are separable came from induced pluripotent stem cells. Reprogramming somatic cells from elderly donors — even centenarians — restores telomere length, mitochondrial respiration, proteostasis, and stress resistance to youthful levels (Lapasset et al., 2011). Crucially, this occurs without correcting accumulated DNA mutations. The hardware remains imperfect, yet function is restored. Age, therefore, is not encoded in irreversible genetic damage; it is encoded in epigenetic state.

Notably, as I already mentioned, embryogenesis itself appears to include an active rejuvenation phase with a clock-defined "ground zero" near gastrulation, making reprogramming best viewed as a controlled re-entry into a native reset logic (Kerepesi et al., 2021; Trapp et al., 2021; Zhang et al., 2023a).

The biggest question after the discovery of the rejuvenating power of reprogramming was whether it can produce rejuvenation without erasing cellular identity. Partial reprogramming answered that in the affirmative. Ocampo and colleagues showed that cyclic, transient expression of OSKM factors *in vivo* could extend lifespan and improve tissue function in progeroid mice (Ocampo et al., 2016). The cells moved back along an aging axis without crossing into pluripotency, demonstrating that aging is a bidirectional epigenetic landscape.

A common point of skepticism points to the inefficiency of iPSC generation: if fewer than 1% of cells reach pluripotency *in vitro*, how could partial reprogramming matter *in vivo*? This confuses initiation with completion. Chromatin opening occurs rapidly and near-universally. What is rare is the final collapse into pluripotency, halted by barriers like H3K36 methylation (Hoetker et al., 2023). For longevity, this "inefficiency" is a feature: it creates a therapeutic window where rejuvenation is common and dedifferentiation is rare.

12. Evolutionary Logic: Lifespan Control as a Lineage-Level Stabilizer

Evolutionary arguments about aging are cheap; the only ones worth keeping are those constrained by natural history. The constraint is simple: lifespan is not a thermodynamic constant. It is routinely shortened, paused, extended, and switched — often within the same genotype — via stereotyped endocrine and developmental state changes. That alone makes a narrow "damage just accumulates" framing incomplete: evolution can tune longevity by regulating life-history mode, not merely by tolerating stochastic decline.

The Strong Epigenetic Theory — aging as a post-maturation, endocrine–epigenetic retuning of maintenance setpoints — aligns with this reality. It builds on prior adaptive proposals, such as Mitteldorf's argument that senescence acts as a life-history governor stabilizing lineages in fluctuating environments (Mitteldorf, 2017; 2018), and Skulachev's (2011) concept of phenoptosis. However, it diverges in several ways: unlike Mitteldorf, it does not strictly require group selection, focusing instead on lineage robustness and extinction risk; unlike Lidsky's pathogen-control hypothesis (Lidsky & Andino, 2022), it views pathogens as one of many contributors rather than the sole driver; and unlike Skulachev's ROS-centered execution, it posits a broad, epigenetically coordinated mechanism.

Ecological niche remains the primary tuning knob: if extrinsic mortality drops, lifespans can stretch dramatically. Powered flight offers a clean natural experiment: bats achieve striking size-corrected longevity compared to similarly sized non-flying mammals, consistent with reduced extrinsic mortality selecting for slower life-history schedules (Wilkinson & South, 2002; Brunet-Rossinni & Austad, 2004).

12.1. What "Program" Means Here

In the Strong Epigenetic Theory, "programmed aging" refers to a pleiotropic life-history policy: a coordinated, system-level shift in endocrine and epigenetic state that retunes maintenance setpoints after sexual maturation. The core idea is not that organisms evolve pathways whose only purpose is to break themselves, but that they evolve timing control — the ability to move the whole organism into a different long-run operating mode once developmental objectives have been met. This is how vertebrate physiology already works: the same control stack that gates puberty, seasonal physiology, pregnancy, and other life-history states is capable, in principle, of re-tuning repair, regeneration, immune tone, and cancer restraint on an age-dependent schedule.

A useful empirical reality check is caloric restriction (CR). Even critics of programmed aging typically concede that CR elicits a coordinated, adaptive state shift in mammals — an endocrine and transcriptional re-tuning that persistently alters maintenance and stress-response priorities. Strikingly, this kind of programmed whole-organism mode switch has produced the largest and most reproducible lifespan extensions in rodents. Whatever one concludes about its ultimate evolutionary purpose, the practical lesson is that mammalian lifespan is highly sensitive to global "policy" settings.

12.2. Standard "Impossibility" Objections

The following subsections address the standard objections raised against the adaptive aging view.

12.2.1. Waning Selection Explains Too Little

Classical evolutionary gerontology emphasizes weakening selection with age (Medawar, 1952; Williams, 1957; Kirkwood, 1977). In Hamilton's framing, forces of selection on survival and fecundity decline after reproduction begins, and this has often been taken to imply senescence as near-inevitable (Hamilton, 1966; Baudisch, 2005). But comparative demography breaks the "near-law" interpretation: adult trajectories across species include increasing, constant, decreasing, humped, and even negative senescence patterns for mortality and fertility (Vaupel et al., 2004; Jones et al., 2014). Declining gradients may permit late-acting trade-offs to matter, but they do not uniquely entail senescence; realized outcomes depend on ecology and life history.

Recent work also notes that the "inexorable" decline of selection in adult ages is not assumption-free and can depend on modeling choices and structure (Giaimo, 2022). In models where aging itself evolves, declining selection can be an outcome of evolved life history rather than its mechanistic cause (Giaimo & Traulsen, 2022). In short, waning selection alone does not explain why mammals so often show coordinated, phase-like late-life reconfiguration rather than idiosyncratic drift.

One empirical fact points toward regulation: selection often delays reproduction for long periods, well beyond the earliest time an animal could reproduce in principle. Large mammals can do puberty fast: horses, cows, and pigs can breed within a year of birth, yet humans keep the reproductive axis gated for over a decade. Greenland sharks take it to the extreme by delaying sexual maturity by over 150 years. The point is not that delay is mysterious — it is that delay is implemented. Evolution doesn't only tune body plans and repair rates; it tunes when reproduction is permitted to begin. And once onset can be actively delayed, cessation becomes harder to treat as an accidental afterthought. Late-life reproductive shutdowns — and, plausibly, broader aging phenotypes — fit naturally into the same class of centrally orchestrated life-history scheduling. In other words, lifespan and reproduction are routinely co-tuned by regulation, not merely left as passive accidents of waning selection.

12.2.2. Mutation–Selection Balance Doesn't Rule Out A Scheduler

A related objection is that mutation-selection balance (MSB) already produces senescence in the wild, so there is no need to invoke an evolved aging program, and any additional "pro-aging" machinery would be unstable under mutation and drift. It is worth separating this from the stronger "thermodynamic destiny" claim. MSB is not an argument that organisms must decline because entropy inevitably wins, it is an

argument about what levels of repair fidelity and late-life performance selection will maintain in an age-structured population, as formalized in the classic "force of selection" framework (Hamilton, 1966).

However, the MSB framing is less decisive than it is often presented. First, the empirical footing for a simple Medawar-style mutation-accumulation story remains thinner than its prominence suggests; recent work explicitly notes that, despite being widely cited, direct empirical support has been limited (Kowald & Kirkwood, 2016). And some canonical equilibrium expectations fail in well-studied laboratory populations: late-life mortality often plateaus far below 100%, contradicting "wall of death" predictions under a wide range of standard assumptions (Pletcher & Curtsinger, 1998; Wachter, 1999). Recent synthesis argues that these plateaus are difficult to reconcile with canonical weakening-selection models without adding implausible auxiliary assumptions (Ringel, 2025). Relatedly, linear Hamilton-style approximations can miss qualitatively different outcomes in nonlinear formulations (Wachter et al., 2013).

Even if MSB is granted, it mainly constrains how much late-life maintenance fidelity selection will pay for, but it does not uniquely predict the form of late-life decline. MSB yields a heterogeneous, organ-by-organ mixture of late-acting failure modes, not a conserved, phase-like schedule. If turnover timing is itself under selection, that heterogeneity is a liability: stochastic unraveling increases variance in functional lifespan, which selection can reduce by canalizing background damage into a more reliable trajectory via coupled control. Cells can die stochastically, yet organisms evolved apoptosis; regulation is valuable precisely because uncontrolled failure is noisy and chaotic.

12.2.3. "Cost Of Reproduction" Is Not The Explanation

The Disposable Soma theory argues that aging reflects an optimal allocation of limited resources between reproduction and maintenance (Kirkwood, 1977). In this zero-sum view, organisms cannot "afford" both maximal reproductive output and perfect repair, so evolution favors breeding while underfunding maintenance. Yet the nature of this "limited resource" remains elusive. It cannot simply be calories or ATP, as caloric restriction reliably extends lifespan across species. If energy were the binding constraint, cutting it further should accelerate aging, not slow it.

Empirically, predicted negative correlations often fail. Drosophila lines selected for delayed senescence evolved higher fecundity and longer lifespans (Leroi et al., 1994). In Mediterranean fruit flies, higher total egg production does not predict early death; the key predictor is the rate of reproductive decline, consistent with shared pacing rather than a fixed-budget war (Müller et al., 2001).

Caste systems provide decisive counter-evidence. Queens routinely live 10–20 times longer than workers despite massive reproductive output. In Harpegnathos ants workers dramatically extend lifespan upon transitioning into reproductive roles. In Ansell's mole-rat, breeders even have higher resting metabolic rates than non-breeders (Schielke et al., 2017).

12.2.4. Cancelling-Out Argument Assumes The Wrong Architecture

Aubrey de Grey's cancelling-out argument (COA) has intuitive force, but only against a specific kind of programmed aging. COA targets architectures where aging is the net result of many weak, largely

independent pro- and anti-aging influences: if component A slightly worsens repair while component B slightly reduces damage, variants can cancel each other's net effect, leaving selection too weak to maintain a stable, directional program (de Grey, 2015).

That is not the architecture proposed by the Strong Epigenetic Theory. A post-maturation mode switch is not a detachable, late-acting sabotage module; it is a pleiotropic policy re-tuning implemented by controllers that already coordinate life-history transitions. Endocrine and neural regulators act broadly and in a coupled fashion: they move suites of traits together (growth, reproduction, stress physiology, immune tone, repair priorities), not one damage class at a time (Finch & Rose, 1995; Zera & Harshman, 2001). In that architecture, "cancellation" is not easy because you are not summing independent sliders; you are turning a small number of high-level knobs whose early- and midlife footprints are large — and therefore strongly visible to selection. COA also relies on an implicit near-neutrality premise: that the scheduling circuitry can drift without consequence. Pleiotropic controllers are the opposite of near-neutral.

A concrete natural-history example illustrates the difference. In Pacific salmon, the lethal post-spawning collapse is driven by a centrally orchestrated endocrine cascade. Interrupt the reproductive trigger (e.g. via gonad removal before maturation), and the downstream death program fails to launch; animals survive, keep growing, and can reach dramatically larger sizes (Robertson & Wexler, 1960; Robertson, 1961). This shows that nature already implements lifespan control as a discrete endocrine state transition. In mammals, puberty can be the same trigger for a slow phenoptosis variant implemented via gradual toning down of maintenance, as proposed by the Strong Epigenetic Theory.

Finally, timing is not fungible. "Slightly worse repair forever" is not equivalent to "high repair early, relaxed repair later," because aging is path-dependent: many late-life failures involve thresholds and feedback loops. A schedule is not a scalar; it is an ordering of states.

In summary, COA is a strong critique of a modular tug-of-war scenario, but it does not work against a life-history mode-switch architecture, where aging emerges when evolution re-tunes organism-wide maintenance permissions after maturation via pleiotropic controllers.

12.2.5. Install Vs Uninstall: Why A Scheduled Decline Can Be Easy To Evolve And Hard To Remove

If selection can "install" scheduled decline, why not "uninstall" it where longer life seems beneficial? Because evolution is path-dependent, not reversible engineering. Development already requires a sophisticated toolkit of timers, gates, and mode switches — embryogenesis, maturation, puberty, pregnancy/lactation, seasonal physiology, famine reallocation — implemented via endocrine broadcasting and epigenetic state control. Once those knobs exist, reusing them for later-life transitions (reproductive shutdown, maintenance throttling, turnover) is an easy evolutionary move.

But removing a coupled, distributed policy is not the mirror image of adding it. If aging is implemented across an endocrine–epigenetic control stack, it is not localized to one "aging gene" that can be deleted cleanly. Accessible mutations are more likely to perturb calibration of growth, reproduction, and immunity than to remove late-life decline in isolation; intermediate states may fall into fitness valleys combining liabilities of both modes.

12.3. Why Turnover Control Can Increase Long-Run Fitness

In a fluctuating world, strategies that maximize short-term individual success can be brittle. Over deep time, what matters is not only doing well in the good years, but avoiding rare catastrophic busts — because one near-zero generation can erase the gains of many good ones. This is a standard result of population growth under environmental randomness: multiplicative compounding makes downside volatility disproportionately costly, so "high average output" can still be a losing strategy if it comes with occasional crashes (Lewontin & Cohen, 1969; Simons, 2011).

Mechanisms that regulate turnover — aging, menopause, senescence, and other life-history governors — can therefore trade peak output for robustness. The curve is lower, but it persists. And this is not a new kind of evolutionary trick: mammals already use long-horizon scheduling to gate life-history states — puberty turns reproduction on, menopause turns it off, and seasonal biology can hold whole systems in standby — so "turnover control" is just one more timed switch in a control stack evolution clearly knows how to build.

One potential stimulus is demographic stabilization. When negative feedback operates with delays (resources, density dependence, maturation time), populations become prone to overshoot-and-crash dynamics. Policies that restrain prolonged adult persistence or damp explosive growth can reduce the amplitude of these swings and lower the risk of collapse in the bad tail of environmental years (May, 1973; Turchin, 2003). Importantly, this isn't just a verbal plausibility argument: modelling work shows that age structure, senescence and post-reproductive phases can act as a built-in "dampening term," smoothing predator-prey volatility and lowering local extinction risk (Mitteldorf & Goodnight, 2013).

A second potential stimulus is infectious burden. For many pathogens, host turnover and age structure shape reservoir dynamics, because they change how long infections can persist in individuals and how efficiently a population can keep transmission going. In practice, the sign can depend on the pathogen: fast life-history species often show higher reservoir competence across zoonotic systems, while long-lived hosts can, for chronic infections, extend the time window over which infection can be carried and transmitted (Anderson & May, 1991; Plourde et al., 2017). More directly, experimental and modelling work shows that host lifespan is itself a trait that can modulate "reservoir potential" through effects on susceptibility/competence and demographic turnover (Hily et al., 2014). This overlaps with the pathogen-control framing of adaptive lifespan limits (Lidsky & Andino, 2022).

None of this requires "the good of the species." In variable environments, selection can favor policies that reduce variance and extinction risk even when they impose costs on individual bearers — the core logic of bet hedging and variance-sensitive selection (Simons, 2011).

Under the Strong Epigenetic framework, the key point is architectural: evolution already built endocrine–epigenetic machinery to time life-history mode switches; once that control stack exists, regulated turnover becomes an evolvable policy knob. Aging, in this view, is not a failure of maintenance or a lapse of evolutionary cleverness. It is a schedule: a controllable mode shift encoded in life-history programs and executed through the same endocrine–epigenetic machinery that already times development.

13. Conclusion

The arc of this chapter has been deliberately cumulative. Natural history shows that lifespan is a tunable parameter — biology can stop, slow, pause, or revert decline — while mammals already run on long-horizon timing programs, and epigenetic clocks reveal a conserved, tissue-synchronized aging trajectory. Together these observations support a layered control stack: neuroendocrine scheduling sets organismal mode via hypothalamus–pituitary axes, the epigenome converts transient signals into durable state, and cells execute that policy as coordinated shifts in gene expression — visible in programmed transitions like reproductive shutdown and in somatic modules such as inflammaging and fibrotic remodeling.

These observations refute the idea that aging is simply an unavoidable tax imposed by entropy. Biology has repeatedly evolved ways to maintain order and to reset state — most clearly in germline continuity and in the rejuvenation that accompanies early development. The simplest synthesis is that mammalian aging is not only something that happens to us, but also something our own regulatory architecture helps do: scheduled, distributed, and written into cellular memory.

While this realization — that our own genes are plotting our demise — can be unpleasant, it is also profoundly hopeful. We cannot easily change the laws of physics, but we can rewrite software. And if our scheduled death is a program, then — as the last decade of reprogramming biology suggests — it is one we are beginning to acquire the tools to interrupt, rewrite, and roll back.

References

1. Amdam, G.V., Aase, A.L.T.O., Seehuus, S.-C., Kim Fondrk, M., Norberg, K. and Hartfelder, K. (2005) 'Social reversal of immunosenescence in honey bee workers', Experimental Gerontology, 40(12), pp. 939–947. doi:10.1016/j.exger.2005.08.004.

2. Anderson, R.M. and May, R.M. (1991) Infectious Diseases of Humans: Dynamics and Control. Oxford: Oxford University Press.

3. Aroua, S., Schmitz, M., Baloche, S., Vidal, B., Rousseau, K. & Dufour, S. (2005) 'Endocrine evidence that silvering, a secondary metamorphosis in the eel, is a pubertal rather than a metamorphic event', Neuroendocrinology, 82(3–4), pp. 221–232. doi:10.1159/000092642.

4. Aschheim, P. (1976). Aging in the hypothalamic-hypophyseal ovarian axis in the rat. In: Everitt, A. V., & Burgess, J. A. (eds). Hypothalamus, pituitary, and aging. Thomas, pp. 376–418.

5. Bacon, E.R., Mishra, A., Wang, Y., Desai, M.K., Yin, F., Brinton, R.D. (2019) Neuroendocrine aging precedes perimenopause and is regulated by DNA methylation. Neurobiology of Aging 74:213–224. https://doi.org/10.1016/j.neurobiolaging.2018.09.029

6. Barlow, J. and Boveng, P. (1991) 'Modelling age-specific mortality for marine mammal populations', Marine Mammal Science, 7(1), pp. 50–65.

7. Bartke, A. (2008) 'Growth hormone and aging: a challenging controversy', Clinical Interventions in Aging, 3(4), pp. 659–665. doi:10.2147/CIA.S3697.

8. Baudisch A. Hamilton's indicators of the force of selection. Proc Natl Acad Sci U S A. 2005 Jun 7;102(23):8263-8. doi: 10.1073/pnas.0502155102.

9. Beani, L., Dallai, R., Cappa, F., Manfredini, F., Zaccaroni, M., Lorenzi, M.C., Mercati, D. (2021) A strepsipteran parasite extends the lifespan of workers in a social wasp. Scientific Reports 11:7235. https://doi.org/10.1038/s41598-021-86182-6

10. Beck SD, Bharadwaj RK (1972) Reversed development and cellular aging in an insect. Science 178:1210–1211

11. Beros, S., Jongepier, E., Hagemeier, F., Foitzik, S., Feldmeyer, B. (2021) Extreme lifespan extension in tapeworm-infected ant workers. Royal Society Open Science 8(5):202118. https://doi.org/10.1098/rsos.202118

12. Blagosklonny, M.V. (2021) 'The hyperfunction theory of aging: three common misconceptions', Oncoscience, 8, pp. 103–117.

13. 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 Jan 16;279(5349):349-52. doi: 10.1126/science.279.5349.349.

14. Brayton, C.F. (2012) 'Pathobiology of aging mice and GEM: background strains and experimental design', Veterinary Pathology, 49(1), pp. 85–105.

15. Bredenkamp, N., Nowell, C.S. and Blackburn, C.C. (2014) 'Regeneration of the aged thymus by a single transcription factor', Development, 141(8), pp. 1627–1637.

16. Brown-Borg, H.M., Borg, K.E., Meliska, C.J. and Bartke, A. (1996) 'Dwarf mice and the ageing process', Nature, 384(6604), p. 33. doi:10.1038/384033a0.

17. Brunet-Rossinni, A.K. and Austad, S.N. (2004) 'Ageing studies on bats: a review', Biogerontology, 5(4), pp. 211–222. doi:10.1023/B:BGEN.0000038022.65024.d8.

18. Buffenstein, R. (2005) 'The naked mole-rat: a new long-living model for human aging research', The Journals of Gerontology: Series A, 60(11), pp. 1369–1377.

19. Bujarrabal-Dueso, A., Sendtner, G., Meyer, D.H., et al. (2023) 'The DREAM complex functions as conserved master regulator of somatic DNA-repair capacities', Nature Structural & Molecular Biology, 30, pp. 475–488. doi:10.1038/s41594-023-00942-8.

20. Burns, K.H. (2017) 'Transposable elements in cancer', Nature Reviews Cancer, 17(7), pp. 415–424. doi:10.1038/nrc.2017.35.

21. Cailliet, G.M., Andrews, A.H., Burton, E.J., Watters, D.L., Kline, D.E. and Ferry-Graham, L.A. (2001) 'Age determination and validation studies of marine fishes: do deep-dwellers live longer?', Experimental Gerontology, 36(4–6), pp. 739–764. https://doi.org/10.1016/S0531-5565(00)00239-4.

22. Chen, B.H., Marioni, R.E., Colicino, E., Peters, M.J., Ward-Caviness, C.K., Tsai, P.-C., et al. (2016) 'DNA methylation-based measures of biological age: meta-analysis predicting time to death', Aging (Albany NY), 8(9), pp. 1844–1865. https://doi.org/10.18632/aging.101020.

23. Chu, C.Y.C., Chien, H.-K. and Lee, R.D. (2008) 'Explaining the optimality of U-shaped age-specific mortality', Theoretical Population Biology, 73(2), pp. 171–180.

24. Coelho, M., Dereli, A., Haese, A., Kuhn, S., Malinovska, L., De Santis, M., Shorter, J., Gross, T. and Tolic-Norrelykke, I.M. (2013) 'Fission yeast does not age under favorable conditions, but does so after stress', Current Biology, 23(19), pp. 1844–1852. doi:10.1016/j.cub.2013.07.084.

25. Cohen, A.A. (2004) 'Female post-reproductive lifespan: a general mammalian trait', Biological Reviews, 79(4), pp. 733–750.

26. Correa, S.M., et al. (2015). An estrogen-responsive module in the ventromedial hypothalamus selectively drives sex-specific body weight regulation. Cell Reports, 10(1), 60-70.

27. van Dalum J, Melum VJ., Wood SH. and Hazlerigg DG. (2020) Maternal Photoperiodic Programming: Melatonin and Seasonal Synchronization Before Birth. Front. Endocrinol. 10:901. doi: 10.3389/fendo.2019.00901

28. De Cecco, M., Criscione, S.W., Peterson, A.L., Neretti, N., Sedivy, J.M. and Kreiling, J.A. (2013) 'Transposable elements become active and mobile in the genomes of aging mammalian somatic tissues', Aging (Albany NY), 5(12), pp. 867–883. doi:10.18632/aging.100621.

29. De Cecco M, Ito T, Petrashen AP, Elias AE, Skvir NJ, Criscione SW, Caligiana A, Brocculi G, Adney EM, Boeke JD, Le O, Beauséjour C, Ambati J, Ambati K, Simon M, Seluanov A, Gorbunova V, Slagboom PE, Helfand SL, Neretti N, Sedivy JM. L1 drives IFN in senescent cells and promotes age-associated inflammation. Nature. 2019 Feb;566(7742):73-78. doi: 10.1038/s41586-018-0784-9. Epub 2019 Feb 6. Erratum in: Nature. 2019 Aug;572(7767):E5. doi: 10.1038/s41586-019-1350-9. PMID: 30728521; PMCID: PMC6519963.

30. Dilman, V.M. (1971) 'Age-associated elevation of hypothalamic threshold to feedback control and its role in development, ageing, and disease', The Lancet, 2(7731), pp. 1211–1212. doi:10.1016/S0140-6736(71)90295-4.

31. Ditzer, N. et al. (2025) 'Epigenome profiling identifies H3K27me3 regulation of extracellular matrix composition in human corticogenesis', Neuron. 2025 Sep 17;113(18):2927-2944.e10. doi: 10.1016/j.neuron.2025.06.016. Epub 2025 Jul 22. PMID: 40701154.

32. Eckersley-Maslin, M.A. et al. (2016) 'MERVL/Zscan4 network activation results in transient genome-wide DNA demethylation of mESCs', Cell Reports, 17(1), pp. 179–192. doi:10.1016/j.celrep.2016.08.087.

33. Elsner, D., Meusemann, K. and Korb, J. (2018) 'Longevity and transposon defense, the case of termite reproductives', Proceedings of the National Academy of Sciences of the United States of America, 115(21), pp. 5504–5509. doi:10.1073/pnas.1804046115.

34. Everitt, A.V. (1973) 'The hypothalamic–pituitary control of ageing and age-related pathology', Experimental Gerontology, 8, pp. 265–277. doi:10.1016/0531-5565(73)90032-5.

35. Fahy, G.M. (2010). Precedents for the Biological Control of Aging: Experimental Postponement, Prevention, and Reversal of Aging Processes. In: Fahy, G.M., West, M.D., Coles, L.S., Harris, S.B. (eds) The Future of Aging. Springer, Dordrecht. https://doi.org/10.1007/978-90-481-3999-6_6

36. Finch CE, Rose MR. Hormones and the physiological architecture of life history evolution. Q Rev Biol. 1995 Mar;70(1):1-52. doi: 10.1086/418864. PMID: 7732161.

37. Flurkey, K., Papaconstantinou, J., Miller, R.A. and Harrison, D.E. (2001) 'Lifespan extension and delayed immune and collagen aging in mutant mice with defects in growth hormone production', Proceedings of the National Academy of Sciences of the United States of America, 98(12), pp. 6736–6741. doi:10.1073/pnas.111158898.

38. Friedrich, M.J., Pham, J., Tian, J. et al. (2025) ‘Transient hepatic reconstitution of trophic factors enhances aged immunity’, Nature. https://doi.org/10.1038/s41586-025-09873-4.

39. Frolkis, V.V. (1976). The Hypothalamic Mechanisms of Aging. In: Everitt, A. V., & Burgess, J. A. (eds). Hypothalamus, pituitary, and aging. Thomas, pp. 614–633.

40. Gage, T.B. (1998) ‘The comparative demography of primates: with some comments on the evolution of life histories’, Annual Review of Anthropology, 27, pp. 197–221.

41. Gaylord EA et al. (2025) Comparative analysis of human and mouse ovaries across age.Science390,eadx0659.DOI:10.1126/science.adx0659

42. George JC, Bada J, Zeh J, Scott L, Brown SE, O'Hara T, Suydam R. Age and growth estimates of bowhead whales (Balaena mysticetus) via aspartic acid racemization. Can. J. Zool. 1999; 77:571-580.

43. Giaimo, S. (2022) ‘Selection on age-specific survival: Constant versus fluctuating environment’, Theoretical Population Biology, 145, pp. 136–149. doi:10.1016/j.tpb.2022.05.001.

44. Giaimo, S. and Traulsen, A. (2022) ‘The selection force weakens with age because ageing evolves and not vice versa’, Nature Communications, 13, 686.

45. van Ginneken, V., Durif, C., Paul Balm, S., Boot, R., Verstegen, M.W.A., Antonissen, E. & van den Thillart, G. (2007) ‘Silvering of European eel (Anguilla anguilla L.): seasonal changes of morphological and metabolic parameters’, Animal Biology, 57(1), pp. 63–77. doi:10.1163/157075607780002014.

46. Gladyshev, V.N., Kerepesi, C., Kinzina, E. et al. (2024) ‘What is aging? A survey of biogerontologists’, PNAS Nexus, 3(12), pgae499.

47. Golubev, A. (2025) ‘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 Nov 19;17(11):2655-2663. doi: 10.18632/aging.206338.

48. Gould, S.J. (1977) Ontogeny and Phylogeny. Cambridge, MA: Harvard University Press.

49. de Grey, A.D.N.J. (2015) ‘Do we have genes that exist to hasten aging? New data, new arguments, but the answer is still no’, Current Aging Science, 8(1), pp. 24–33. doi:10.2174/1874609808666150421131304.

50. Gribble KE, Mark Welch DB. Genome-wide transcriptomics of aging in the rotifer Brachionus manjavacas, an emerging model system. BMC Genomics. 2017 Mar 1;18(1):217. doi: 10.1186/s12864-017-3540-x

51. Haak, A.J. et al. (2019) ‘Selective YAP/TAZ inhibition in fibroblasts via dopamine receptor D1 agonism reverses fibrosis’, Science Translational Medicine, 11(516), eaau6296. doi: 10.1126/scitranslmed.aau6296.

52. Hamilton, W.D. (1966) ‘The moulding of senescence by natural selection’, Journal of Theoretical Biology, 12(1), pp. 12–45. doi:10.1016/0022-5193(66)90184-6.

53. Hashizume, O., Ohnishi, S., Mito, T. et al. Epigenetic regulation of the nuclear-coded GCAT and SHMT2 genes confers human age-associated mitochondrial respiration defects. Sci Rep 5, 10434 (2015). https://doi.org/10.1038/srep10434

54. Helman, E., Lawrence, M.S., Stewart, C., Sougnez, C., Getz, G. and Meyerson, M. (2014) ‘Somatic retrotransposition in human cancer revealed by whole-genome and exome sequencing’, Genome Research, 24(7), pp. 1053–1063. doi:10.1101/gr.163659.113.

55. Herb, B.R., Wolschin, F., Hansen, K.D., Aryee, M.J., Langmead, B., Irizarry, R., Amdam, G.V. and Feinberg, A.P. (2012) ‘Reversible switching between epigenetic states in honeybee behavioral subcastes’, Nature Neuroscience, 15(10), pp. 1371–1373. doi:10.1038/nn.3218.

56. Herman, W.S. (1981) ‘Studies on the adult reproductive diapause of the monarch butterfly, Danaus plexippus’, The Biological Bulletin, 160(1), pp. 89–106.

57. Herman, W.S. and Tatar, M. (2001) ‘Juvenile hormone regulation of longevity in the migratory monarch butterfly’, Proceedings of the Royal Society of London. Series B: Biological Sciences, 268(1485), pp. 2509–2514.

58. Hernebring, M., Brolen, G., Aguilaniu, H., Semb, H. and Nystrom, T. (2006) ‘Elimination of damaged proteins during differentiation of embryonic stem cells’, Proceedings of the National Academy of Sciences of the United States of America, 103(20), pp. 7700–7705. doi:10.1073/pnas.0510944103.

59. Hernebring, M., Fredriksson, A., Liljevald, M., Cvijovic, M., Norrman, K., Wiseman, J., Semb, H. and Nystrom, T. (2013) ‘Removal of damaged proteins during ES cell fate specification requires the proteasome activator PA28’, Scientific Reports, 3, 1381. doi:10.1038/srep01381.

60. Hily, J.M., Garcia, A., Moreno, A., Plaza, M., Wilkinson, M.D., Fereres, A., et al. (2014) ‘The relationship between host lifespan and pathogen reservoir potential: an analysis in the system Arabidopsis thaliana–cucumber mosaic virus’, PLoS Pathogens, 10(11), e1004492.

61. Hirata, T. et al. (2012) ‘Zscan4 transiently reactivates early embryonic genes during the generation of induced pluripotent stem cells’, Scientific Reports, 2, 208. doi:10.1038/srep00208.

62. Hoetker, M.S., Yagi, M., Di Stefano, B. et al. H3K36 methylation maintains cell identity by regulating opposing lineage programmes. Nat Cell Biol 25, 1121–1134 (2023). https://doi.org/10.1038/s41556-023-01191-z

63. Hölldobler, B. and Wilson, E.O., 1990. The ants. Harvard University Press.

64. Holland, P., Istre, M., Ali, M. M., Gedde-Dahl, T., Buechner, J., Wildhagen, M., Brunvoll, S. H., Horvath, S., Matsuyama, S., Dahl, J. A., Stolzel, F., & Soraas, A. (2024). Epigenetic aging of human blood cells is influenced by the age of the host body. Aging Cell, 23, e14112. https://doi.org/10.1111/acel.14112

65. Horvath S. DNA methylation age of human tissues and cell types. Genome Biol. 2013;14(10):R115. doi: 10.1186/gb-2013-14-10-r115.

66. Houwing, S., Kamminga, L.M., Berezikov, E., Cronembold, D., Girard, A., van den Elst, H., Filippov, D.V., Blaser, H., Raz, E., Moens, C.B., Plasterk, R.H.A., Hannon, G.J., Draper, B.W. and Ketting, R.F. (2007) 'A role for Piwi and piRNAs in germ cell maintenance and transposon silencing in Zebrafish', Cell, 129(1), pp. 69–82. doi:10.1016/j.cell.2007.03.026.

67. Hu, X. et al. (2024) 'Dux activates metabolism-lactylation-MET network during early iPSC reprogramming with Brg1 as the histone lactylation reader', Nucleic Acids Research, 52(10), pp. 5529–5549. doi:10.1093/nar/gkae362.

68. Ivanter, E.V., Ivanter, T.V. and Tumanov, I.L. (1985) Adaptivnye osobennosti melkikh mlekopitayushchikh [Adaptive features of small mammals; in Russian]. Leningrad: Nauka.

69. Jachowicz, J.W., Bing, X., Pontabry, J., Bošković, A., Rando, O.J. and Torres-Padilla, M.-E. (2017) 'LINE-1 activation after fertilization regulates global chromatin accessibility in the early mouse embryo', Nature Genetics, 49(10), pp. 1502–1510. doi:10.1038/ng.3945.

70. Jeong M, Park HJ, Celik H, Ostrander EL, Reyes JM, Guzman A, Rodriguez B, Lei Y, Lee Y, Ding L, Guryanova OA, Li W, Goodell MA, Challen GA. Loss of Dnmt3a Immortalizes Hematopoietic Stem Cells In Vivo. Cell Rep. 2018 Apr 3;23(1):1-10. doi: 10.1016/j.celrep.2018.03.025.

71. Jones, O.R. et al. (2014) 'Diversity of ageing across the tree of life', Nature, 505, pp. 169–173.

72. Juliano, C., Wang, J. and Lin, H. (2011) 'Uniting germline and stem cells: the function of Piwi proteins and the piRNA pathway in diverse organisms', Annual Review of Genetics, 45, pp. 447–469. doi:10.1146/annurev-genet-110410-132541.

73. Karttunen, K., Patel, D., Xia, J., Fei, L., Palin, K., Aaltonen, L. and Sahu, B. (2023) 'Transposable elements as tissue-specific enhancers in cancers of endodermal lineage', Nature Communications, 14(1), 5313. doi:10.1038/s41467-023-41081-4.

74. Kerepesi, C., Zhang, B., Lee, S.-G., Trapp, A. and Gladyshev, V.N. (2021) 'Epigenetic clocks reveal a rejuvenation event during embryogenesis followed by aging', Science Advances, 7(26), eabg6082. doi:10.1126/sciadv.abg6082.

75. Kim, I.V., Duncan, E.M., Ross, E.J., Gorbovytska, V., Nowotarski, S.H., Elliott, S.A., Sánchez Alvarado, A. and Kuhn, C.-D. (2019) 'Planarians recruit piRNAs for mRNA turnover in adult stem cells', Genes & Development, 33(21–22), pp. 1575–1590. doi:10.1101/gad.322776.118.

76. Kinzina, E.D., Podolskiy, D.I., Dmitriev, S.E. and Gladyshev, V.N. (2019) 'Patterns of aging biomarkers, mortality, and damaging processes during the life span in humans', Cell Rep. 2019 Dec 24;29(13):4276-4284.e3. doi: 10.1016/j.celrep.2019.11.091. PMID: 31875539.

77. Kirkwood TB. Evolution of ageing. Nature. 1977 Nov 24;270(5635):301-4. doi: 10.1038/270301a0. PMID: 593350.

78. Klass M, Hirsh D (1976) Non-ageing developmental variant of Caenorhabditis elegans. Nature 260:523–525

79. Koch, Z., Nandi, S.P., Licon, K., et al. (2025) 'The DREAM complex links somatic mutation, lifespan, and disease', bioRxiv (preprint). doi:10.1101/2025.09.15.676396.

80. Kojima, M.L., Hoppe, C. and Giraldez, A.J. (2025) 'The maternal-to-zygotic transition: reprogramming of the cytoplasm and nucleus', Nature Reviews Genetics, 26(4), pp. 245–267. doi:10.1038/s41576-024-00792-0.

81. Kowald, A. and Kirkwood, T.B.L. (2016) 'Can aging be programmed? A critical literature review', Aging Cell, 15(6), pp. 986–998. doi:10.1111/acel.12510.

82. Krepelova, A., Rasa, M., Annunziata, F., Lu, J., Giannuzzi, C., Omrani, O., Wyart, E., Porporato, P.E., Ansari, I., Bilenko, D., Bergman, Y. and Neri, F. (2025) 'Iron homeostasis and cell clonality drive cancer-associated intestinal DNA methylation drift in aging', Nature Aging, 5(12), pp. 2432–2448. doi: 10.1038/s43587-025-01021-x.

83. Labbadia J, Morimoto RI. Repression of the Heat Shock Response Is a Programmed Event at the Onset of Reproduction. Mol Cell. 2015 Aug 20;59(4):639-50. doi: 10.1016/j.molcel.2015.06.027. Epub 2015 Jul 23. PMID: 26212459; PMCID: PMC4546525.

84. Lapasset L, Milhavet O, Prieur A, Besnard E, Babled A, Ait-Hamou N, Leschik J, Pellestor F, Ramirez JM, De Vos J, Lehmann S, Lemaitre JM. Rejuvenating senescent and centenarian human cells by reprogramming through the pluripotent state. Genes Dev. 2011 Nov 1;25(21):2248-53. doi: 10.1101/gad.173922.111. PMID: 22056670; PMCID: PMC3219229.

85. Larson, B.J., Longaker, M.T. and Lorenz, H.P. (2010) 'Scarless fetal wound healing: a basic science review', Plastic and Reconstructive Surgery, 126(4), pp. 1172–1180.

86. Lee, M., Zhang, Y., Lim, J.Y.S., Dai, T., Ye, J., Cervantes, M.B., Sondhi, V., Zheng, S., Kim, Y.J., Chen, B., DeBerardinis, R.J. and Xu, J. (2026) 'LINE-1 Locus Transcription Nucleates Oncogenic Chromatin Architecture', Cancer Discovery. doi:10.1158/2159-8290.CD-25-1085.

87. Lehallier, B. et al. (2019) 'Undulating changes in human plasma proteome profiles across the lifespan', Nature Medicine, 25, pp. 1843–1850.

88. Leroi, A. M., Chen, W. R., & Rose, M. R. (1994). Long-Term Laboratory Evolution of a Genetic Life-History Trade-Off in Drosophila melanogaster. 2. Stability of Genetic Correlations. Evolution, 48(4), 1258–1268. https://doi.org/10.2307/2410383

89. Levitis, D.A. and Martinez, D.E. (2013) 'The two halves of U-shaped mortality', Frontiers in Genetics, 4, 31.

90. Lewontin, R.C. and Cohen, D. (1969) 'On population growth in a randomly varying environment', Proceedings of the National Academy of Sciences, 62(4), pp. 1056–1060.

91. Li J, Wang H, Zhu P, Chen H, Zuo H, Liu C, Liu L, Ye X, Feng G, Wu Y, Liu Q, Yang T, Keefe DL, Bai X, Shang W, Wu X, Liu L. Ribosome dysregulation and intervention in age-related infertility. Cell Rep Med. 2025 Nov 18;6(11):102424. doi: 10.1016/j.xcrm.2025.102424. Epub 2025 Oct 27.

92. Lidsky, P.V. and Andino, R. (2022) 'Could aging evolve as a pathogen control strategy?', Trends in Ecology & Evolution, 37(12), pp. 1046–1057. doi:10.1016/j.tree.2022.08.003.

93. de Lima Camillo, L.P. et al. (2025) 'Inhibition of mesenchymal drift as a strategy for rejuvenation', Frontiers in Pharmacology, 16, 1715559. doi: 10.3389/fphar.2025.1715559.

94. Loison, A., Festa-Bianchet, M., Gaillard, J.-M., Jorgenson, J.T. and Jullien, J.-M. (1999) 'Age-specific survival in five populations of ungulates: evidence of senescence', Ecology, 80(8), pp. 2539–2554.

95. Love, M.S., Yoklavich, M. and Thorsteinson, L.K. (2002) The Rockfishes of the Northeast Pacific. Berkeley, CA: University of California Press.

96. Lu, A.T., Fei, Z., Haghani, A. et al. Universal DNA methylation age across mammalian tissues. Nat Aging 3, 1144–1166 (2023a). https://doi.org/10.1038/s43587-023-00462-6

97. Lu, J.Y. et al. (2025) 'Prevalent mesenchymal drift in aging and disease is reversed by partial reprogramming', Cell, 188(21), pp. 5895–5911.e17. doi: 10.1016/j.cell.2025.07.031.

98. Lu, Y.R., Tian, X. & Sinclair, D.A. The Information Theory of Aging. Nat Aging 3, 1486–1499 (2023b). https://doi.org/10.1038/s43587-023-00527-6

99. Lynch, H.E., Goldberg, G.L., Chidgey, A. et al. (2009) 'Thymic involution and immune reconstitution', Trends in Immunology, 30(7), pp. 366–373.

100. Mäkinen, V.-P. et al. (2025) 'Metabolic transition from childhood to adulthood based on two decades of biochemical time series in three longitudinal cohorts', International Journal of Epidemiology. doi:10.1093/ije/dyaf026.

101. Martínez DE, Bridge D. Hydra, the everlasting embryo, confronts aging. Int J Dev Biol. 2012;56(6-8):479-87. doi: 10.1387/ijdb.113461dm. PMID: 22689361.

102. Marttila S, Kananen L, Häyrynen S, et al. Ageing-associated changes in the human DNA methylome: genomic locations and effects on gene expression. BMC Genomics. 2015 Mar 14;16(1):179. doi: 10.1186/s12864-015-1381-z. PMID: 25888029; PMCID: PMC4404609.

103. May, R.M. (1973) Stability and Complexity in Model Ecosystems. Princeton, NJ: Princeton University Press.

104. McCay, C.M., Crowell, M.F. and Maynard, L.A. (1935) 'The effect of retarded growth upon the length of life span and upon the ultimate body size', Journal of Nutrition, 10(1), pp. 63–79.

105. McDonald, I.R., Lee, A.K., Bradley, A.J. and Than, K.A. (1981) ‘Endocrine changes in dasyurid marsupials with differing mortality patterns’, General and Comparative Endocrinology, 44(3), pp. 292–301. https://doi.org/10.1016/0016-6480(81)90004-6.

106. Medawar, P.B. (1952) An Unsolved Problem of Biology: An Inaugural Lecture Delivered at University College, London, 6 December, 1951. London: H.K. Lewis.

107. Mehmood, A., Xue, Y.Z., Yassin, H.M., Zubair, M., Rahmat, S.A. and Ahmad, A. (2025) ‘LINE-1 retrotransposon activation drives age-associated inflammation via cytoplasmic cDNA–STING/type I interferon signalling: therapeutic potential of reverse transcriptase inhibition’, Contemporary Oncology (Poznan), 29(3), pp. 240–246. doi:10.5114/wo.2025.152369.

108. Meyer, D.H., Schumacher, B. (2024) Aging clocks based on accumulating stochastic variation. Nature Aging 4(6):871–885. https://doi.org/10.1038/s43587-024-00619-x

109. Miller, S.E. and Hadfield, M.G. (1990) ‘Developmental arrest during larval life and life-span extension in a marine mollusc’, Science, 248(4952), pp. 356–358. https://doi.org/10.1126/science.248.4952.356.

110. Mitteldorf, J. (2017) Aging is a Group-Selected Adaptation: Theory, Evidence, and Medical Implications. Boca Raton, FL: CRC Press.

111. Mitteldorf, J. (2018) ‘Can Aging be Programmed?’, Biochemistry (Moscow), 83(12), pp. 1524–1533. doi:10.1134/S0006297918120106.

112. Mitteldorf, J.J. and Goodnight, C. (2013) ‘Post-reproductive life span and demographic stability’, Biochemistry (Moscow), 78(9), pp. 1013–1022.

113. Moore, G.H. (1974) Aetiology of the die-off of male Antechinus stuartii. PhD thesis. Canberra: The Australian National University.

114. Muller HG, Carey JR, Wu D, Liedo P, Vaupel JW. Reproductive potential predicts longevity of female Mediterranean fruitflies. Proc Biol Sci. 2001 Mar 7;268(1466):445-50. doi: 10.1098/rspb.2000.1370. PMID: 11296855; PMCID: PMC1088626.

115. NOAA Fisheries (n.d.) American Lobster. Available at: NOAA Fisheries website: https://www.fisheries.noaa.gov/species/american-lobster

116. NOAA Fisheries (n.d.) Blue Crab. Available at: NOAA Fisheries website: https://www.fisheries.noaa.gov/species/blue-crab

117. NOAA Fisheries (n.d.) Salmon Life Cycle and Seasonal Fishery Planning. Available at: NOAA Fisheries website: https://www.fisheries.noaa.gov/west-coast/sustainable-fisheries/salmon-life-cycle-and-seasonal-fishery-planning

118. Newham, E., Gill, P.G., Brewer, P., Benton, M.J., Fernandez, V., Gostling, N.J., Haberthur, D., Jernvall, J., Kankaanpaa, T., Kallonen, A., Navarro, C., Pacureanu, A., Richards, K., Robson Brown, K., Schneider, P., Suhonen, H., Tafforeau, P., Williams, K.A., Zeller-

Plumhoff, B. and Corfe, I.J. (2020) ‘Reptile-like physiology in Early Jurassic stem-mammals’, Nature Communications, 11, 5121. https://doi.org/10.1038/s41467-020-18898-4.

119. Ng, B., Dong, J., D’Agostino, G., Viswanathan, S., Widjaja, A.A., Lim, W.-W. et al. (2019) ‘Interleukin-11 is a therapeutic target in idiopathic pulmonary fibrosis’, Science Translational Medicine, 11(511), eaaw1237. doi:10.1126/scitranslmed.aaw1237.

120. Nielsen, J., Hedeholm, R.B., Heinemeier, J., Bushnell, P.G., Christiansen, J.S., Olsen, J., Ramsey, C.B., Brill, R.W., Simon, M., Steffensen, K.F. and Steffensen, J.F. (2016) ‘Eye lens radiocarbon reveals centuries of longevity in the Greenland shark (Somniosus microcephalus)’, Science, 353(6300), pp. 702–704.

121. Ocampo A, Reddy P, Martinez-Redondo P et al. (2016) In Vivo Amelioration of Age-Associated Hallmarks by Partial Reprogramming. Cell. 2016 Dec 15;167(7):1719-1733.e12. doi: 10.1016/j.cell.2016.11.052.

122. Olenev, V.G., Pokrovskii, A.V. and Olenev, G.V. (1980) ‘Analysis of the features of hibernating generations of mouse-like rodents’ [in Russian], in Adaptation of animals to winter conditions. Moscow: Nauka, pp. 64–69.

123. Oviedo, N.J. and Beane, W.S. (2009) ‘Regeneration: the origin of cancer or a possible cure?’, Seminars in Cell & Developmental Biology, 20(5), pp. 557–564.

124. Palstra, A.P. & van den Thillart, G.E.E.J.M. (2010) ‘Swimming physiology of European silver eels (Anguilla anguilla L.): energetic costs and effects on sexual maturation and reproduction’, Fish Physiology and Biochemistry, 36(3), pp. 297–322. doi:10.1007/s10695-010-9397-4.

125. Pan, R., Ren, J., Chen, X. et al. Editing DNA methylation in vivo. Nat Commun (2025). https://doi.org/10.1038/s41467-025-67222-5

126. Panciroli, E., Benson, R.B.J., Fernandez, V., Fraser, N.C., Humpage, M., Luo, Z.-X., Newham, E. and Walsh, S. (2024) ‘Jurassic fossil juvenile reveals prolonged life history in early mammals’, Nature, 632(8026), pp. 815–822. https://doi.org/10.1038/s41586-024-07733-1.

127. Parkening, T.A. and Collins, T.J. (1985) ‘Orthotopic ovarian transplantations in young and aged C57BL/6J mice’, Biology of Reproduction, 32(4), pp. 989–997.

128. Penin, X., Berge, C. and Baylac, M. (2002) ‘Ontogenetic study of the skull in modern humans and the common chimpanzees: neotenic hypothesis reconsidered with a tridimensional Procrustes analysis’, American Journal of Physical Anthropology, 118(1), pp. 50–62.

129. Percharde, M., Lin, C.-J., Yin, Y., Guan, J., Peixoto, G.A., Bulut-Karslioglu, A., Biechele, S., Huang, B., Shen, X. and Ramalho-Santos, M. (2018) ‘A LINE1–Nucleolin Partnership Regulates Early Development and ESC Identity’, Cell, 174(2), pp. 391–405.e19. doi:10.1016/j.cell.2018.05.043.

130. Pettan-Brewer, C. and Treuting, P.M. (2011) ‘Practical pathology of aging mice’, Pathobiology of Aging and Age-related Diseases, 1, 7202.

131. Pletcher, S.D. and Curtsinger, J.W. (1998) ‘Mortality plateaus and the evolution of senescence: Why are old-age mortality rates so low?’, Evolution, 52(2), pp. 454–464. doi:10.1111/j.1558-5646.1998.tb01645.x.

132. Plourde, B.T., Burgess, T.L., Eskew, E.A., Roth, T.M., Stephenson, N. and Foley, J.E. (2017) ‘Are disease reservoirs special? Taxonomic and life history characteristics’, PLoS ONE, 12(7), e0180716.

133. Policarpi, C., Munafo, M., Tsagkris, S. et al. Systematic epigenome editing captures the context-dependent instructive function of chromatin modifications. Nat Genet 56, 1168–1180 (2024). https://doi.org/10.1038/s41588-024-01706-w

134. Porrello, E.R., Mahmoud, A.I., Simpson, E., Hill, J.A., Richardson, J.A., Olson, E.N. and Sadek, H.A. (2011) ‘Transient regenerative potential of the neonatal mouse heart’, Science, 331(6020), pp. 1078–1080.

135. Ringel, M.S. (2025), Why we age. Biol Rev. https://doi.org/10.1002/brv.70109

136. Robertson, O.H. (1961) ‘Prolongation of the life span of kokanee salmon (Oncorhynchus nerka kennerlyi) by castration before beginning of gonadal maturation’, Proceedings of the National Academy of Sciences of the United States of America, 47(4), pp. 609–621. https://doi.org/10.1073/pnas.47.4.609.

137. Robertson, O.H. and Wexler, B.C. (1960) ‘Histological changes in the organs and tissues of migrating and spawning Pacific salmon (genus Oncorhynchus)’, Endocrinology, 66(2), pp. 222–239. https://doi.org/10.1210/endo-66-2-222.

138. Rockey, D.C., Bell, P.D. and Hill, J.A. (2015) ‘Fibrosis—A common pathway to organ injury and failure’, New England Journal of Medicine, 372(12), pp. 1138–1149. doi: 10.1056/NEJMra1300575.

139. Rodriguez-Martin, B. et al. (2020) ‘Pan-cancer analysis of whole genomes identifies driver rearrangements promoted by LINE-1 retrotransposition’, Nature Genetics, 52(3), pp. 306–319. doi:10.1038/s41588-019-0562-0.

140. Rose, N.R. & Klose, R.J., 2014. Understanding the relationship between DNA methylation and histone lysine methylation. Biochimica et Biophysica Acta (Gene Regulatory Mechanisms), 1839(12), pp.1362–1372.

141. Ryu, Y. et al. (2021) ‘A shift in tissue stiffness during hippocampal maturation correlates to the pattern of neurogenesis and composition of the extracellular matrix’, Frontiers in Aging Neuroscience.

142. Sarkar, T.J. & Sebastiano, V. (2016) ‘Rejuvenation on the Road to Pluripotency’, in M. Tomizawa (ed.) Pluripotent Stem Cells – From the Bench to the Clinic. IntechOpen. doi:10.5772/63219

143. Sauer, D.J., Heidinger, B.J., Kittilson, J.D. et al. No evidence of physiological declines with age in an extremely long-lived fish. Sci Rep 11, 9065 (2021). https://doi.org/10.1038/s41598-021-88626-5

144. Schafer, S., Viswanathan, S., Widjaja, A.A., Lim, W.-W., Moreno-Moral, A., DeLaughter, D.M. et al. (2017) ‘IL-11 is a crucial determinant of cardiovascular fibrosis’, Nature, 552(7683), pp. 110–115. doi:10.1038/nature24676.

145. Schielke, C.K.M., Burda, H., Henning, Y. et al. Higher resting metabolic rate in long-lived breeding Ansell’s mole-rats (Fukomys anselli). Front Zool 14, 45 (2017). https://doi.org/10.1186/s12983-017-0229-6

146. Schultz, R.M. (1993) ‘Regulation of zygotic gene activation in the mouse’, BioEssays, 15(8), pp. 531–538. doi:10.1002/bies.950150806.

147. Segel, M. et al. (2019) ‘Niche stiffness underlies the ageing of central nervous system progenitor cells’, Nature, 573, pp. 130–134.

148. Shavlakadze T, Morris M, Fang J, et al. (2019) Age-Related Gene Expression Signature in Rats Demonstrate Early, Late, and Linear Transcriptional Changes from Multiple Tissues. Cell Rep. 2019 Sep 17;28(12):3263-3273.e3. doi: 10.1016/j.celrep.2019.08.043. PMID: 31533046.

149. Shen, X. et al. (2024) ‘Nonlinear dynamics of multi-omics profiles during human aging’, Nature Aging, 4, pp. 1619–1634.

150. Shivananjappa, S., Floate, K.D., Fields, P.G. & Laird, R.A. (2023) Retrogressive moulting in khapra beetle, Trogoderma granarium (Coleoptera: Dermestidae). Physiological Entomology, 48(2-3), 75–82. https://doi.org/10.1111/phen.12404

151. Shvarts, S.S., Ishchenko, V.G., Ovchinnikova, N.A., Olenev, V.G., Pokrovskii, A.V. and Pyastolova, O.A. (1964) ‘Alternation of generations and life span of rodents’ [in Russian], Zhurnal Obshchei Biologii, 25(6), pp. 417–433.

152. Simon M, Van Meter M, Ablaeva J et al. (2019) LINE1 Derepression in Aged Wild-Type and SIRT6-Deficient Mice Drives Inflammation. Cell Metab. 2019 Apr 2;29(4):871-885.e5. doi: 10.1016/j.cmet.2019.02.014

153. Simons, A. M. (2011). Modes of response to environmental change and the elusive empirical evidence for bet hedging. Proceedings of the Royal Society B: Biological Sciences, 278(1712), 1601–1609. https://doi.org/10.1098/rspb.2011.0176

154. Skulachev, V.P. (2011) ‘Aging as a particular case of phenoptosis, the programmed death of an organism (a response to Kirkwood and Melov “On the programmed/non-programmed

nature of ageing within the life history")', Aging (Albany NY), 3(11), pp. 1120–1123. doi:10.18632/aging.100403.

155. Skulachev, V.P., Holtze, S., Vyssokikh, M.Y., Bakeeva, L.E., Skulachev, M.V., Markov, A.V., Hildebrandt, T.B. and Sadovnichii, V.A. (2017) 'Neoteny, Prolongation of Youth: From Naked Mole Rats to "Naked Apes" (Humans)', Physiological Reviews, 97(2), pp. 699–720. doi:10.1152/physrev.00040.2015.

156. Somel, M., Franz, H., Yan, Z. et al. (2009) 'Transcriptional neoteny in the human brain', Proceedings of the National Academy of Sciences of the United States of America, 106(14), pp. 5743–5748.

157. Stewart, E.J., Madden, R., Paul, G. and Taddei, F. (2005) 'Aging and death in an organism that reproduces by morphologically symmetric division', PLoS Biology, 3(2), e45. doi:10.1371/journal.pbio.0030045.

158. Sutherland, J.S., Goldberg, G.L., Hammett, M.V. et al. (2005) 'Activation of thymic regeneration in mice and humans following androgen blockade', Journal of Immunology, 175(4), pp. 2741–2753.

159. Svoboda, P. (2018) 'Mammalian zygotic genome activation', Seminars in Cell & Developmental Biology, 84, pp. 118–126. doi:10.1016/j.semcdb.2017.12.006.

160. Sziraki, A., Tyshkovskiy, A. & Gladyshev, V.N., 2018. Global remodeling of the mouse DNA methylome during aging and in response to calorie restriction. Aging Cell, 17, e12738.

161. Takasugi, M., Nonaka, Y., Takemura, K., Yoshida, Y., Stein, F., Schwarz, J.J., Adachi, J., Satoh, J., Ito, S., Tombline, G., Biashad, S.A., Seluanov, A., Gorbunova, V. and Ohtani, N. (2024) 'An atlas of the aging mouse proteome reveals the features of age-related post-transcriptional dysregulation', Nature Communications, 15, 8520. doi:10.1038/s41467-024-52845-x.

162. Trapp, A., Kerepesi, C. and Gladyshev, V.N. (2021) 'Profiling epigenetic age in single cells', Nature Aging, 1(12), pp. 1189–1201. doi:10.1038/s43587-021-00134-3.

163. Thalheim, T., Herberg, M. and Galle, J. (2018) 'Linking DNA damage and age-related promoter DNA hyper-methylation in the intestine', Genes (Basel), 9(1), 17. doi: 10.3390/genes9010017.

164. Tubio, J.M.C. et al. (2014) 'Mobile DNA in cancer. Extensive transduction of nonrepetitive DNA mediated by L1 retrotransposition in cancer genomes', Science, 345(6196), 1251343. doi:10.1126/science.1251343.

165. Turchin, P. (2003) Complex Population Dynamics: A Theoretical/Empirical Synthesis. Princeton, NJ: Princeton University Press.

166. U.S. Fish & Wildlife Service (n.d.) Lake Trout (Salvelinus namaycush). Available at: U.S. Fish & Wildlife Service website: https://www.fws.gov/species/lake-trout-salvelinus-namaycush

167. Unal, E., Kinde, B. and Amon, A. (2011) 'Gametogenesis eliminates age-induced cellular damage and resets life span in yeast', Science, 332(6037), pp. 1554–1557. doi:10.1126/science.1204349.

168. Vaupel, J.W. et al. (2004) 'The case for negative senescence', Theoretical Population Biology, 65(4), pp. 339–351.

169. Velardi, E., Tsai, J.J. and van den Brink, M.R.M. (2015) 'Sex steroid ablation: an immuno-regenerative strategy for transplantation and aging', Frontiers in Immunology, 6, 570.

170. Viji Babu PK and Radmacher M (2019) Mechanics of Brain Tissues Studied by Atomic Force Microscopy: A Perspective. Front. Neurosci. 13:600. doi: 10.3389/fnins.2019.00600

171. Vogt, G. (2012) 'Ageing and longevity in the Decapoda (Crustacea): a review', Zoologischer Anzeiger, 251(1), pp. 1–25. https://doi.org/10.1016/j.jcz.2011.05.003 ScienceDirect

172. Vogt, G. (2019) 'A compilation of longevity data in decapod crustaceans', Nauplius, 27, e2019011. https://doi.org/10.1590/2358-2936e2019011 SciELO

173. Wachter, K.W. (1999) 'Evolutionary demographic models for mortality plateaus', Proceedings of the National Academy of Sciences of the United States of America, 96(18), pp. 10544–10547. doi:10.1073/pnas.96.18.10544.

174. Wachter, K.W., Evans, S.N. and Steinsaltz, D.R. (2013) 'The age-specific force of natural selection and biodemographic walls of death', Proceedings of the National Academy of Sciences of the United States of America, 110(25), pp. 10141–10146. doi:10.1073/pnas.1306656110.

175. Weigl, R. (2005) Longevity of Mammals in Captivity: From the Living Collections of the World. A List of Mammalian Longevity in Captivity. Kleine Senckenberg-Reihe 48. Stuttgart: E. Schweizerbart'sche Verlagsbuchhandlung.

176. Widjaja, A.A. et al. (2024) 'Inhibition of IL-11 signalling extends mammalian healthspan and lifespan', Nature, 632(8023), pp. 157–165. doi: 10.1038/s41586-024-07701-9.

177. Wilkinson, G.S. and South, J.M. (2002) 'Life history, ecology and longevity in bats', Aging Cell, 1(2), pp. 124–131. doi:10.1046/j.1474-9728.2002.00020.x.

178. Williams, G.C. (1957), PLEIOTROPY, NATURAL SELECTION, AND THE EVOLUTION OF SENESCENCE. Evolution, 11: 398-411. https://doi.org/10.1111/j.1558-5646.1957.tb02911.x

179. Winkler, I. and Goncalves, A. (2023) 'Do mammals have menopause?', Cell, 186(22), pp. 4729–4733. https://doi.org/10.1016/j.cell.2023.09.026.

180. Wodsedalek JE (1917) Five years of starvation of larvae. Science 46:366–367

181. Wynn, T.A. (2008) 'Cellular and molecular mechanisms of fibrosis', The Journal of Pathology, 214(2), pp. 199–210. doi: 10.1002/path.2277.

182. Xu, P., et al. (2011). Distinct hypothalamic neurons mediate estrogenic effects on energy homeostasis and reproduction. Cell Metabolism, 14(4), 453-465.

183. Yan, H., Opachaloemphan, C., Carmona-Aldana, F., Mancini, G., Mlejnek, J., Descostes, N., et al. (2022) 'Insulin signaling in the long-lived reproductive caste of ants', Science, 377(6610), pp. 1092–1099. https://doi.org/10.1126/science.abm8767.

184. Yang, J., Huang, T., Petralia, F., Long, Q., Zhang, B., Argmann, C., Zhao, Y., Mobbs, C.V., Schadt, E.E., Zhu, J., Tu, Z. and The GTEx Consortium (2015) 'Synchronized age-related gene expression changes across multiple tissues in human and the link to complex diseases', Scientific Reports, 5, 15145.

185. Yang, J.H., Hayano, M., Griffin, P.T., Amorim, J.A., Bonkowski, M.S., Apostolides, J.K. et al. (2023) 'Loss of epigenetic information as a cause of mammalian aging', Cell, 186(2), pp. 305–326.e27. https://doi.org/10.1016/j.cell.2022.12.027

186. Yang, L. et al. (2020) 'Transient Dux expression facilitates nuclear transfer and induced pluripotent stem cell reprogramming', EMBO Reports, 21(9), e50054. doi:10.15252/embr.202050054.

187. Yokosawa, R. and Noma, K. (2025) 'A Nuclear Hormone Receptor nhr-76 Induces Age-Dependent Chemotaxis Decline in C. elegans', Aging Cell, 24, e70277. doi:10.1111/acel.70277.

188. Zera, A.J. and Harshman, L.G., 2001. The Physiology of Life History Trade-Offs in Animals. Annual Review of Ecology, Evolution, and Systematics, 32, pp. 95–126.

189. Zhang B, Gladyshev V. (2023a) EPIGENETIC AGE DYNAMICS AND EMBRYONIC MORTALITY POINT TO GASTRULATION AS AGING GROUND ZERO IN XENOPUS LAEVIS. Innov Aging. 2023 Dec 21;7(Suppl 1):769. doi: 10.1093/geroni/igad104.2485. PMCID: PMC10735926.

190. Zhang, B., Lee, D.E., Trapp, A., Tyshkovskiy, A., Lu, A.T., Bareja, A., Kerepesi, C., McKay, L.K., Shindyapina, A.V., Dmitriev, S.E., Baht, G.S., Horvath, S., Gladyshev, V.N. and White, J.P. (2023b) 'Multi-omic rejuvenation and lifespan extension on exposure to youthful circulation', Nature Aging, 3, pp. 948–964.

191. Zhang, G., Li, J., Purkayastha, S., Tang, Y., Zhang, H., Yin, Y. et al. (2013) 'Hypothalamic programming of systemic ageing involving IKK-β, NF-κB and GnRH', Nature, 497(7448), pp. 211–216.

192. Zhang, Y., Kim, M.S., Jia, B., Yan, J., Zuniga-Hertz, J.P., Han, C. and Cai, D. (2017) 'Hypothalamic stem cells control ageing speed partly through exosomal miRNAs', Nature, 548(7665), pp. 52–57.

193. Zhao, M. et al. (2016) ‘Distinct epigenomes in CD4+ T cells of newborns, middle-ages and centenarians’, Scientific Reports, 6, Article number: 38411. doi:10.1038/srep38411.

194. Ziuganov, V.V. (2005) ‘A long-lived parasite extending the host life span: the pearl mussel Margaritifera margaritifera elongates host life by turns out the program of accelerated senescence in salmon Salmo salar’, Doklady Biological Sciences, 403, 291–294.