

THE IN A HURRY SERIES

Longevity *in a Hurry*

Ageing science without the hype

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The Whole Thing in One Page

Ageing arrives disguised as a clock. Birthdays advance at the same speed, hair changes colour, skin loosens, and a number rises until the body appears to have used up its allotted time. The picture is convenient and measurable. It is also the wrong mechanism. Chronological age says how long a person has existed, not what is failing inside them.

A living body is an exercise in continuous maintenance. DNA is inspected and repaired. Proteins are folded, tested, dismantled and replaced. Damaged parts of cells are recycled. Immune cells remove threats and organise repair. Stem cells replenish tissues. Hormones and nutrient sensors alter growth, storage and maintenance according to conditions. None of these systems is perfect, and none works alone.

Ageing becomes visible as their errors accumulate, coordination weakens and reserve narrows. A younger body can absorb an infection, a fall, lost sleep or an operation and return close to its previous state. An older body may look stable at rest yet recover slowly, overshoot into inflammation or fail in several systems after one disturbance. Kidneys, muscle, immunity, blood vessels and memory can age at different rates inside the same person. The common pattern is rising vulnerability.

Evolution explains why maintenance has limits without requiring a death programme. Natural selection strongly rewards traits that improve survival and reproduction early in life. It has less power to remove effects that appear late, after many organisms would already have died from infection, injury or hunger. A pathway may help growth, fertility or wound repair when young and carry a cost decades later. Biology was selected to reproduce under real conditions, not to preserve every tissue indefinitely.

The science sharpened when researchers found that lifespan could be altered. Restricted feeding lengthened life in laboratory rodents. A mutation in one insulin-like signalling gene doubled the adult lifespan of a tiny worm. Rapamycin extended life in genetically varied mice even when treatment began late. Clearing selected senescent cells improved several outcomes in

mice. These results demolished the claim that ageing is untouchable. They did not establish a treatment that adds healthy human decades.

Human evidence is now more than a list of registered intentions, but it remains far behind the animal work. Recent randomised rapamycin trials found a null primary body-composition result in one setting and no primary functional gain in another, alongside selected signals and possible costs that require larger tests. An epigenetic clock can predict risk without becoming a personal verdict or a validated treatment surrogate. A phase I reprogramming study in one eye is a safety experiment, not proof of whole-body rejuvenation. This distance between mechanism and outcome is where most hype enters.

The serious goal is healthspan: more years with function and fewer years in which chronic conditions accumulate together. Geroscience asks whether altering shared mechanisms of ageing can delay several diseases or disabilities at once. It is a strong hypothesis with extensive animal support and incomplete human proof.

The useful question is not which molecule makes you younger. It is whether an intervention preserves the ability to repair, adapt and recover, and whether people then feel better, function better or live longer without an equal cost elsewhere.

That is the book.

Why You Should Care

In 1825, an English mathematician named Benjamin Gompertz described a pattern hidden inside mortality tables. Across much of adult life, the chance of dying does not rise by the same amount each year. It rises roughly exponentially. The exact slope differs by population and period, but the broad shape remains: age turns many small vulnerabilities into a rapidly increasing risk.

That curve is more revealing than a list of grey hairs and aching joints. It says that ageing is a change in susceptibility. Pneumonia, a hip fracture,

cancer, a heatwave and an operation are different events, yet age increases the danger of all of them. The common feature is reduced capacity to withstand disturbance, contain damage and recover. Longevity science matters because it asks whether that shared vulnerability can be delayed rather than waiting for each disease to declare itself.

The first reason to care is personal but not cosmetic. Most people who say they want a longer life are imagining usable life, not prolonged final illness. Lifespan counts years lived. Healthspan tries to capture years lived without major disease, disability or loss of function. Functional ability asks whether a person can move, think, communicate, maintain relationships and do what matters in their environment. These measures overlap, but they are not interchangeable. A treatment that adds frail years has met a different goal from one that postpones several diseases and preserves independence.

The second reason is scientific. Age is the strongest risk factor for many chronic disorders, but medicine usually divides the consequences by organ. Cardiologists treat arteries, oncologists tumours, neurologists degeneration and endocrinologists metabolism. That division is necessary for care. It can also hide shared upstream processes such as chronic inflammation, damaged proteins, altered nutrient sensing, exhausted stem cells and senescent-cell accumulation. If one intervention could modestly delay several of these processes, its public-health effect could exceed a dramatic treatment for one uncommon disease.

The third reason is defensive. Longevity has become a market before it has become an established branch of clinical medicine. Blood panels are converted into a single biological-age score. Supplements are sold through pathways discovered in worms. Drugs licensed for other conditions are used in healthy people on the strength of mouse studies, observational associations or enthusiastic physicians. The language sounds technical because the underlying science is real. The inference from that science to a product is often where the structure fails.

A useful reader therefore needs two skills at once. One is enough biology to understand why telomeres, mitochondria, senescent cells, autophagy and

mTOR matter. The other is enough evidence discipline to ask what organism was studied, what endpoint changed, how long follow-up lasted, whether harms were measured and whether the result survives outside one laboratory. Without the first skill, every claim sounds magical. Without the second, every mechanism sounds like a treatment.

The subject also corrects a bleak assumption. Ageing is not fixed in every detail. Species differ enormously in lifespan. Individuals of the same chronological age differ in reserve and disease burden. Laboratory interventions can lengthen life in several organisms, sometimes by large amounts. Public health, safer work, vaccination, blood-pressure control and other ordinary advances have allowed more people to reach old age. Biology is modifiable.

The correction in the other direction matters equally. Modifiable does not mean mastered. As of 2 September 2026, human geroscience still lacks a long, large trial showing that a drug given to broadly healthy people delays several major diseases, preserves function and produces an acceptable balance of harm. Recent rapamycin trials supplied useful human data, but no broad answer. TAME remains unlaunched.

Understanding the field rewards neither cynicism nor faith. It is calibration. You can recognise a discovery without buying the forecast attached to it, value established prevention without confusing it with immortality, and judge each claim by the distance between its measurement and the life you care about.

The Core Ideas

Ageing Is a Loss of Reliability, Not a Clock

A clock gives the same answer wherever you put it. Biology does not. Two people can share a birthday while differing sharply in strength, cognition, arterial damage, immune response and recovery from illness. Even within one person, the liver may retain considerable capacity while muscle, bone or kidney reserve has fallen. Chronological age is a powerful predictor because time permits damage and change to accumulate. It is not the mechanism doing the work.

The better model begins with reliability. A body has thousands of ways to fail, yet most do not happen on most days because cells detect errors, replace components and compensate for lost capacity. Paired organs provide redundancy. Stem and progenitor cells replace some damaged tissue. The immune system removes infected or abnormal cells. Protein quality-control systems refold or destroy defective molecules. Feedback loops keep temperature, blood pressure, glucose and salts within usable ranges. Survival depends less on preventing every fault than on catching enough faults before they interact.

Ageing raises the chance that several defences will be weak at the same time. A younger person may lose fluid during an infection, increase heart rate, conserve salt through the kidneys, mobilise energy and rebuild afterwards. An older person can face the same infection with less cardiac reserve, reduced kidney response, lower muscle mass and a more inflammatory immune system. Each change may be tolerable alone. Together they narrow the route back to stability.

This is why frailty is more informative than appearance. In research, frailty may be described through a phenotype such as weakness, slow walking, exhaustion, low activity and unintentional weight loss, or through an index counting accumulated deficits across many domains. The methods differ, but both capture vulnerability. A person can function well at rest and still have little spare capacity when demand rises. Reserve is the distance

between ordinary operation and failure.

Mortality curves reveal the population version. Gompertz noticed that adult mortality often rises approximately exponentially with age. The curve does not mean every person carries the same internal timer. It describes a growing probability that hidden weaknesses, exposures and random events will align. In advanced ages the pattern can flatten in some datasets, partly because the most vulnerable have already died and because age validation and small samples become difficult. The broad lesson survives: ageing changes risk faster than the calendar alone suggests.

Reliability also clarifies why ageing can look sudden. The processes are often gradual, but compensation hides them. Bone density can fall for years before a fracture. Arteries can stiffen while resting blood pressure remains controlled. Neurons can tolerate molecular damage until networks lose enough redundancy. Once reserve crosses a threshold, one event exposes several long developments at once. The final failure feels abrupt because maintenance had been spending its remaining margin in silence.

The model carries one warning. Describing the body as a system does not make it an engineered machine with replaceable standard parts. Living tissues adapt, reproduce, communicate and alter their own repair. Their failures are shaped by development, evolution and environment. Reliability is useful because it organises vulnerability, not because it supplies one numerical master score.

Evolution Did Not Optimise Us for Indefinite Repair

Why would natural selection permit bodies to deteriorate? The tempting answer is that ageing benefits the species by clearing space for the young. That explanation asks selection to favour an individual's death for a distant group advantage, when a variant that kept its bearer alive and reproducing would often spread instead. Modern evolutionary accounts begin elsewhere: the force of selection weakens with age.

Imagine a harmful mutation that kills its carriers before they reproduce. It is

strongly exposed to selection and tends to be removed. Move the same effect to late life, after many carriers have reproduced or died from other causes, and selection sees it less clearly. Peter Medawar used this logic to explain how late-acting damage could accumulate in a population. Ageing did not need to be selected for. It could emerge because selection became increasingly unable to prevent it.

George Williams added a sharper trade-off. A genetic effect may improve growth, fertility, immune defence or wound repair early in life while increasing disease or tissue damage later. If the early benefit is large enough, selection can favour the package. This is antagonistic pleiotropy: one inherited influence with effects that pull in opposite directions across the life course. The mechanism need not be one gene with one neat pair of outcomes. It is a way of understanding why pathways that support growth and reproduction may become costly when kept active for decades.

Tom Kirkwood's disposable soma theory shifted attention to allocation. Energy and materials used for reproduction cannot also be spent on flawless repair, but the crude phrase “body versus babies” can mislead. Organisms do not carry a fixed maintenance purse divided once. They adjust growth, reproduction, immunity and repair according to conditions. The evolutionary prediction is narrower: maintenance is selected to be good enough for expected survival and reproductive success, not perfect enough for indefinite preservation.

Species comparisons fit the logic better than a single universal formula. Animals protected from predators, cold or starvation can gain more from investing in durable bodies because they are likely to live long enough to collect the return. Flight reduces external mortality for many birds and bats, and several live longer than similarly sized terrestrial mammals. Naked mole rats live in protected colonies and show unusual resistance to some age-linked diseases. Yet ecology, body size, development, social structure and metabolism are entangled, so no one trait explains the whole range.

Humans are another special case. Culture, cooperation, food sharing and care can allow older adults to contribute beyond direct reproduction. Long

childhoods and intergenerational support may have favoured longer adult survival. These ideas help explain why humans outlive other apes, but they do not turn every late-life feature into an adaptation. Evolutionary stories become cheap when any observed trait is declared useful after the fact.

The practical consequence is severe. A pathway can be protective at one age and harmful at another. Cellular senescence suppresses damaged-cell division and helps wound repair, then persistent senescent cells may promote inflammation. Growth signalling builds bodies and supports reproduction, then sustained activity may impair later maintenance. Strong immune reactions defend against infection, then chronic activation can damage tissue. The same biology changes its balance as context changes.

Ageing therefore has no obligation to be elegant. It is the residue of compromises that worked well enough under ancestral conditions. That makes intervention possible, because a late cost may be reduced after its early benefit has been collected. It also makes intervention dangerous, because the apparent defect may still be performing work that a healthy adult needs.

Damage Is Inevitable; Failed Cleanup Makes It Ageing

Life creates damage by operating. DNA is exposed to replication errors and chemical attack. Proteins misfold, stick together or acquire unwanted modifications. Membranes are oxidised. Mitochondria leak reactive molecules while converting nutrients into usable energy. Mechanical load strains connective tissue. The surprise is not that damage occurs. It is that a body remains coherent for decades while producing, finding and removing so much of it.

Damage theories of ageing have repeatedly become total theories. Denham Harman proposed in 1956 that free radicals generated during metabolism could drive ageing. The idea became influential because reactive oxygen species can damage DNA, proteins and lipids, and oxidative damage often rises with age. It also generated a commercial simplification: if oxidation is

bad, antioxidants must stop ageing. Biology refused the syllogism. Reactive oxygen species also act as signals, trigger adaptive defences and help immune cells kill microbes. High-dose antioxidant supplements have not delivered general life extension and some have caused harm in trials.

The deeper issue is maintenance. Cells carry DNA repair enzymes, molecular chaperones, proteasomes and autophagy systems. Chaperones help proteins fold. Proteasomes break selected proteins into reusable parts. Autophagy encloses damaged components and delivers them to lysosomes for digestion. Mitochondria can be split, fused and selectively removed. These systems do not erase entropy. They keep local disorder below the level at which the cell loses identity or function.

Proteostasis is the name for this moving balance of protein production, folding, trafficking and destruction. Its decline appears across several age-linked disorders, especially those involving protein aggregates in the brain. Yet an aggregate can be cause, consequence or containment. Cells sometimes package dangerous soluble proteins into larger deposits that are easier to isolate. Removing a visible deposit will not necessarily repair the upstream failure that produced it.

Mitochondria provide another warning against one-way stories. They are descendants of bacteria living inside cells, carry a small genome and supply much of the cell's ATP. Ageing is associated with changes in mitochondrial DNA, turnover, shape, signalling and energy production. But “old mitochondria make less energy” is too blunt. Different tissues show different patterns, and mild mitochondrial stress can activate protective responses. In worms, some disturbances that look harmful can extend lifespan by prompting wider adaptation.

The same principle applies to the genome. Mutations accumulate in somatic cells, but their rate, distribution and consequences differ by tissue. Cancer is one outcome of selected clones gaining growth advantages. Other mutations may have little effect because they fall in unused DNA, occur in replaceable cells or remain a minority. Genomic instability matters without every mutation becoming ageing's master cause.

A useful synthesis is that damage becomes ageing when the relationship between production and control shifts. More faults appear, repair may become slower or less accurate, damaged cells persist, and compensatory responses create costs elsewhere. A clogged recycling system raises the burden on quality control. Mitochondrial stress alters inflammation. DNA damage can push cells into senescence. Chronic inflammation then creates further damage. The mechanisms form loops.

This is why removing one class of damage may help yet fail to restore youth. The organism has adapted around the burden, and several systems may already have changed state. The target is not pristine molecules. It is enough maintenance, recycling and coordination to preserve function without disabling useful stress responses.

Cells Change State and Alter Their Neighbourhood

Some ageing damage is carried by cells that remain alive. Cellular senescence is a durable state in which a cell stops dividing, changes its metabolism and often releases a mixture of signals into surrounding tissue. The arrest can be triggered by damaged DNA, shortened or dysfunctional telomeres, oncogene activation and other stress. It is one of biology's most instructive compromises.

Stopping division protects against cancer. A damaged cell that cannot copy itself is less able to found a tumour. Senescent cells also appear during development and can assist wound repair by recruiting immune cells and helping organise temporary tissue responses. The problem is persistence. With age, more senescent-like cells accumulate and immune clearance can become less effective. Their secretions, often grouped under the term senescence-associated secretory phenotype, can include inflammatory molecules, growth factors and enzymes that alter the extracellular matrix.

The neighbourhood then changes. Nearby cells may divide less effectively, become senescent themselves or receive signals that favour fibrosis and chronic inflammation. Tissue stem cells may face an environment less able to support renewal. A small population can therefore exert effects far

beyond its numbers. The cell has not died, yet its relationship with the tissue has shifted from temporary containment towards continuing disturbance.

Mouse experiments made the idea unusually testable. In 2011, Darren Baker and colleagues engineered mice with a progeroid condition so that selected p16-expressing cells could be removed. Clearance delayed several age-associated disorders. In 2016, a related system in normally ageing mice improved aspects of health and extended median lifespan. These experiments showed causation in their models: the targeted cells were helping produce decline rather than merely marking it.

They did not prove that every p16-positive cell is harmful, that all senescent cells share one identity or that clearing them from healthy humans will extend life. Senescence is heterogeneous across tissues and triggers. Markers overlap with useful cell states. Some senescent cells support repair or limit fibrosis, and indiscriminate removal could damage those functions. Early human studies of senolytic combinations have reported feasibility and changes in selected tissue markers, but they remain too small and condition-specific to establish general geroprotection.

Ageing also changes cell identity without full senescence. Epigenetic marks influence which genes are accessible and active. During development they help a liver cell remain a liver cell and a neuron remain a neuron. With age, methylation patterns and chromatin organisation drift, some regulatory boundaries weaken and gene expression becomes noisier. This does not mean an epigenetic programme deliberately schedules death. It means the systems preserving identity are themselves maintained biological structures.

Stem-cell exhaustion belongs in the same neighbourhood model. Blood, skin, gut and other tissues rely on stem or progenitor cells, but function depends on more than their count. The surrounding niche supplies physical support and signals controlling renewal, quiescence and differentiation. Chronic inflammation, altered matrix and metabolic change can make a capable cell behave poorly. Replacing the cell without repairing the niche may fail.

These processes converge in inflammaging, the chronic, low-grade inflammatory tendency associated with older age. It is not one substance circulating at one level. Sources include immune remodelling, senescent-cell signals, damaged molecules, microbial changes and persistent disease. Acute inflammation remains necessary. The problem is a response that is easier to start, harder to resolve and increasingly woven into tissue function.

Ageing, on this view, is partly ecological. Cells carry histories, react to neighbours and remodel the conditions in which other cells must work. Treating one cell type can change the tissue, but the tissue can also recreate the old state. The unit of intervention may need to be the conversation rather than the speaker alone.

Metabolism Is a Control Network, Not a Calorie Meter

The most repeatable lifespan interventions in laboratory organisms often touch nutrient sensing. That can sound as though ageing is caused by eating too much. The underlying biology is richer. Cells must decide whether conditions favour growth, reproduction, storage, repair or conservation. Nutrients and hormones supply information for that allocation.

Insulin and insulin-like growth factor signalling respond to energy and growth conditions. The mTOR complex integrates amino acids, energy status, oxygen and growth signals, then promotes protein synthesis and cell growth when resources are available. AMPK responds to low cellular energy and shifts activity towards generating ATP. Sirtuins depend on NAD and influence metabolism, stress responses and gene regulation. These pathways intersect with autophagy, inflammation, mitochondrial function and protein production.

The central trade-off is between building and maintaining. Growth requires new proteins, lipids and cells. Maintenance requires quality control, recycling and restraint. A young organism in favourable conditions gains from growth and reproduction. Continuous growth signalling later can

suppress autophagy, increase synthetic burden and support abnormal cell proliferation. Reducing a pathway may free maintenance responses, but too much reduction can impair immunity, wound healing, fertility and muscle.

Calorie restriction became the classic demonstration. In 1935, Clive McCay, Mary Crowell and Leonard Maynard reported that retarding growth through restricted feeding lengthened life in rats. Since then, restriction without malnutrition has extended lifespan in many laboratory settings, from yeast and worms to rodents. The size and even direction of the effect depend on species, strain, sex, diet, age of onset and control feeding. A laboratory mouse eating freely can become overweight, so part of an apparent longevity benefit may come from avoiding an unhealthy control state.

Rhesus-monkey studies exposed the context problem. Parallel long-running programmes at the University of Wisconsin and the US National Institute on Aging initially produced different survival conclusions. Their monkeys differed in diet composition, feeding practice, genetic origin and the degree to which control animals could eat freely. A later joint analysis found consistent health benefits and suggested that adult restriction can help, while showing that “thirty per cent fewer calories” is not one identical treatment across studies.

Human evidence remains narrower. The two-year CALERIE trial randomised healthy adults without obesity to a calorie-restriction intervention or usual intake. Participants assigned to restriction achieved an average reduction of about twelve per cent, lost weight and improved several cardiometabolic measures. A later DNA-methylation analysis found a small slowing on one pace-of-ageing measure, while two other clocks did not change significantly. The trial was not designed or long enough to prove longer life or delayed major disease.

Rapamycin provides a pharmacological route into the same network. It inhibits mTOR and is used clinically in transplantation and some other conditions. In the National Institute on Aging's Interventions Testing Program, late-life rapamycin extended lifespan in genetically heterogeneous mice of both sexes. The result is important because treatment began after

much of the animals' lives had passed. It is not permission for unsupervised use. mTOR helps immunity, tissue growth and repair, and rapamycin can increase infection risk and cause metabolic, blood-count and wound-healing problems depending on dose and context.

The lesson is not that hunger is youth or that one pathway rules ageing. Nutrient sensing demonstrates that lifespan is regulated, environmental and responsive to allocation. It also demonstrates why intervention is hard. The same switch controls work a body needs. Longevity may come from changing timing, tissue and dose rather than turning growth off.

Biology Can Be Slowed in Animals; Translation Is the Hard Part

In 1993, Cynthia Kenyon and colleagues reported that mutations in a single gene, *daf-2*, could double the adult lifespan of the nematode worm *Caenorhabditis elegans*. The worms did not spend an extra lifetime inert. Their extended survival depended on *daf-16*, a transcription factor that coordinates many protective responses. A pathway related to insulin and growth signalling could alter the rate of ageing across the organism.

The experiment changed the field because it replaced a vague search for accumulated decay with a manipulable network. Worms, flies and yeast then revealed conserved pathways involving nutrient sensing, stress resistance, autophagy and protein maintenance. Their speed is a scientific advantage. A worm lives for weeks, breeds quickly and can be studied in large numbers. A human longevity trial can outlast a research career.

The same advantage creates the first translation gap. A worm has no bones, coronary arteries or adaptive immune system. Its short natural life and laboratory environment change the balance among infection, cancer, reproduction and degeneration. A mutation that doubles a worm's three-week lifespan cannot be converted into a percentage forecast for eighty human years. Conservation of a pathway means the parts are related, not that changing them produces the same whole-organism outcome.

Mice narrow the gap and introduce others. They are mammals with many comparable tissues, can develop cancers and metabolic disease, and allow controlled lifespan experiments. Yet laboratory mice are small, short-lived, housed in protected conditions and often genetically uniform. They die from a different mixture of causes from humans. Their drug exposure per kilogram, tumour biology, immune environment and thermal stress differ. Even a strong mouse result may depend on strain or sex.

The Interventions Testing Program was designed to reduce one source of false confidence. Candidate compounds are tested at several sites in genetically heterogeneous mice under harmonised protocols. Replication across sites and both sexes makes a positive result harder to dismiss as one colony or one laboratory. Rapamycin has performed repeatedly. Several fashionable compounds have not. The programme is valuable partly because it publishes disappointment.

A translation ladder therefore matters. Cell studies can establish a mechanism. Short-lived organisms can show that the mechanism regulates lifespan. Mice can test mammalian effects, toxicity and disease patterns. Early human trials can establish pharmacology and safety. Larger randomised trials must then ask whether people preserve function, avoid disease or live longer. Each step answers a different question. Skipping a rung does not supply the answer the next one must provide.

Human observational studies sit beside this ladder rather than above it. People taking metformin, statins or other medicines can appear to live longer, but users differ from non-users in disease, healthcare access, adherence and many other traits. Statistical adjustment can reduce confounding without abolishing it. A drug associated with lower mortality may be beneficial, neutral or a marker of who received and tolerated it.

The present frontier includes rapalogs, metformin, senolytics, immune interventions and partial cellular reprogramming. Reprogramming tries to restore younger patterns of gene regulation without erasing cell identity. In 2026, a small first-in-human phase I study began testing an OSK-based gene therapy in one eye of adults with glaucoma or non-arteritic anterior

ischaemic optic neuropathy. Its primary task is safety and tolerability. This is a transition into human testing, not evidence of whole-body rejuvenation.

Translation is not the dull administrative stage after discovery. It is a second science. It asks whether the effect survives human diversity, long exposure, competing causes of disease, feasible dosing and the obligation to leave a broadly healthy person better off. Candidates often weaken, change meaning or reveal costs somewhere along that road. A null or adverse result is information, not betrayal.

A Longevity Treatment Must Preserve Function, Not Merely Move a Marker

Human ageing is slow enough to make proof awkward. Waiting for deaths provides an unambiguous endpoint but requires large groups and long follow-up. Waiting for several major diseases is faster, though still expensive. Measuring a molecule can produce a result within months. The field therefore needs biomarkers, and the pressure to use them can exceed their validation.

A biomarker may predict an outcome without causing it. Grey hair predicts age but dyeing it changes no mortality risk. Blood pressure is more useful because interventions that lower it through established routes can reduce clinical events. A surrogate endpoint earns trust when changing it reliably captures a treatment's effect on how people feel, function or survive within a defined context. Prediction alone is not enough.

Epigenetic clocks combine DNA-methylation measurements at selected sites to estimate age-related patterns. Steve Horvath's 2013 clock showed that methylation across many tissues could predict chronological age with striking accuracy. Later clocks were trained on mortality, disease-related traits or longitudinal physiological change. They can stratify risk in populations and reveal biological response. They are not one thermometer reading a single substance called ageing.

Different clocks use different training targets and can disagree about the same intervention. CALERIE moved DunedinPACE modestly but did not

significantly change PhenoAge or GrimAge in the same analysis. Longitudinal evidence strengthened in 2026: changes in several clocks added information about mortality beyond baseline measurements in a cohort of 699 adults followed for up to 24 years. That supports repeated clocks as prognostic signals. It did not test an intervention, came from one Italian cohort and cannot turn a commercial result of “seven years younger” into seven added years. Prediction improved; surrogate validation did not.

The validation problem extends beyond methylation. Measures based on proteins, metabolites, immune cells, organ imaging, physical performance and combinations of clinical tests may each capture part of ageing. A useful biomarker should be reliable within a person, responsive when biology changes, predictive across relevant populations and connected to outcomes that matter. It should also tell us whether an apparent improvement is beneficial rather than a short-term compensation or a harmful suppression of response.

Geroscience proposes a way to use clinical outcomes without waiting for one disease at a time. If ageing mechanisms contribute to cancer, cardiovascular disease, cognitive decline and frailty, a trial could use a composite endpoint covering the onset or progression of several age-related conditions. The planned Targeting Aging with Metformin trial was designed around that logic. Its scientific importance lies in the endpoint and regulatory strategy. As of 2 September 2026 it remains in planning and fundraising rather than supplying results.

Function must remain visible. Walking speed, grip strength, cognition, recovery after stress, independence and freedom from disability may detect value that a disease count misses. They can also be influenced by training, pain, environment and motivation. No single measure escapes context. The answer is a coherent set: mechanism, biomarker, clinical events, function, harms and durability.

This repays the reliability problem. A young-looking methylation profile is not the goal. The goal is a body that retains enough reserve to withstand disturbance, repair damage and continue doing valued work. Success may

look modest at the molecular level and large across a population if several diseases arrive later. It may also fail to increase maximum lifespan while compressing illness into a shorter final period.

The standard protects hope from marketing. A credible intervention should state which people it is for, what it changes, how long the effect lasts, what harms occur and which meaningful outcomes improve. Until those pieces exist, the honest description is research. A moved marker can nominate a treatment for a harder test. It cannot pass that test on the treatment's behalf.

How It Actually Works

A curve before a cause

Benjamin Gompertz was studying life contingencies, not looking for a molecular theory. Insurers needed to know how mortality changed with age, and in 1825 he proposed a mathematical law in which the force of mortality rises exponentially through much of adult life. Later demographers refined the model, populations shifted and extreme old age proved less tidy, but the curve supplied a durable fact: ageing is expressed as an accelerating risk of failure.

For more than a century, biology had no comparable mechanism. Researchers described wear, endocrine change, immune decline and the exhaustion of some undefined vital reserve. Old age was obvious at the level of bodies and obscure at the level of causes. The field also carried an ancient burden. Every serious result stood beside a market of tonics, glands, transfusions and rejuvenation schemes. Caution was intellectually sensible and reputationally necessary.

The first modern experiments did not begin with a longevity pill. They began with food.

The rats that stayed small

In a 1935 paper, Clive McCay, Mary Crowell and Leonard Maynard described an odd result from rats whose growth had been retarded by restricted feeding. The animals remained smaller and lived longer than controls. The study's methods belong to an earlier era, and later work transformed the protocol into calorie restriction without malnutrition. Its importance was conceptual. Lifespan had responded to an environmental intervention.

Restriction studies multiplied in rodents. Timing mattered. Diet composition mattered. Genetic background mattered. Some animals gained much more than others, and some gained little. Yet the broad result survived enough variation to force a change in question. Instead of asking only what breaks with age, researchers could ask what regulatory programme had shifted when less food was available.

The response made evolutionary sense. Scarcity is a poor time to spend heavily on growth and reproduction. Organisms that redirect resources towards survival and maintenance can wait for better conditions. In short-lived animals, that waiting strategy can produce a large fraction of extra life. The same logic later drew attention to insulin-like signalling, mTOR, AMPK, sirtuins and autophagy.

Calorie restriction also created the field's recurring trap. A robust laboratory phenomenon became a proposed human lifestyle before long-term human outcomes existed. Rodents can be fed precisely from youth and followed until death. People have preferences, changing bodies, pregnancies, illnesses and social lives. Severe restriction can reduce bone, muscle, fertility and quality of life. The human question was never whether eating less changes metabolism. It was whether a safe, sustainable intervention delays important age-related outcomes.

Why natural selection left the work unfinished

The 1950s supplied the organising theory. Peter Medawar imagined inherited effects that appear only at older ages. Because fewer individuals survive to express them and many have already reproduced, selection removes them weakly. George Williams then proposed antagonistic pleiotropy: an effect can be favoured because it helps early life even if it causes damage later. Tom Kirkwood later formalised maintenance as an allocation problem in disposable soma theory.

These accounts moved ageing away from a death programme. The body is not ordered to fail on schedule for the good of the species. It is built by selection whose priorities change across age. Late-life maintenance is incomplete because ancestral organisms often died before perfect maintenance could repay its cost, and because early benefits can outweigh late penalties.

The theories also made specific patterns intelligible. Growth pathways could increase early fitness and later disease. Strong inflammatory responses could fight infection when young and contribute to tissue injury when chronically active. Cells could suppress tumours by halting division, then damage their surroundings if they lingered. Ageing began to look like the afterlife of useful biology.

Evolution did not choose among the cellular mechanisms. It explained why several imperfect ones could coexist.

Free radicals, finite cells and chromosome ends

Denham Harman's 1956 free-radical theory gave damage a chemical form. Reactive molecules generated in metabolism could attack cellular components and start self-reinforcing decline. Evidence of oxidative damage accumulated, and the theory expanded towards mitochondria, where oxygen use and reactive chemistry meet.

Then intervention results complicated it. Antioxidants could quench reactive molecules in a test tube, yet supplementation did not produce the expected

broad protection in people. Some reactive oxygen species were found to be signals that induce defensive responses. In several model organisms, mild oxidative stress could lengthen life through adaptation. The free-radical theory had identified a real process and overstated its monopoly.

Leonard Hayflick and Paul Moorhead supplied a different limit in 1961. Normal human foetal fibroblasts divided a finite number of times in culture. At the time, many researchers assumed cultured cells were intrinsically immortal and that failed cultures reflected poor technique. Hayflick showed that ordinary cells could enter a stable non-dividing state. The finding later became linked to telomeres, repeated DNA sequences protecting chromosome ends.

Chromosomes create an end-replication problem. Conventional DNA replication cannot fully copy their tips, so telomeres often shorten as somatic cells divide. Carol Greider, Elizabeth Blackburn and Jack Szostak's work established telomeres and telomerase as a maintenance system, recognised by the 2009 Nobel Prize in Physiology or Medicine. In 1990, Calvin Harley, Bruce Futcher and Greider reported telomere shortening during the ageing of cultured human fibroblasts.

The result looked like a clock, but the mechanism was conditional. Telomere length differs among tissues and individuals, changes with cell turnover and stress, and is maintained by telomerase in germ cells, many stem cells and most cancers. Short or dysfunctional telomeres can trigger senescence and disease. Keeping every telomere long would also remove one barrier to uncontrolled cell division. The same limit that constrains tissue renewal helps suppress tumours.

The worm that doubled

Ageing became genetically tractable in small steps. Researchers working with *Caenorhabditis elegans* had identified long-lived mutants before 1993, including age-1. Cynthia Kenyon and colleagues then showed that reducing the activity of daf-2, a gene encoding an insulin-like receptor, could double adult lifespan. The effect depended on daf-16, which encodes a FOXO-family transcription factor.

That dependence mattered more than the headline. The mutation did not preserve worms through one repair mechanism. DAF-16 altered the expression of many genes involved in stress resistance, metabolism, immunity and maintenance. A regulatory pathway was coordinating a different state of the organism.

The worm offered speed and control. Researchers could alter genes, count hundreds of deaths and repeat an entire lifespan experiment in weeks. Yeast and flies supplied complementary systems. Mutations and interventions repeatedly pointed towards nutrient sensing, protein quality control, autophagy, mitochondria and stress responses. Conservation across distant species suggested deep biological roots.

It did not erase differences. A worm's insulin-like pathway participates in development and a dormant survival stage with no direct human equivalent. A mutation from conception is not a drug begun at seventy. Doubling a short life under laboratory conditions says that lifespan regulation exists. It does not say how much human life is available through the same lever.

A soil compound reaches old mice

Rapamycin entered medicine by a route too neat for marketing departments to improve. A microorganism isolated from soil collected on Rapa Nui produced a compound with antifungal activity. It later became an immunosuppressant, while related rapalogs entered cancer treatment. Its target, mTOR, became recognised as a central regulator of growth, protein synthesis and nutrient response.

In 2009, David Harrison and colleagues reported a result from the National Institute on Aging's Interventions Testing Program. Genetically heterogeneous mice received rapamycin beginning at about 600 days of age, late enough to resemble late middle age in that species. Lifespan increased in males and females across three testing sites. The treatment had begun late partly because of a formulation delay, turning an inconvenience into a stronger experiment.

Human evidence began to sharpen in 2025. PEARL randomised healthy adults to placebo or weekly compounded rapamycin for 48 weeks. Among 114 completers, visceral fat, the primary endpoint, did not differ. A few secondary signals appeared, including lean tissue and pain in a small subgroup of women and self-reported health in one dose group, while most measures did not change. Interpretation is constrained by the completer analysis, low female enrolment, lower-than-expected exposure from the compounded product and the investigators' financial ties to the trial sponsor. It is a useful safety and feasibility study, not proof of slower human ageing.

Another randomised trial in 2026 asked a functional question. RAPA-EX-01 assigned 40 sedentary adults aged 65 to 85 to weekly sirolimus or placebo while both groups completed 13 weeks of home exercise. Both groups improved. The primary intention-to-treat comparison in chair-stand performance was not significant, while prespecified sensitivity analyses favoured placebo. Secondary functional outcomes also leaned towards placebo without statistical certainty. Eighty-five per cent of each arm reported at least one adverse event, but the total event burden was higher with sirolimus and one pneumonia was judged possibly drug-related. The trial was small and brief, so it is neither a verdict nor a rounding error.

Together, these studies show why regimen, population and endpoint matter. Mouse lifespan, human body composition and human response to exercise are different questions. A null primary result does not erase the mouse evidence, and a selected secondary signal does not establish healthspan. The Interventions Testing Program remains valuable because candidate agents are tested at independent sites in genetically mixed mice under

harmonised protocols. Several compounds popular in the supplement market have failed there. Negative results improve the map.

Removing cells and resetting identity

Cellular senescence moved from culture dish to whole animal through genetic tools. Baker and colleagues created mice in which cells expressing high levels of p16 could be selectively killed. In a progeroid mouse model, removal delayed several disorders. In naturally ageing mice, related clearance improved aspects of health and extended median lifespan.

The causal result encouraged a search for senolytics, drugs intended to kill senescent cells by exploiting their dependence on survival pathways. Dasatinib plus quercetin, fisetin and other candidates entered early human studies. Small trials in specific conditions have shown that treatment can be delivered and can alter selected markers. The evidence does not yet establish that periodic clearance in healthy adults delays general ageing. The target itself is not one uniform cell class, and some senescent cells assist repair.

A more radical approach emerged from cellular reprogramming. Introducing factors associated with induced pluripotent stem cells can erase parts of a cell's differentiated state. Partial reprogramming aims to move age-related molecular patterns in a younger direction without taking the cell all the way back to pluripotency. Mouse and cell experiments have reported tissue repair and molecular rejuvenation under controlled conditions.

In 2026 the approach crossed into a small first-in-human phase I study. ER-100 delivers instructions for three reprogramming factors, commonly shortened to OSK, to retinal cells in one eye, with expression controlled by doxycycline. Participants have glaucoma or non-arteritic anterior ischaemic optic neuropathy, and the trial's primary purpose is safety and tolerability, with follow-up planned for years. That is a clinical milestone. It is not a test of systemic rejuvenation, lifespan or ageing in healthy people.

The attraction is obvious. Instead of clearing damage one category at a time, reset the regulatory state that handles it. The danger follows from the

same power. Losing cell identity and permitting uncontrolled growth are routes to tumours and organ failure. Reprogramming research is a demonstration of possibility, not a consumer therapy hiding behind regulatory delay.

From hallmarks to geroscience

By 2013, the field had enough mechanisms to need a shared map. Carlos López-Otín and colleagues proposed nine hallmarks of ageing: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem-cell exhaustion and altered intercellular communication. A 2023 update expanded the framework to twelve by separating disabled macroautophagy, chronic inflammation and dysbiosis. Later reviews proposed further categories, including extracellular-matrix change and psychosocial isolation in 2025, then mesenchymal drift as a possible convergent process in 2026. These are proposals, not intervention-validated additions to a settled answer key. The list is useful precisely because it remains revisable.

The hallmarks helped laboratories place results inside a larger system. They were never a claim that twelve independent dials add up to age. The categories overlap and influence one another. DNA damage can induce senescence. Autophagy affects mitochondria and protein quality. Microbial communities influence immunity and metabolism. A useful hallmark should change when ageing is accelerated, produce ageing when worsened and improve healthy life when treated, but evidence is uneven across categories and species.

Geroscience added the clinical argument. Rather than treating cancer, cardiovascular disease, dementia, diabetes and frailty as unrelated late-life accidents, study the mechanisms that make age a common risk factor. The US National Institutes of Health formed a cross-institute Geroscience Interest Group around that hypothesis. The aim is not to rename every disease as ageing. It is to test whether altering shared upstream biology can delay several conditions or functional losses together.

This shift changes trial design. A therapy might have modest effects on each disease yet a large combined effect on years lived without several of them. It might also exchange one cause of illness for another, which is why broad outcomes and long follow-up are necessary.

The longest lives and the wrong lessons

Exceptional survival looks like a shortcut to causes. Jeanne Calment's documented life of 122 years and 164 days remains the longest fully authenticated human lifespan. The record shows what one body achieved. It is nearly useless as an intervention study. One person supplies no control group, and every memorable detail about olive oil, chocolate, cycling or temperament is selected after the outcome is known.

Centenarians are survivors of many filters: childhood infection, accidents, war, smoking patterns, cardiovascular risk, cancer, social conditions and chance. Comparing them with other groups can identify genetic variants, immune profiles or behaviours associated with survival. Families also show that exceptional longevity has an inherited component. Yet the effects vary by population, common variants explain only part of the pattern and different protections can offset ordinary risks. Mechanisms can emerge from these studies; household instructions cannot.

Life expectancy and maximum lifespan answer different questions. Clean water, vaccination, safer childbirth, antibiotics, cardiovascular treatment and reduced smoking raised average survival by preventing deaths across the life course. Those gains allowed many more people to approach old age without requiring the outer record to move at the same speed. Calment's record has stood since 1997 while average survival has continued to change.

A 2024 demographic analysis by S. Jay Olshansky and colleagues argued that gains in life expectancy have slowed in long-lived populations and that radical extension is implausible this century unless biological ageing itself is markedly slowed. That is a projection from present mortality patterns, not proof of a fixed ceiling. A therapy that changed ageing biology could change

the pattern on which the forecast rests.

The extreme tail is shaped by biology, history and chance. Study it for protective mechanisms, not for a centenarian's formula.

The human evidence bottleneck

Human trials cannot begin with lifespan as a convenient laboratory endpoint. Researchers use intermediate measures: immune responses, metabolic function, inflammation, physical performance, imaging and molecular biomarkers. Epigenetic clocks became prominent because methylation patterns can estimate chronological age and predict later outcomes.

The first clocks demonstrated measurement, not rejuvenation. Later versions were trained on mortality-related traits or longitudinal decline. In CALERIE, two years of calorie restriction produced cardiometabolic improvements and a small change in DunedinPACE, while PhenoAge and GrimAge did not show significant treatment effects. The participants were healthy, mostly middle-aged volunteers, and the study did not observe enough years or events to establish longer life.

A 2026 analysis added an important piece without finishing the puzzle. Among 699 adults from two towns in Tuscany, changes in several clocks carried information about mortality over follow-up of up to 24 years, beyond the starting measurements. That supports longitudinal use as a risk signal. The cohort was of European ancestry, and the study observed natural variation rather than testing whether deliberately moving a clock changes an outcome.

Drug trials face a related endpoint problem. TAME was designed to test whether metformin could delay a composite of several age-related diseases in adults aged 65 to 79, with function among the wider outcomes. Its scientific value lies in making a multisystem claim testable. As of 2 September 2026, its official programme page still described a prepared design, fundraising to launch and participants yet to be recruited. It has no result to report.

Rapamycin evidence has moved beyond registrations to preliminary randomised findings. PEARL did not change its primary visceral-fat endpoint. RAPA-EX-01 did not improve its primary functional endpoint and raised a possible trade-off under one short exercise regimen. Neither trial was designed to establish delay of multiple diseases or longer survival. Senolytic studies remain small or condition-specific. No current drug result establishes durable multisystem benefit in broadly healthy adults with an acceptable balance of harm.

Ordinary prevention has stronger human outcome evidence: avoiding smoking, controlling blood pressure and lipids when indicated, vaccination, physical activity and treatment of established risks. Those practices are not proof that a shared molecular rate of ageing has been slowed. They are proof that much age-linked disease can already be postponed. A future geroscience treatment will still need that ordinary medicine around it.

How we know

Ageing science uses evidence at different scales. Demographic records reveal mortality and survival patterns but rarely isolate mechanisms. Longitudinal cohorts connect earlier measurements with later disease, disability and death, though association can reflect confounding. Human genetics can identify variants linked to exceptional survival, but extreme longevity is rare and population-specific.

Cells permit precise intervention but remove the organism. Worms, flies and yeast make lifespan experiments fast and mechanistic. Mice add mammalian tissues, disease and drug testing, while differing from humans in lifespan, environment and causes of death. Non-human primates narrow some gaps at great cost and small sample size.

Randomised human trials provide the strongest test of intervention, yet ageing demands years of follow-up and broad outcomes. Biomarkers can shorten that delay only after validation shows that intervention-driven changes predict how people feel, function or survive. No universal ageing biomarker has yet earned that role. The clearest claims therefore concern

mechanisms in models. Human healthspan extension by a specific gerotherapeutic remains an open clinical question.

What People Get Wrong

"Ageing has one root cause"

Single-cause theories are attractive because they turn a difficult system into a target. Free radicals, telomere shortening, mitochondrial decline, chronic inflammation and epigenetic change have each been promoted as the master defect. Every one describes real biology. None explains the whole pattern across tissues, species and interventions.

The problem is interaction. DNA damage can push cells into senescence. Senescent cells can release inflammatory signals. Inflammation can impair stem-cell function and protein maintenance. Faulty autophagy can leave damaged mitochondria in place, while mitochondrial signals can alter gene regulation. The categories in the hallmarks framework are therefore a map of connected failures, not twelve independent switches.

A root cause would need to show that worsening it reliably accelerates broad ageing, correcting it delays several important outcomes, and rival mechanisms become secondary once it is controlled. No candidate has cleared that standard in humans.

This matters because a product can be biologically active and still be narrow. Lowering one inflammatory marker or raising one recycling signal does not show that the organism has become younger. The stronger claim requires broad function, durable benefit and acceptable trade-offs.

"Telomeres are the body's countdown clock"

Telomeres shorten at the ends of many chromosomes as cells divide, and critically short or damaged telomeres can trigger senescence, loss of tissue renewal and disease. That makes them important. The countdown image adds more certainty than the mechanism permits.

Telomere length varies at birth, differs among cell types and is affected by turnover, inheritance and measurement. Blood-cell telomeres are not a direct reading from every organ. Some cells divide rarely. Stem cells and germ cells use telomerase to maintain chromosome ends, while most cancers reactivate telomere maintenance to keep dividing. A long telomere is therefore neither a universal sign of youth nor an unqualified good.

The trade-off is the correction. Limiting division can prevent damaged cells from expanding into tumours. Extending cellular replicative capacity may support renewal in one context and weaken cancer suppression in another. Diseases caused by severe telomere-maintenance defects show that the system can fail dangerously, but they do not show that increasing telomerase in healthy adults is a general longevity treatment.

A useful telomere result must specify the tissue, assay, starting length, intervention and clinical outcome. A change in average blood-cell length can be interesting evidence. It cannot by itself tell a person how long they will live.

"Antioxidants cancel ageing"

Oxidative chemistry can damage DNA, proteins and lipids. The mistake is to infer that reactive oxygen species are pure waste and that more antioxidant intake must produce more protection.

Cells use reactive molecules as signals. Exercise, infection control and metabolic adaptation depend partly on brief, local changes in redox state. A mild stress can activate repair and defence, a response sometimes described as hormesis. Blunting every signal is not the same as preventing chronic oxidative injury.

Human supplementation trials also failed to deliver the broad result the simple theory predicted. Effects differ by compound, dose, nutritional status, smoking history and disease. Some high-dose antioxidant supplements have been neutral in major trials; some have caused harm in particular populations. Food containing antioxidant molecules is not equivalent to an isolated capsule given at pharmacological dose.

The free-radical theory was productive because it identified a genuine source of damage and drove work on mitochondria and stress response. It became misleading when damage was treated as one-way rust. Redox biology is regulated communication as well as chemistry.

The relevant question is not whether a substance scores highly in a test tube. It is whether a defined dose improves a meaningful human outcome without disrupting useful signalling or creating another risk.

"Your biological-age score reveals your true age"

A biological-age test compresses many measurements into one familiar unit. That makes a complicated result easy to sell. It also encourages the belief that an algorithm has discovered the hidden number chronological age failed to show.

Different clocks are trained for different jobs. Some predict calendar age from DNA methylation. Others are trained on mortality-related traits, disease or longitudinal change. Protein, metabolite, immune and organ-specific measures capture other patterns. Two valid tools can disagree because they are summarising different information.

A score may predict future risk across a population and still be noisy for one person. Sample handling, cell composition, recent illness, the reference dataset and the algorithm all matter. Repeating a commercial assay can produce movement without proving that the underlying rate of ageing changed. Expressing the result in years does not make those years interchangeable with added or lost lifespan.

For intervention research, the hard test is stronger. The biomarker must respond reliably, predict several age-relevant outcomes and capture the treatment's effect on function or survival. Current reviews find promising measures but no universal surrogate endpoint for ageing.

Use a clock as a research instrument or risk summary within its validated setting. Do not let the unit disguise the model underneath it.

"Calorie restriction is proven to extend human life"

Calorie restriction is among the most reproducible longevity interventions in laboratory animals, and it has improved several human risk markers. The human lifespan claim remains unproved.

Rodent studies can begin early, control food precisely and continue until every animal dies. Results still vary with strain, sex, diet and housing. Two long rhesus-monkey studies differed in design and initial findings, then converged on health benefits while leaving the lifespan effect sensitive to feeding conditions and comparison groups.

CALERIE supplied the strongest randomised human test of sustained restriction without malnutrition. Participants achieved a moderate reduction rather than the prescribed twenty-five per cent, lost weight and improved several cardiometabolic measures over two years. One methylation measure of ageing pace shifted modestly; two others did not. The trial did not last long enough or include enough late-life events to establish longer life.

Restriction also carries costs when pushed too far: loss of muscle or bone, impaired fertility, cold intolerance, nutritional deficiency and reduced quality of life.

The established conclusion is that energy intake changes human physiology and some disease risks. The stronger conclusion, that long-term restriction adds human years by slowing ageing, still needs long follow-up and clinical outcomes.

"A treatment that works in mice is nearly ready for people"

A strong mouse experiment is a reason to begin translation, not evidence that translation is almost finished.

Mice share mammalian organs, pathways and many diseases with humans. They also live in protected colonies, mature quickly, have different causes of

death and process drugs differently. Laboratory temperature, microbiota, strain and sex can change results. A treatment started at twenty months in a mouse is not a precise model of one started at a particular human birthday.

Good design reduces these problems. Genetically heterogeneous animals, independent sites, pre-specified analysis and replication make a result more credible. The Interventions Testing Program uses several of these safeguards, which is why its positive and negative findings carry weight. They still answer a mouse question.

Human development must establish dose, exposure, interaction, side effects and whether a feasible regimen changes a useful endpoint. A drug that adds mouse lifespan may suppress immunity, impair healing or alter glucose in people. A therapy safe for a severe disease can have an unacceptable risk balance in healthy adults.

The phrase “human trials have begun” can also mislead. An early trial may test short-term safety or one marker in a small group. It is the first rung of evidence, not the last administrative step before approval.

"Centenarians have discovered the formula"

People who reach one hundred or more deserve study, but their lives are not controlled experiments. They are a selected group who survived genetics, infections, accidents, social conditions and chance. Looking backwards after survival makes ordinary habits appear causal because unsuccessful people with similar habits are absent.

Exceptional longevity does cluster in some families, and studies of centenarians have identified variants and physiological profiles worth investigating. The effects are diverse and population-specific. A protective pathway can suggest a drug target without implying that the person carrying it followed a reproducible routine.

Lifestyle stories are especially vulnerable. One centenarian reports daily wine, another abstinence; one ate little, another enjoyed sweets.

Contradictory anecdotes survive because the outcome makes each one

memorable. They cannot estimate benefit, dose or harm.

The same caution applies to long-lived places. Social connection, movement, diet, healthcare, migration and accurate birth records can all shape the observed pattern. A branded list can combine sensible habits with uncertain attribution.

Study the longest-lived to find hypotheses about protection, resilience and delayed disease. Test those hypotheses in cohorts, genetics, experiments and trials. The formula is not hidden in one breakfast. The evidence begins where the biography stops.

Use It

Separate the four promises

Longevity claims often move among four outcomes without admitting the change. Lifespan is time alive. Maximum lifespan concerns the extreme outer tail. Healthspan concerns years with low burden of disease or disability, though studies define it differently. Functional span concerns what a person can still do.

A treatment can reduce one disease while leaving total survival unchanged because other causes replace it. It can extend median lifespan without moving the maximum. It can add years while increasing the period lived with disability. It can preserve walking and independence without altering the oldest verified age.

Before assessing any claim, rewrite it in one sentence with the outcome named. “This intervention lowered an inflammatory marker for twelve weeks” is different from “this delayed multimorbidity” and far from “this extended healthy human life”. The first may be valuable. It cannot borrow the emotional force of the third.

Longer lives are not one social outcome. Extra healthy years affect work, care, retirement and family differently from extra years of severe dependency. Precision about the promise is the beginning of honest

judgement, not a technical distraction.

Ask what moved, in whom and for how long

A result becomes more informative when three questions are attached to it.

What moved? A molecular signal, a composite clock, grip strength, one disease, several diseases, disability or death each sits at a different distance from the goal. Measures near the mechanism can change quickly without predicting benefit. Clinical outcomes matter more and take longer.

In whom? Young mice under controlled feeding, old mice with varied genetics, people with a specific disease and broadly healthy older adults are different populations. An intervention can be worthwhile for someone at high risk and unjustified for someone with little to gain. Results from volunteers who tolerate a demanding protocol may not transfer to frailer or more diverse populations.

For how long? A transient shift can reflect adaptation, measurement noise or suppression of a useful response. Ageing interventions require durability because the proposed exposure may last for years. Follow-up must also be long enough for delayed harms such as infection, cancer, metabolic change or loss of tissue repair to appear.

This lens turns a headline into a testable proposition. It also reveals when a study has answered its narrow question well and the surrounding marketing has answered a larger one without data.

Follow the translation ladder

Place every discovery on a ladder: biochemical system, cultured cell, short-lived organism, mouse, non-human primate, early human study, large randomised trial, replicated clinical use.

Each rung removes some uncertainty and introduces new constraints. A cell experiment can show that a compound clears senescent cells, but not whether an organ benefits. A worm can show that a pathway regulates lifespan, but not whether a drug is tolerable for decades. A mouse can

reveal mammalian effects and toxicity, but not human dose or disease balance. A small human trial can show exposure and short-term safety without establishing healthspan.

Movement up the ladder is not automatic. The intervention may fail because the mechanism differs, the required dose is unsafe, the human tissue cannot be reached or the animal endpoint does not represent the human problem. A company may announce each rung as independent confirmation when the evidence is still one chain built on the same assumption.

Praise the result at its own level. A replicated mouse lifespan extension is a substantial scientific achievement. That is more respectful than pretending it is nearly a prescription.

Separate geroscience from ordinary prevention

The strongest current methods for reaching later life in good condition are often unglamorous: avoiding tobacco, treating high blood pressure and harmful lipid levels when appropriate, vaccination, physical activity, injury prevention and effective care for established disease. These measures have human outcome evidence. They can postpone death and disability without proving that one general rate of biological ageing has slowed.

Geroscience asks a different question. Can a shared mechanism be altered so that several age-related conditions and losses arrive later together? A positive answer would add something important to disease-specific prevention. It would not make ordinary care obsolete.

This distinction blocks two errors. The first is dismissing established prevention because it does not claim rejuvenation. Preventing a stroke preserves more functional life than improving an unvalidated age score. The second is relabelling every healthy behaviour as an anti-ageing intervention. Exercise, sleep and diet influence many pathways, but their practical evidence and recommendations belong to their own domains.

When a new treatment appears, compare it with the care already available. The relevant question is incremental benefit: what does it add beyond

known risk reduction, for which people, at what cost and harm?

Look for reserve, recovery and connected failure

Ageing is often easiest to see under demand. Compensation can keep resting measurements normal. The difference appears when a person stands, climbs stairs, fights infection, undergoes surgery or recovers from a fall.

Reserve is the unused capacity between ordinary function and failure. Recovery is the route back after disturbance. Both can be measured imperfectly through physical performance, stress tests, rehabilitation, immune challenge and longitudinal change. They are closer to the reliability model than surface youthfulness.

This lens changes how apparently separate events are interpreted. A fracture can lead to immobility, muscle loss, infection and cognitive decline because systems depend on one another. A small loss in several reserves may be more dangerous than one dramatic abnormality in an otherwise robust person. Multimorbidity is often connected failure, not a random pile of diagnoses.

For research, ask whether an intervention widens reserve or speeds recovery rather than merely improving a resting number. For care, the answer is individual and belongs with clinicians who understand disease, medication and goals. Stability at rest does not prove resilience.

Price the trade-off

Every plausible ageing intervention touches biology that has a current job. mTOR supports growth, immunity and repair. Senescence restrains damaged cells and helps some wounds. Inflammation fights infection. Telomere limits suppress uncontrolled division. Partial reprogramming alters cell identity. Turning a mechanism down because it contributes to late-life decline can weaken the function that made it useful.

The trade-off depends on timing, tissue, dose and baseline risk. A short course after disease may differ from lifelong exposure in health. A drug

acceptable after organ transplantation may be unacceptable for prevention. An effect beneficial at seventy may impair development or fertility at twenty.

This is why “natural” and “already approved” are weak safety arguments. Natural compounds have pharmacology. Approval applies to a defined indication, dose and population, not every proposed use. Off-label prescribing can be medically legitimate, but evidence and monitoring do not appear merely because a product is familiar.

A serious claim should name the bill: adverse events, interactions, opportunity cost, monitoring burden and the biological function being reduced. An intervention with no stated downside is a sales description, not a complete model.

The limits

This book cannot tell an individual how fast they are ageing or which intervention they should use. Current biomarkers do not supply a universal personal rate, and treatment decisions depend on medical history, medication, body composition, reproductive status, disease risk and values.

The reliability model is also compression. Ageing includes developmental change, social environment, disease, chance and organ-specific processes that do not fit one curve. Some late-life decline is preventable pathology. Some reflects trade-offs built into tissue maintenance. Some people live with disability while retaining high function and meaning, so healthspan must not become a moral ranking of bodies.

The science will change. A trial may validate a biomarker, disprove a favoured mechanism or show that one therapy delays several outcomes. The correct response is to update the claim, not defend the present map as doctrine.

The one thing to keep

Keep the distance between mechanism and outcome visible.

A pathway can be real, a molecule can hit it and a marker can move, while

the promised human benefit remains unknown. That distance is not a reason to ignore the discovery. It is the work still required.

Ageing science has already shown that lifespan and late-life function are biologically malleable in animals. It has mapped interacting failures, found conserved control pathways and made broad prevention a testable clinical ambition. What it has not yet shown is that a drug given to broadly healthy people can safely preserve multiple functions and delay multiple diseases for years.

The field deserves interest because that question is open, not because it has secretly been answered. Judge every claim by whether the intervention leaves the organism more reliable when life applies pressure. Youth is an appearance. Longevity worth having is retained capacity to recover, adapt and continue.

Terms

Ageing. The progressive change that raises vulnerability and reduces repair, reserve and recovery over time. It is a collection of interacting processes, not one universal clock. Its pace and expression differ among tissues and people.

Longevity. Length of life, whether for an individual, population or species. The word says nothing by itself about health, function, distribution or the mechanism producing survival. An apparent gain can hide extra years of disability.

Lifespan. The duration from birth to death for an organism. Studies may report mean, median or maximum lifespan, which answer different questions and must not be exchanged casually. Survival curves show the distribution better than one average.

Life expectancy. The average remaining years predicted from current age-specific mortality rates. It is a population calculation, not a guaranteed personal deadline or a biological maximum. It changes when mortality rates, not birthdays, change.

Maximum lifespan. The greatest verified age reached within a species or population. A record can reveal possibility while remaining too rare to identify an intervention or fixed ceiling.

Healthspan. The period lived with relatively good health or without specified disease and disability. Definitions vary, so every study must state the conditions and functions it counts. The label is useless unless its endpoint is declared.

Compression of morbidity. The aim of postponing disease and disability so that a shorter share of life is spent seriously unwell. Longer survival alone does not guarantee it.

Mortality hazard. The instantaneous risk of death among those still alive at a given age. Its rise through adulthood is one demographic signature of ageing. It differs from the probability of surviving from birth.

Gompertz law. A model in which adult mortality hazard rises roughly exponentially with age. Real populations deviate, especially at extremes, but the accelerating pattern remains informative.

Frailty. Increased vulnerability to stress caused by reduced reserve across several systems. It can be measured through a physical phenotype or an index of accumulated deficits.

Resilience. The ability to withstand disturbance and return towards previous function. Recovery after infection, surgery or exertion may reveal ageing more clearly than a resting measure. Repeated stress tests may reveal change before disability appears.

Reserve. Capacity beyond what ordinary activity requires. A person can appear stable at rest while having little cardiac, muscular, cognitive or immune capacity available under pressure. Loss can remain hidden until demand exposes it.

Homeostasis. Active regulation that keeps internal variables within usable ranges. Ageing often narrows the range and slows correction rather than causing immediate loss of all control.

Cellular senescence. A durable state in which a stressed or damaged cell stops dividing and changes its behaviour. Senescence can suppress tumours and aid repair, then become harmful when persistent.

SASP. The senescence-associated secretory phenotype, a mixture of signals released by some senescent cells. It can recruit repair and immune activity or drive chronic inflammation and tissue disruption.

Senolytic. A treatment intended to kill selected senescent cells by exploiting their survival dependencies. The class is experimental for general human ageing and may affect useful senescent cells. Selectivity and timing are central safety problems.

Telomere. Repetitive DNA and associated proteins protecting chromosome ends. Telomere dysfunction can limit renewal, while indiscriminate lengthening may weaken a barrier against cancer.

Telomerase. The enzyme that extends telomeres in germ cells, some stem cells and most cancers. Its dual role in maintenance and uncontrolled growth makes intervention difficult.

Proteostasis. The network that makes, folds, transports, repairs and removes proteins. Its decline allows damaged or aggregated proteins to interfere with cells and tissues.

Autophagy. Cellular recycling in which components are enclosed, delivered to lysosomes and broken down. It supports quality control, nutrient adaptation and removal of damaged structures.

Mitochondrial dysfunction. Loss or alteration of mitochondrial energy production, signalling and quality control. Mitochondria participate in ageing through more than accumulated oxidative damage.

Genomic instability. Increased damage, mutation or structural error in DNA and chromosomes. Causes include replication, radiation, metabolism and declining repair, with effects differing among tissues.

Epigenetics. Chemical and structural regulation of gene activity without

changing the DNA sequence. Age-related epigenetic change can reflect damage, adaptation, altered cell composition or all three.

Epigenetic clock. An algorithm using DNA-methylation patterns to estimate age or age-related risk. Different clocks have different training targets and can disagree about one intervention.

Inflammaging. Persistent low-grade inflammatory activity associated with later life. It can arise from immune change, tissue damage, infection, metabolism and senescent-cell signalling rather than one source.

Stem-cell exhaustion. Reduced ability of tissue stem cells to replenish specialised cells when needed. Depletion, altered niches, senescence and lineage bias can all contribute.

Nutrient sensing. Cellular systems that adjust growth, storage, repair and recycling according to energy and amino-acid availability. Major pathways include insulin signalling, mTOR, AMPK and sirtuins.

mTOR. A protein kinase coordinating growth, protein synthesis, nutrient response and autophagy. Inhibiting it can extend animal lifespan while also affecting immunity, metabolism and healing.

Surrogate endpoint. A measure used in place of how people feel, function or survive. It earns clinical trust only when intervention-driven changes reliably capture treatment benefit in a defined setting. Prediction alone is insufficient.

Geroscience. Research testing whether shared mechanisms of ageing can be targeted to delay several diseases and functional losses together. It is a clinical hypothesis, not a completed treatment system. Its success requires broad outcomes and long human trials.

Go Deeper

The accessible critical overview

Venki Ramakrishnan, *Why We Die: The New Science of Ageing and the Quest for Immortality* (Hodder & Stoughton, 2024). Ramakrishnan is a molecular biologist and Nobel laureate who approaches the field with interest and resistance to salesmanship. He moves from evolution and cellular maintenance through worms, mice, telomeres, senescence and current interventions, then asks what longer life would mean. This is the best next book for a general reader who wants more people, experiments and ethical range without being told that a breakthrough is already a treatment. The detail can become dense, but the scepticism is earned rather than theatrical.

The deeper biology

Coleen T. Murphy, *How We Age: The Science of Longevity* (Princeton University Press, 2023). Murphy studies ageing in *Caenorhabditis elegans* and gives model organisms the space a short survey cannot. The book explains how genetics, reproduction, sensory systems, memory, metabolism, inheritance and the microbiome became experimentally connected to lifespan. Read it for the logic of discovery: why worms are powerful, where conservation across species matters and where it does not. It is longer and more laboratory-centred than Ramakrishnan, which makes it a strong bridge from popular science to the research literature.

The organising framework

Carlos López-Otín, Maria A. Blasco, Linda Partridge, Manuel Serrano and Guido Kroemer, “Hallmarks of Aging: An Expanding Universe” (*Cell*, 2023). This review updates the 2013 hallmarks framework from nine categories to twelve and sets criteria for treating a process as a hallmark. It is the clearest technical map of genomic instability, proteostasis, autophagy, nutrient sensing, mitochondria, senescence, stem cells, inflammation, dysbiosis and communication. Read it as a research agenda rather than a solved wiring diagram. The categories overlap, evidence strength varies and a commercial product touching one hallmark has not thereby altered organismal ageing.

The measurement problem

Mahdi Moqri and colleagues, “Validation of Biomarkers of Aging” (*Nature Medicine*, 2024). This review explains why predicting chronological age or mortality is not enough to make a biomarker a clinical surrogate. It lays out requirements for reliability, longitudinal sensitivity, population generalisability and connection to functional decline, disease and death. Read it before buying a biological-age test or interpreting a trial through one clock. The paper is technical, but its central lesson is plain: a useful marker must survive validation at the exact job it is being asked to perform. It is the best antidote to a seductive number presented without context.

Notes and Sources

Current scientific, clinical-trial and institutional material was checked on 2 September 2026. Dates below are publication dates unless a current-status note says otherwise.

The Whole Thing in One Page and Why You Should Care. The description of ageing as rising vulnerability draws on Gompertz’s 1825 mortality law, modern frailty research and the geroscience hypothesis. Gompertz described an approximately exponential adult mortality pattern, not a universal cellular mechanism or fixed personal schedule. Fried and

colleagues established a widely used frailty phenotype; Mitnitski, Mogilner and Rockwood developed the accumulated-deficits approach. The World Health Organization's healthy-ageing framework supplies the emphasis on functional ability rather than survival alone. Kennedy and colleagues set out the modern geroscience argument that shared ageing mechanisms may connect several chronic diseases. The statement that no gerotherapeutic has shown durable multisystem benefit in broadly healthy humans was checked against the published PEARL and RAPA-EX-01 trials, current trial registries, the US National Institute on Aging and the American Federation for Aging Research.

Core Idea 1: Ageing Is a Loss of Reliability, Not a Clock. The reliability model is a synthesis rather than a claim that one accepted engineering equation describes the body. It combines demographic hazard, physiological reserve, resilience and frailty. Fried et al. support the phenotype examples; Mitnitski et al. support deficit accumulation. Gompertzian mortality is strongest through much of adult life and does not fit every species, population or extreme age. Jones and colleagues documented diverse mortality and fertility trajectories across the tree of life, which is why the text avoids treating the Gompertz pattern as a law of all living things.

Core Idea 2: Evolution Did Not Optimise Us for Indefinite Repair. Medawar's 1952 lecture supplied the mutation-accumulation argument; Williams's 1957 paper formulated antagonistic pleiotropy; Kirkwood's 1977 paper developed disposable-soma reasoning. These are related evolutionary models, not mutually exclusive proven causes for every age-associated change. Comparative claims about birds, bats and other long-lived species are bounded by Jones et al. and Kirkwood and Austad. The discussion of intergenerational contribution in human life history is a live evolutionary interpretation rather than a settled explanation of human longevity, so the wording remains conditional.

Core Idea 3: Damage Is Inevitable; Failed Cleanup Makes It Ageing. Harman's 1956 paper is the source for the free-radical theory's historical

form. Later research established signalling and adaptive roles for reactive oxygen species, which is why oxidation is not treated as one-way rust. The Cochrane review by Bjelakovic and colleagues supports the narrow claim that antioxidant supplementation has not produced general mortality benefit and that beta-carotene and vitamin E have shown harm in some settings. López-Otín et al. 2013 and 2023 support the accounts of genomic instability, proteostasis, autophagy and mitochondrial dysfunction. The text does not claim that protein aggregates are always protective or always causal; that uncertainty is tissue and disease specific.

Core Idea 4: Cells Change State and Alter Their Neighbourhood.

Hayflick and Moorhead established finite serial cultivation of normal human diploid cells. Harley, Futcher and Greider linked telomere shortening to replicative ageing in cultured human fibroblasts. The Nobel Prize official record confirms the 2009 award to Blackburn, Greider and Szostak for telomeres and telomerase. Baker et al. 2011 showed that clearing selected p16-expressing cells delayed age-associated disorders in a progeroid mouse model; Baker et al. 2016 extended the causal case in normally ageing mice and reported increased median lifespan. Those experiments targeted defined engineered cell populations and do not establish that all senescent cells are harmful. Hickson et al. provides an early human senolytic example in diabetic kidney disease, with changes in senescence markers but no proof of general healthspan extension. Franceschi et al. introduced the inflammaging framing used here.

Core Idea 5: Metabolism Is a Control Network, Not a Calorie Meter.

McCay, Crowell and Maynard's 1935 rat study is the historical calorie-restriction anchor. Mattison and colleagues reconciled the two long-running rhesus-monkey programmes and documented the importance of diet, feeding protocol, age and control conditions. The human evidence comes from CALERIE. Kraus et al. reported that participants assigned to two years of restriction achieved about 12 per cent average energy reduction and improved several cardiometabolic risk factors. Waziry et al. found a small treatment effect on DunedinPACE but no significant effect on PhenoAge or GrimAge. That analysis was post hoc, blood based and too

short to establish disease delay or longer life.

Harrison et al. 2009 is the source for late-life rapamycin extending lifespan in genetically heterogeneous mice at three sites. The National Institute on Aging's Interventions Testing Program supplied the programme description and current context. Rapamycin's established clinical uses and adverse-effect profile are not treated as proof of the effects of lower or intermittent regimens.

Core Idea 6: Biology Can Be Slowed in Animals; Translation Is the Hard Part. Kenyon et al. 1993 is the source for daf-2 mutations doubling adult lifespan in *Caenorhabditis elegans* through daf-16-dependent biology. The text treats this as evidence that conserved regulatory pathways can alter organismal lifespan, not a numerical forecast for humans. The Interventions Testing Program supports the value of genetically heterogeneous mice, independent sites and publication of negative results. Ocampo et al. 2016 supplies the principal preclinical partial-reprogramming example. ClinicalTrials.gov record NCT07290244 describes ER-100 as a first-in-human phase I study in open-angle glaucoma and non-arteritic anterior ischaemic optic neuropathy, using a single ocular dose and long safety follow-up. It does not test systemic rejuvenation or ageing in healthy people.

Core Idea 7: A Longevity Treatment Must Preserve Function, Not Merely Move a Marker. Horvath 2013 established a multi-tissue DNA-methylation age estimator. Later clocks were trained on different outcomes, so agreement is not expected by design. Kuo and colleagues' 2026 InCHIANTI analysis followed 699 adults with repeated measurements for up to 24 years and found that changes in several clocks added mortality information beyond baseline values. The authors also reported limitations in ancestry and setting. The finding strengthens longitudinal prediction, not the claim that an intervention-driven clock change is a validated surrogate. Moqri et al. 2024 supplies the wider biomarker-validation framework. The CALERIE clock disagreement comes directly from Waziry et al.

Barzilai et al. 2016 described the planned Targeting Aging with Metformin

strategy. AFAR's official TAME page still described fundraising to launch, a prepared design and recruitment yet to occur when checked on 2 September 2026. The book therefore reports a planned design rather than a result. This remains a time-sensitive point.

How It Actually Works: the early science. Gompertz, McCay, Medawar, Williams, Harman, Hayflick and Moorhead, Harley et al. and Kenyon et al. support the chronology. Vézina, Kudelski and Sehgal's 1975 paper supports the account of rapamycin's isolation from a microorganism in an Easter Island soil sample and the origin of its name; Harrison et al. supports the late-life mouse experiment. The formulation delay is documented in accounts of the Interventions Testing Program result and is included because it changed the experimental timing.

How It Actually Works: human rapamycin evidence. PEARL was a 48-week decentralised, double-blind, randomised placebo-controlled study of weekly compounded rapamycin in a healthy ageing cohort. Its primary visceral-adiposity endpoint was null. Selected secondary signals appeared, but interpretation is limited by analysis of 114 completers, low female enrolment, lower-than-expected exposure from the compounded product and the authors' employment or ownership interests in AgelessRx. RAPA-EX-01 randomised 40 sedentary adults aged 65 to 85 to 6 mg weekly sirolimus or placebo during 13 weeks of home exercise. The intention-to-treat primary chair-stand comparison was not significant; prespecified complete-case and per-protocol analyses favoured placebo. Total adverse-event burden was higher with sirolimus, including one possibly drug-related pneumonia. The trial was exploratory, short and too small to settle long-term benefit or harm.

How It Actually Works: senescence, reprogramming, hallmarks and geroscience. Baker et al. 2011 and 2016 support the causal senescent-cell experiments. Ocampo et al. supports partial reprogramming in animals, while NCT07290244 establishes only the purpose and status of the current human eye trial. López-Otín et al. 2013 proposed nine hallmarks; the 2023 update proposed twelve. Kroemer and colleagues' 2025

precision-geromedicine review proposed extracellular-matrix alterations and psychosocial isolation as additions. Lu and colleagues' 2026 *Cell* review proposed mesenchymal drift as a convergent framework. Both later proposals come from reviews and are not presented as consensus replacements or intervention-validated causes. The NIA Geroscience Interest Group supplied institutional context.

How It Actually Works: exceptional survival and the human bottleneck.

Robine and Allard support Jeanne Calment's authenticated age of 122 years and 164 days. Centenarian genetics can identify associations and mechanisms, but survivorship, population structure and rare combinations prevent conversion into a routine. Olshansky and colleagues' 2024 demographic analysis supports the claim that gains in life expectancy have decelerated in long-lived populations and that radical extension is implausible without a marked change in ageing biology. The paper is a projection from observed mortality, not proof of an immutable human ceiling.

CALERIE sources support the human-restriction account. Horvath, Waziry, Kuo and Moqri support the clock discussion. AFAR supports the September 2026 TAME status. The statement that ordinary prevention has stronger human outcome evidence is deliberately generic and does not turn this book into a prevention protocol; disease-specific recommendations depend on clinical context and belong to neighbouring titles and professional guidance.

What People Get Wrong. The seven corrections draw mainly on the same primary evidence already noted. Telomere claims are bounded by Hayflick and Moorhead, Harley et al. and the role of telomerase in most cancers. Antioxidant claims are bounded by Harman and Bjelakovic et al. Biological-age claims are bounded by Horvath, Waziry, Kuo and Moqri. Calorie-restriction claims are bounded by Mattison, Kraus and Waziry. Mouse-to-human claims are bounded by the Interventions Testing Program and the mixed early human rapamycin evidence. Centenarian claims are bounded by Robine and Allard and the observational nature of exceptional-longevity research.

Use It and Terms. The distinction among lifespan, maximum lifespan,

healthspan and functional span follows demographic, WHO and geroscience usage, but healthspan definitions vary across studies. The translation ladder is an explanatory synthesis, not an official regulatory sequence. The discussion of reserve, recovery, trade-offs and connected failure draws on frailty, geroscience and hallmarks research. The surrogate-endpoint definition follows the distinction between prognostic association and validated capture of treatment benefit. This section is an evidence-reading framework, not individual medical advice.

Go Deeper. Publisher, year and title details were checked for Ramakrishnan and Murphy. López-Otín et al. 2023 and Moqri et al. 2024 were checked against the journal records. The recommendations were selected for different purposes: critical overview, model-organism depth, organising framework and biomarker validation.

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