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Time to Talk SENS: Critiquing the Immutability of Human Aging

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Abstract

Aging is a three-stage process: metabolism, damage and pathology. The biochemical processes that sustain life generate toxins as an intrinsic side-effect. These toxins cause damage, of which a small proportion cannot be removed by any endogenous repair process and thus accumulates. This accumulating damage ultimately drives age-related degeneration. Interventions can be designed at all three stages. However, intervention in metabolism can only modestly postpone pathology, because production of toxins is so intrinsic a property of metabolic processes that greatly reducing that production would entail fundamental redesign of those processes. Similarly, intervention in pathology is a "losing battle" if the damage that drives it is accumulating unabated. By contrast, intervention to remove the accumulating damage would sever the link between metabolism and pathology, so has the potential to postpone aging indefinitely. We survey the major categories of such damage and the ways in which, with current or foreseeable biotechnology, they could be reversed. Such ways exist in all cases, implying that indefinite postponement of aging – which we term "engineered negligible senescence" – may be within sight. Given the major demographic consequences if it came about, this possibility merits urgent debate.

Introduction

The term “negligible senescence” was coined[1] to denote the absence of a statistically detectable increase with organismal age in a species’ mortality rate. It is accepted as the best operational definition of the absence of aging, since aging is itself best defined as an increase with time in the organism’s susceptibility to life-threatening challenges. It has been compellingly shown to exist only in one metazoan, *Hydra*;[2] certain cold-blooded vertebrates may exhibit negligible senescence but limitations of

sample size leave the question open;[1] and it has not been suggested that any warm-blooded animal (homeotherm) does so. Indeed, humans are among the slowest-aging homeotherms.

Since Gilgamesh, civilization has sought to emulate *Hydra* – to achieve a perpetually youthful physiological state – by intervention to combat the aging process. Such efforts may appropriately be termed "strategies for engineered negligible senescence" (SENS). This phrase makes explicit the inevitable exposure to extrinsic, age-independent causes of death (which is blurred by more populist terms such as "immortality" or "eternal youth"), while also stressing the goal-driven, clinical nature of the task (in contrast to the basic-science tenor of, for example, "interventive biogerontology"). Here we discuss the feasibility, within about a decade, of substantive progress towards that goal.

Plausibility of engineered negligible senescence

It is worth stressing, at the outset, civilization's considerable untapped ability to increase mean lifespan. One of us (B. N. A.) has devoted much energy to spreading awareness of the extremely cheap and straightforward measures already available for reducing one's age-specific susceptibility to the major life-threatening diseases, particularly cancer, by micronutrient supplementation.[3] In poorer societies, micronutrient deficiency is endemic due to poor diet; efforts to induce better dietary habits (particularly the greater consumption of fruit and vegetables) have been notably unsuccessful. However, such dietary shortfalls can also be avoided with a daily multivitamin costing just 3 cents. A large increase in such societies' mean healthy lifespan should result, just as has been achieved by public health measures in the past century.

Given our failure to exploit existing opportunities to maximize *average* lifespan, it is perhaps unsurprising that progress in extending *maximum* lifespan has been extremely limited (albeit non-zero[4]), at least if measured by the most established statistic, the age at death of the longest-lived subset (typically 10%) of the population. By contrast, our progress in understanding aging has continued to accelerate. This dichotomy underlies the virtual absence of serious anti-aging biotechnology: while success in understanding aging has bred enthusiasm, failure in intervention has engendered disillusionment, which extends to the general public. In our view, this disillusionment has brought about an unwarranted neglect of interventive biogerontology, manifest as a deep-seated but unjustified reluctance to aim high.

The claim that this reluctance is unjustified is bold and controversial, and the main purpose of this article is to examine it in detail. One side of the argument is entirely uncontested within the biogerontology community (though perhaps less well appreciated by other biomedical experts, and certainly by the public): that *if* efforts to engineer negligible senescence have any real chance of success, then investment in such efforts is incomparably the most cost-effective long-term approach to diminishing the incidence of age-related diseases. This is a direct corollary of the exponential rise with age in the susceptibility of individuals to all such ailments. What is controversial is the premise that there is any real chance of such progress, however great the investment. The prevalence of pessimism in this regard leaves a vacuum that allows – indeed, arguably promotes – the diversion of much public and private money into putatively anti-aging therapies whose availability is immediate but whose efficacy is evidently negligible.

A popular source of pessimism regarding anti-aging research is that, as noted above, all homeotherms age. Does this mean that the quest to engineer negligible senescence in humans is illusory, as noted gerontologists have suggested?[5,6] No. Natural selection optimises each species' rate of aging for its evolutionary niche, and that optimum is thought never to be infinitesimal[7] – in other words, negligible senescence is always sub-optimal. (*Hydra* escape the logic underlying this generalisation because their lack of long-lived cells means that the "maintenance cost" of living indefinitely is no more than that of living a few months.) Thus, the nonexistence of negligibly-senescing homeotherms in nature does not prove that attempts to engineer one are forever bound to fail.

Another central reason why biogerontologists have doubted that negligible senescence can be engineered is because it necessarily involves *reversing* any age-related decline that has already occurred, not merely retarding or postponing further decline. Reversing a process is, intuitively, enormously harder than retarding it; hence, the goal of reversing aging – when we are presently so powerless to postpone it – is deemed unreasonable. We note several critical flaws in this logic.

One derives from the fact that the public are simply not inspired by the idea of retarding aging, especially when it is presented as the *ultimate* goal of biogerontology research. This is understandable, since the public remain poorly aware that anti-aging research is not simply anti-death research – that it seeks to diminish, not extend, age-related debilitation. By contrast, reversing aging – restoring the vitality and function whose progressive loss attends (and, to a greater or lesser degree, haunts) everyone over 50 – is a goal which everyone understands and nearly everyone actively desires. In our view, this greater public appeal (and consequent fundability) of such work far outweighs any greater ambition and difficulty that it may possess.

A further criticism of the view that reversing aging is not yet appropriate for serious consideration is the most direct: we suggest that **reversing mammalian aging is not necessarily any harder than dramatically postponing it**. The most influential molecular changes in age-related decline, such as accumulation of mutations and undegradable material in long-lived cells, are irreversible by natural cellular processes. Moreover, the pathways by which they arise begin as intrinsic side-effects of fundamental metabolic processes such as respiration and DNA replication. Cells already possess prodigiously intricate defenses against these side-effects; it may be unrealistic to suppose that those defenses can be appreciably improved and aging thereby retarded (though studies with novel dietary antioxidants continue to attract interest[8,9]). On the other hand, reversing changes that cells cannot reverse is not tantamount to being cleverer than evolution, given our possession of technology that cells lack – particularly, our increasingly sophisticated ability to alter an organism's DNA sequence (and hence the gene expression of some or all of its cells) to an extent that evolution, in the time it has had, could not. In mice, retarding aging by a large amount – much more than human aging has been retarded by 20th-century medicine[4] – appears much easier than reversing it,[10,11] but this may be a peculiarity of short-lived laboratory strains.[12,13]

Finally, we warn against overestimating the difficulty of implementing interventions that rely on somatic gene therapy. Several measures whose pursuit we advocate below are in this category; moreover, they require the particularly challenging transfection of most of our postmitotic cells. Transgenic interventions are always developed in short-lived mammals (particularly mice) before any attempt to translate them to humans, and germ-line transformation of mice is already routine. Conversely, gene therapy has enormous potential in areas of medicine which do not face the same obstacle of public and professional pessimism that confronts anti-aging research, with the result that (despite well-publicized setbacks) efforts to improve its versatility continue apace in numerous laboratories worldwide. Furthermore, we contend that the impact on public opinion and (inevitably) public policy of unambiguous aging-reversal in mice would be so great that whatever work remained necessary at that time to achieve adequate somatic gene therapy would be hugely accelerated. For these reasons, while acknowledging the formidable hurdles remaining in the way of truly comprehensive gene therapy, we choose to focus on mice, rather than humans, as the target organism for developing anti-aging interventions that require genetic manipulation. We accept that the distinctive lifespan-limiting pathologies of different mammals may sometimes recommend other model organisms; however, the interventions discussed below target highly ubiquitous aspects of mammalian aging, lessening the need to study unfamiliar species.

Components of a strategy for engineered negligible senescence

We next survey several specific interventions which we feel are especially promising medium-term approaches to reversing age-related decline (Table 1). In each case we anticipate that adequately-funded efforts to develop such technology have a good chance of success in mice within ten years, and in some cases much sooner; moreover, we argue below that translation of it to humans may occur rapidly thereafter.

A low-technology, but nonetheless important, aging-reversal strategy with considerable promise is appropriate exercise. Though conventional sporting activity will not extend maximum lifespan, other regimes (particularly pliometric contraction, where the muscle is extended while in tension) have the potential to restore both muscle mass and bone density, and are indeed used by body-builders. This appears to operate by releasing a splice variant of liver IGF-1 that is secreted by skeletal muscle and operates in an autocrine and paracrine fashion.[14]

Muscle and bone are also rejuvenated by hormone supplementation, since hormonal changes underlie (for example) the change in relative activity of osteoblasts and osteoclasts that causes loss of bone density and eventually osteoporosis.[15] Similarly, growth factor-induced reversal of thymic involution has been reported recently[16] and may comprehensively restore youthful immune function.[17] Such supplementation has side-effects which many find unacceptable.[18] Logically, however, these must arise from the coexistence of a youthful level of the relevant hormones with an aged state of other aspects of physiology. Coordinated restoration of all hormones and growth factors to youthful levels may thus be anticipated to induce more widespread reversal of age-related gene expression changes, particularly if supplementation is administered by a slow-release delivery system that closely mirrors natural patterns of hormone release. In some cases that pattern is inducible or rhythmic, especially circadian;[19] this should also be feasible to emulate (if that is found to be necessary) by placing transgenes under the regulatory regions of genes whose natural expression has a similar profile. Such delivery systems must initially be developed in mice; genetic engineering of muscle to express hormones shows great promise in this regard.[20]

On the other hand, there is strong evidence that youthful levels of some hormones and growth factors promote cancer; thus, such intervention in isolation might well be life-shortening. The extended lifespan of mice deficient for growth hormone or its receptor[21] indicates, because most laboratory mice die of cancer, that cancer appears and/or grows more slowly in a growth hormone-deficient environment. Growth hormone also promotes other pathologies, including insulin resistance.[22] We therefore advocate further judicious testing of low-dose, late-onset supplementation of growth factors in combination with other interventions, and the countering of side-effects by other means (discussed below). An important hormone whose levels typically rise, not fall, with age is insulin.[23] In this case the process that declines is the response to the hormone, so the hormone level itself is not the appropriate target for rejuvenating intervention.

Importantly, the ability of muscle mass to respond to growth factors or to exercise depends on the availability of muscle precursor cells (myoblasts, or satellite cells). Endogenous myoblasts are confined within the basal lamina of muscle fibers, so new myocytes can be laid down only if other cell types are induced to differentiate into myoblasts.[24] Such cells could be engineered and cultured *ex vivo* and introduced into the body before differentiation. This technique has been applied, with physiological benefits, even in the heart (which lacks natural precursor cells[25]). Similar therapy is already known to be effective for pancreatic islets[26] in modulating diabetes, of which the non-insulin-dependent variety is another major disease of (which is to say, component of) aging.

Loss of muscle mass and function with age is not limited to muscle fibers, however: the greatest proportional change is in the number of motor neurons controlling those fibers.[27] Loss of neurons also underlies various neurodegenerative diseases. Neural stem cells, cultured *ex vivo*, have been induced to differentiate and replace lost neurons after injection into the brain.[28] We feel that such technology presently shows more promise for reversing age-related neurodegeneration than the better-known

discovery of neural progenitor cells within the adult brain, since the latter's capacity to replace lost neurons appears inadequate.

Perhaps even more promising, especially in the short term, as a technique to reverse age-related neural decline is to induce re-growth of lost synapses in neurons that, though still alive, have lost many of their connections to other neurons (or to muscle) resulting in functional impairment. Neurons of most brain areas are now known not to be greatly depleted with age except in neurodegenerative diseases (though white matter volume does decrease[29]), so the window of opportunity for such treatment is substantial; successful re-growth in response to growth factors, with associated cognitive benefits, has already been reported in rats.[30] This concept extends previous successes in rodents of technically simpler interventions to restore bioenergetic capacity and resistance to atrophy.[31,32]

Cell senescence, the finite replicative potential and associated gene-expression changes seen in cell culture, has been suggested to underlie many aspects of aging and to be treatable by telomerase activation.[33] However, senescent cells are very rare *in vivo* and may often arise by telomere-independent pathways.[34] We therefore feel that any pro-aging role of cell senescence arises from intercellular toxicity and would be best combated by selective ablation of senescent cells. Pro-apoptotic signals can realistically be designed to target cells expressing surface markers diagnostic of the senescent state.

Attention to cellular aging has sometimes distracted attention from the important role of extracellular age-related changes. These include deposition of undegradable aggregates such as amyloid in the brain and elsewhere,[35,36] discussed below, and protein-protein cross-linking impairing elasticity-dependent functions such as vascular tone.[37] Small molecules that selectively cleave sugar-induced cross-links show remarkable efficacy *in vivo* in restoring youthful elasticity.[38,39]

While many aspects of aging revolve around loss of cells, others are caused by the opposite – unconstrained proliferation of cells that should be quiescent, the most extreme manifestation of which is cancer. Though many ingenious and promising anti-cancer therapies (including angiogenesis inhibitors[40] and autologous vaccines[41]) are being pursued, we fear that they, like the body's natural defenses, will ultimately be outsmarted by the intra-organismal natural selection that generates a cancerous cell. But the absolute requirement of telomere maintenance (generally by telomerase reactivation) for indefinite cell division gives us cause for optimism. Only our germ line and stem cell pools actually need telomere maintenance for life-long function; if the gene encoding a telomerase subunit could be deleted from all other cells, cancer progression would be powerfully impeded. This would be therapeutically equivalent to repairing all somatic mutations in tumor-suppression genes, but whereas such repair is wholly impractical, gene deletion can be performed by comprehensive gene therapy (simulated in mice by germ-line transformation). Gene therapy is normally considered as a means of introducing replacement genes into cells that harbor mutations in them, but this unconventional application of it is equally feasible. It could also be used for any secondary telomere maintenance mechanisms that we may discover; one, termed ALT, is already known.[42]

Gene deletion is not the only unorthodox use of gene therapy that has anti-aging potential. Another is allotopic expression of normally mitochondrial DNA (mtDNA)-encoded proteins from suitably modified nuclear transgenes. Most of the several hundred mitochondrial proteins are nuclear-coded and imported from the cytosol; only 13 (totaling under 4000 amino acids) are encoded in the mtDNA, so it is both conceptually simple and realistic to engineer them to be synthesised by the majority pathway. Such transgenes would complement the spontaneous mutations that accumulate in our mtDNA, a phenomenon whose role as the nexus of respiration-driven (i.e. oxidative damage-mediated) aging has been suggested for nearly 30 years.[43,44] Success in this approach was first reported in 1986,[45] but subsequent progress has been slow; that this is largely due to lack of funding rather than intrinsic technical difficulties is shown by the recent successful allotopic expression (conferring rescue of the inactive mtDNA-encoded copy) of a medium-sized such protein in a mammalian system.[46]

Finally we consider augmentation of the mammalian genome with genes conferring functions that we entirely lack. The anti-aging potential of such manipulation resides mainly in the incomplete (though impressive) ability of our lysosomes to degrade all the damaged and cross-linked substances which arise within cells as a side-effect of normal metabolism. While small molecule drugs can (as noted above) cleave the most prevalent extracellular cross-links that accumulate with age, which are molecularly well-characterized, the immensely heterogeneous lipid and protein aggregates that accumulate in lysosomes are not realistically amenable to such an approach. It remains controversial[47,48] whether the best-studied such aggregate, lipofuscin, is truly deleterious to the function of cells in which it accumulates to high levels (such as motor neurons and cardiomyocytes), but there is no such doubt regarding the corresponding substances found in the pigmented epithelium of the retina[49] and in arterial macrophages,[50] leading respectively to macular degeneration[49] and atherosclerosis.[51] Such aggregates are, like mtDNA mutations, plausible mediators of respiration-driven aging.[52] It is also likely that the lysosomal inclusions associated with various neurodegenerative diseases contribute substantially to the course of those pathologies;[53] finally, endocytosis of extracellular aggregates can be promoted by immune stimulation.[54] Soil bacteria such as *Rhodococcus* demonstrate a stunning variety of hydrolytic capabilities, including the commercially relevant breakdown of fuels, solvents, plastics – even explosives such as TNT.[55] It is by no means fanciful to identify strains which break down pathologically significant aggregates, isolate the relevant enzymes and introduce them transgenically into mammalian lysosomes. Lysosomal integrity should not be compromised, since the lysosomal membrane's robustness against mammalian hydrolases derives from a specialized molecular structure very unlike these target materials.[56] Bacteria that appear able to digest lipofuscin have indeed proven easy to isolate;[57] different aggregates will doubtless require different hydrolases, but such aggregates are few in number.

We fully appreciate that it is easy, in the case of most of the interventions discussed above, to identify potential obstacles to success. That is true of any highly innovative technological venture. We claim, however, that in no case is there a foreseeable obstacle of a magnitude that justifies delaying the attempt to develop these interventions. We argue that now is the time to heed the old adage "nothing ventured, nothing gained."

Anticipated impact on public opinion and aspirations; policy implications

The transgenic measures above are mostly achievable far more quickly in mice than in humans. Mouse transgenics, however, since it involves germ-line transformation, usually demonstrates only retardation of aging, not its reversal, so may fail to ignite great public interest. We therefore urge that these techniques be tested not only in the simplest manner, by arranging for the manipulation to be active throughout the organism's lifetime, but also in an inducible context (such as the increasingly widespread hormone- or drug-induced Cre-*loxP* system[58]) so that the intervention more directly emulates the possible effects of somatic gene therapy in a middle-aged or elderly adult. Increasing mouse lifespan by only a year, but with a panel of interventions that was activated only when the treated mice had an expected six months to live, would be a far more spectacular result than a two-year increase in lifespan resulting from a lifelong intervention. We feel that this justifies the greater complexity of such studies. This would also impact the highly active social and policy debate surrounding human germ-line transformation.[59]

Direct evidence that mammalian aging can be reversed is, plainly, still lacking. On the other hand, obtaining such evidence is tantamount to achieving that reversal, and the ever-accelerating pace of progress in biology and medicine frequently reminds us that judgements of what will be feasible in a few years tend to be very over-conservative. Nonetheless, our optimism that the above measures jointly have the potential to bring aging-reversal about needs careful justification. It does not arise simply because those measures are numerous: it is because they are comprehensive. We believe that few major features of mammalian aging are omitted from the above survey and would thus be in danger of continuing

unabated even if the interventions we have discussed were all implemented successfully. Nuclear mutations other than those leading to cancer, for example, have been compellingly excluded from relevance to mammalian aging within anything approaching a normal lifespan.[60] Accordingly, while we accept that implementation of only a subset of the measures we have discussed may not truly restore youthful physiology, coordinated implementation of them all should indeed do so – albeit, initially, only in mice. Since none requires enormous advances in either our understanding of aging or our biotechnological arsenal, engineered negligible senescence may finally be within reach. We therefore urge abandonment of the despondency that currently prevails with regard to engineering negligible senescence. We acutely recognize the social upheavals that such progress may well bring about,[61] and join with others[62] in stressing the need to prepare for them as best we can. However, apprehension of that transition must not divert us from pursuing a goal that, after millennia of frustration, may now be within sight.

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Table 1. Major molecular and cellular changes associated with aging and feasible methods for their reversal. Some are already feasible in humans; the remainder can presently be developed only in mice, but will become applicable to humans as and when comprehensive somatic gene therapy is available. For details, see text.

Damage rising with age	Effects reversible by
Nuclear mutations	Telomerase gene deletion in quiescent cell types; angiostasis; autologous vaccines
Cell senescence	Ablation of senescent cells
Mitochondrial mutations	Allotopic expression of normally mtDNA-encoded proteins
Diverse lysosomal aggregates	Addition of bacterial hydrolase genes
Extracellular aggregates	Phagocytosis via immune stimulation
Extracellular cross-links	AGE-breaking small molecules
Cell loss	Exercise combined with gene therapy; stem cell therapy; growth factor-induced cell replacement
Immune system decline	IL-7-stimulated thymopoiesis
Hormone secretion decline	Genetically engineered muscle