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Aging: A Foreseeable Target of Stem Cells and Regenerative Medicine

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Introduction

Aging is unequivocally a degenerative condition. Hence, it would seem to be a natural target of regenerative medicine. Nevertheless, it is paradoxical that biogerontology does not greatly overlap with regenerative medicine, as measured by the content of conferences or the scope of academic journal articles. Perhaps this situation has arisen because aging has historically been considered too complex to be amenable to "divide-and-conquer" challenge – which a regenerative medicine assault on it would require. In recent years, however, there has been the realization that this logic, which justifies the view that a *disease*-specific approach to extending healthy life is impractical, applies much less compellingly to the molecular and cellular precursors of those age-related diseases -- whose precursors are precisely what regenerative medicine (especially stem cell therapy) has the potential to target.

As a result, it is realistic to conclude that *now is the time to focus regenerative medicine squarely on the most ubiquitous degenerative condition of all, namely aging*, and reciprocally to focus biogerontology on the rapidly increasing potential of regenerative medicine to contribute to gerontology's ultimate goal.

Aging Occurs by Default, Not by Design

The first prominent biologist to attempt an explanation of aging in the context of Darwinism was August Weismann, a towering figure in late 19th-century biology. Weismann made the creative and compelling suggestion that aging is evolutionarily valuable to a species because it facilitates adaptation to changing environmental circumstances: without older individuals competing with them for resources, younger ones can compete more effectively with each other, and more rapid selection for traits conducive to contemporary fitness will result.[1cite]

So seductive was this proposal that it was not seriously challenged for over half a century. Finally, however, Peter Medawar observed in 1952 that, in the wild, most individuals do not enjoy the luxury of reaching an age at which appreciable loss of function emerges, because they are so vulnerable to causes of death that are poorly (if at all) determined by age, such as predation, starvation or hypothermia.[2cite]

Medawar and those who elaborated on his concept were in fact guilty of overstatement: the idea that the incidence of aging in the wild is negligible is in fact inconsistent not only with the evolution (or retention) of genetic machinery that *orchestrates* aging but also with the maintenance of a stable quality of genetic machinery to defend *against* aging. In fact, aging absolutely *must* impact fitness in the wild to some degree, otherwise the inbuilt repair-and-maintenance machinery that a species possesses will progressively accumulate mild mutations until aging does impact fitness (i.e., until there is a non-negligible fitness consequence of incurring even more "anti-anti-aging" mutations).

Understanding of the genetic basis of aging reveals that regenerative medicine in general, and stem cell therapy in particular, is clearly promising for combating aging and postponing the age at which functional decline and disease becomes ubiquitous.

"Genes for Aging" Are a Boon But Also a Distraction

The fundamental explanation for this paradox is to be found in the history of biogerontology. Until 15-20 years ago, biogerontology was held in low regard by most biologists – despite the fact (so obvious to non-biologists) that aging is the single most important thing society wants biologists to tackle, given the astronomical amount of disease, suffering and death that it causes. This was ultimately a consequence of the indisputable fact that aging affects the organism at all levels of organisation, and thus is a formidably complex problem. Formidable problems, by definition, must first be addressed by a long period of observation and description – a component of science that has become increasingly poorly respected within biology, as more tractable subfields have advanced to a more hypothesis-driven stage. Yet, there was a tendency for biologists not to acknowledge the distinctive status of aging in this regard and thus to dismiss biogerontology as "overly" descriptive.

This all changed, remarkably abruptly, with the discovery of mutations in the nematode *Caenorhabditis elegans* (and, subsequently, other species) that markedly extended its lifespan. This opened the way for an avalanche of unassailably hypothesis-driven work by a far wider range of investigators – including, importantly, established high-profile investigators – than had occurred previously: a situation that still pertains.

So far so good – but there is a serious downside to this development, which is increasingly diminishing the impact of biogerontology's rise to respectability and which is in danger of going so far as negating it. The problem is that, according to the absolutely iron-clad evolutionary biogerontology logic summarized above, life-extending mutations should not exist. Indeed, this was the initial reaction of mainstream biogerontologists when Johnson's group first announced the discovery of *age-1*;[3cite] not until Kenyon's group replicated that result with the discovery of *daf-2* did the phenomenon gain true credibility.[4cite]

The resolution of this conundrum is simple, but is still inadequately incorporated into mainstream biogerontological thinking. There is one clear circumstance in which it does indeed make evolutionary sense to have genetic machinery that accelerates aging: namely, when that machinery is present for other purposes but affects aging as a side-effect. And it turns out that the pathways identified by Johnson, Kenyon and others are of just this character. In all cases (with the sole exception that a relatively mild life extension results, in *C. elegans* but in no other model organism, from indiscriminate suppression of oxidative metabolism), the mutations that have been found to extend lifespan are ones that manipulate the organism's response to nutrient deprivation.[5cite] While there remains considerable uncertainty as to the details, it is widely understood that the impact of nutrient availability on fecundity and mortality has profound consequences for the optimal partitioning of resources between growth, maintenance and reproduction, and thus that it is advantageous to possess the wherewithal to respond to nutrient deprivation by varying that partitioning. But this must be understood as a feature *overlaid* on the mechanisms driving aging per se, and not as a determinant of those mechanisms. Unfortunately, failure to emphasise this has fostered an unjustified belief that simple manipulations of hypothetical pro-aging machinery might be the way for us to postpone human aging, and has distracted attention from the effort to identify ways in which regenerative medicine can attack aging.

The Definition of Regenerative Medicine is Broadening

A reasonable abstract definition of regenerative medicine is the restoration of a tissue's structure to something resembling its state prior to some insult. A key feature of this definition is that it does not specify the scale at which that structure is defined. Historically, the fields that have been grouped under the regenerative medicine banner have focused on the cellular or organ level – the replacement of lost cells, or the removal of damaged organs in favour of ones built ex vivo. But it is every bit as important to consider the subcellular and intercellular dimensions of regeneration. In aging above all, there are not

only changes to cell number but also to cell function, and in many cases the option of destroying and replacing the dysfunctional cell may be much more challenging than the restoration of cellular composition (such as the removal of unwanted intracellular material). The operative word is clearly "may" – the relative difficulty can be evaluated only once specific strategies for the latter approach are proposed – but that has now to some extent occurred. Gene therapy, arguably only a tangential aspect of regenerative medicine hitherto, plays a big role here: we may be able to remove such "junk" by introducing genes found in other species, especially bacteria, that encode enzymes capable of breaking them down. Similarly, the use of immunotherapy to remove amyloid is a strategy that should clearly be classed as regenerative medicine, because it reverses a change in the composition of tissue that is widely held to be causative in a range of major age-related degenerative conditions. Other examples are surveyed in my publications of recent years.

Regenerative Medicine Does Not Yet Address Aging Enough

My own efforts to further the anti-aging cause have many facets, but the principal theme I have pursued in the past decade is to elevate the regenerative medicine approach to combating aging – in other words, the development of bona fide rejuvenation therapies – to prominence in the thinking of those scientists, clinicians and others who view aging as a problem. The failure of this to happen spontaneously cannot be laid at only one community's door: I feel that both biogerontologists and regenerative medicine researchers must also take responsibility.

Biogerontology has remained excessively fixated on the allure of the single-gene "magic bullets" mentioned above, and has implicitly rejected any prospect that a "divide-and-conquer" approach (as regenerative medicine for aging would certainly be) has promise. I believe that this is a short-sighted and invalid extrapolation from geriatric medicine, defined as the direct assault on the diseases and debilities of aging, which is indeed impractically short-termist. The distinction is that geriatrics targets phenomena that are the consequences of accumulating molecular and cellular side-effects of metabolism, hence the geriatrician's job becomes progressively harder as the precursors of its targets continue to accumulate. Regenerative medicine, by contrast, targets those side-effects of metabolism directly – and that approach does not have the same limitation, simply because, by definition, those targets do not have accumulating precursors.

Correspondingly, the regenerative medicine community has not adequately bitten the biogerontology bullet. Despite Haseltine's audacious call to arms a decade ago,[6cite] the majority of researchers in stem cell therapy and tissue engineering (the main strands of contemporary regenerative medicine) focus on specific conditions (often late-onset conditions); yet, by and large, are not aligned with the natural target of regenerative medicine, namely the early-stage phenomena whose unimpeded progression eventually results in the diseases familiar to medicine as a whole.

Certainly exceptions exist. Within academia, researchers such as Conboy, Patel, Minger and Mason are conspicuous in their explicit application of stem cells to problems of "aging itself" and not merely to the diseases of aging.[7-9cite] The same is true of the private sector, in which West and Haseltine have been foremost in furthering this line of thought and action. But the lead shown by these researchers must be much more widely followed if regenerative medicine is truly to come into its own with regard to applications to aging. Regenerative medicine researchers who do not think of themselves as gerontologists must not let themselves be dissuaded or discouraged by the lack of emphasis on the regenerative approach exhibited by gerontologists in general since this lack of emphasis is the product of a poor appreciation of what regenerative medicine can offer.

Conclusion

It is my view that stem cell research remains central to regenerative medicine and thus to the future of human health care – both in the context of biogerontology and the overall medical context. In addition to the direct use of stem cell transplantation, it has become well understood over recent years that stem cell

manipulation is intrinsic to effective tissue engineering; moreover, the continued low efficiency of somatic gene therapy means that *ex vivo* genetic manipulation of cells followed by selection and introduction of those with the desired modification remains a key methodology in gene therapy. If we add to this the fact that stem cell types are continuing to be discovered with unforeseen regenerative versatility and potency, and also the continued discovery of ways to activate the regeneration of complex structures seen in some lower vertebrates, it is clear that stem cell therapy lies at the heart of regenerative medicine, and does so just as strongly in respect of the combating of aging as elsewhere.

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Author Bio

Dr. Aubrey de Grey is a biomedical gerontologist based in Cambridge, UK, and is the Chairman and Chief Science Officer of the Methuselah Foundation, a 501(c)(3) non-profit charity dedicated to combating the aging process. He is also Editor-in-Chief of Rejuvenation Research, the world's only peer-reviewed journal focused on intervention in aging. His research interests encompass the causes of all the accumulating and eventually pathogenic molecular and cellular side-effects of metabolism ("damage") that constitute mammalian aging and the design of interventions to repair and/or obviate that damage. He has developed a potentially comprehensive plan for such repair, termed Strategies for Engineered Negligible Senescence (SENS), which breaks the aging problem down into seven major classes of damage and identifies detailed approaches to addressing each one. A key aspect of SENS is that it can potentially extend healthy lifespan without limit, even though these repair processes will probably never be perfect, as the repair only needs to approach perfection rapidly enough to keep the overall level of damage below pathogenic levels. Dr. de Grey has termed this required rate of improvement of repair therapies "longevity escape velocity".