Is SENS a farrago?

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Abstract

SENS (Strategies for Engineered Negligible Senescence) is a panel of proposed interventions in mammalian aging that I have suggested may be sufficiently feasible, comprehensive, and amenable to subsequent incremental refinement that it could prevent death from old age (at any age) within a timeframe of decades, leading to four-digit lifespans of many people alive today. This extreme conclusion has drawn sharp criticism from some colleagues, especially because the methodology of SENS departs radically from approaches generally considered the most promising ways to combat aging and because it is perceived as endangering biogerontology’s respectability. Here I briefly respond to these criticisms.

In July 2005 I published a wide-ranging critique\(^1\) of the rhetoric currently preferred by most mainstream biogerontologists in their dealings with policy-makers and the public. I took issue with three main planks of that rhetoric: the emphasis that aging is not a disease, the focus on compression of morbidity as a goal of biomedical gerontology, and the highlighting of the potential for late-onset calorie restriction mimetics to postpone human aging. (None of these opinions is by any means universally held within biogerontology, and I did not claim otherwise; however, I did claim that these views are disproportionately and inappropriately emphasised in gerontologists’ interactions with the wider world.) I also criticised the community’s reluctance to engage in open-minded public scrutiny of novel and radically different approaches to postponing aging, especially my own “SENS” (Strategies for Engineered Negligible Senescence) proposal. My essay provoked 28 eminent biogerontologists into penning or signing a strongly-worded rejoinder,\(^2\) which was published in November 2005 together with my reply;\(^3\) the debate on this matter has since continued to occupy gerontologists’ attention.\(^4\) Thus far, unfortunately, only the legitimacy of SENS has been addressed in this debate, leaving my other criticisms entirely unchallenged.

SENS departs from traditional approaches to combating aging in two main ways: it is a divide-and-conquer strategy, addressing many aspects of aging individually and simultaneously, and it is a repair strategy, not preventing metabolism from laying down the side-effects (“damage”) that eventually cause functional decline but instead eliminating those side-effects before they reach pathogenic levels of abundance. SENS identifies seven major categories of such damage, as set out in Table 1, and claims that they are “adequately comprehensive” (see below). The comprehensiveness of the SENS categories is a hypothesis which, I claim, is unlikely to be testable other than by implementing treatments for the seven categories and determining their joint effect on mammalian lifespan. This particular classification arises from the interventions that presently seem most plausible for repairing (or, in two cases, obviating) the respective type of damage: within each category, broadly the same therapy applies to all affected tissues, with only the details being tissue-specific.
<table>
<thead>
<tr>
<th>Type of damage</th>
<th>Proposed repair (or obviation)</th>
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<tr>
<td>Cell loss, cell atrophy</td>
<td>Cell therapy, with adjuncts including growth factors</td>
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<tr>
<td>Death-resistant cells</td>
<td>Ablation of unwanted cells, e.g. by suicide gene therapy</td>
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<tr>
<td>Oncogenic nuclear mutations</td>
<td>“WILT” (Whole-body Interdiction of Lengthening of Telomeres)</td>
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<td>and epimutations</td>
<td>Allotopic expression of 13 proteins from nuclear transgenes</td>
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<td>Mitochondrial mutations</td>
<td>Microbe-derived hydrolyses targeted to the lysosome</td>
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<tr>
<td>Intracellular aggregates</td>
<td>Immune-mediated phagocytosis of amyloid</td>
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<tr>
<td>Extracellular aggregates</td>
<td>AGE-breaking molecules and/or enzymes</td>
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<td>Extracellular crosslinks</td>
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Table 1. The seven SENS categories of age-related damage and the corresponding interventions.

For details, see ref. 5 and articles cited therein.

SENS is an immensely ambitious project, justifiable only by the enormity of its health benefits were it successful. I claim that, with funding of $100 million per year, its components could probably all be implemented in mice within 10 years, leading to a trebling of the life expectancy of naturally long-lived mice on which treatment began when their remaining life expectancy was one year. (It is this life-extension result that defines “adequately comprehensive” above.) I also claim that with 15 further years of intensive (and much more expensive) research we would have a 50% chance of adding 30 years to the remaining life expectancy of humans who are 55 when treatment is begun. I invariably stress, however, that any prediction concerning 25-year timeframes is highly speculative and that unforeseen obstacles could extend that timeframe indefinitely. Finally, I note that this degree of late-onset life extension would in all probability “buy time” sufficient to improve the SENS therapies, making them more comprehensive, so that the same people who obtained the extra 30 or so years from the initial therapies would thereafter gain more years from better therapies, without limit, thus avoiding disability and death from old age at any age and living, on average, at least an order of magnitude longer than we do today.\textsuperscript{5}

SENS has been presented both in the scientific literature and at conferences since 2000, so public discussion of it has been paradoxically long in coming. Warner et al. gave one reason for this delay: they asserted that SENS is not merely misguided, it is so misguided that it should be suppressed. Specifically, they called it a “farrago” and stated that “pretending that such a collection of ill-founded speculations is a useful topic for debate, let alone a serious guide to research planning, does more harm than good both for science and for society.” However, the arguments that Warner et al. provided in support of this position were deeply flawed.

Some of these flaws were oversights of published experimental work. For example, Warner et al. asserted that telomerase ablation has not yet been shown to prevent cancer in animal models and that no evidence exists that aspects of ageing can be reversed by phenacyldimethylthiazolium chloride, both contrary to reports published in top journals at least five years ago.\textsuperscript{6,7} (Telomerase ablation would have major side-effects in humans and would not prevent telomerase-independent telomere elongation, but I and expert colleagues have thoroughly addressed those issues.\textsuperscript{8}) Clearly the difficulty of any project depends on how far we have already progressed towards implementing its components, so such oversights may partially explain gerontologists’ pessimism about SENS.

Negative commentaries on SENS have also tended to elide the differences between how goal-directed work (such as medicine) is done and the curiosity-driven methods of basic science. For example, Warner et al. suggested that the failure of any SENS component to extend animal lifespan in isolation constitutes evidence that they will not do so in unison – but the components of a machine are never supposed to perform the whole machine’s function. They also recommended that “research programmes should be based on fact and extrapolation from earlier successes and failures” – but if engineers always followed scientists’ lead in extrapolating from the most direct
evidence, we would still be trying to fly by flapping. Similarly, various commentators have described SENS as “not testable,” despite my clear and specific life-extension predictions outlined above. There is thus good reason to be cautious in accepting declarations such as “the SENS agenda is easily recognized as a pretence by those with scientific experience” at face value.

Perhaps partly because it has not encountered persuasive scientific criticism, SENS has gained considerable media attention. This is a major source of some gerontologists’ concern at SENS: that its ascendancy could harm gerontology’s reputation. For example, Warner et al. stated that “Ageing research is a discipline that is only just emerging from a reputation for charlatanry ... From this hard-won perspective, we are concerned when we see scientific journals and meetings give space and attention to empty fantasies of immortality.” They also noted, however, that “a politician who was rash enough to campaign on a pledge to slow the ageing process would be judged as lunatic” – in other words, that biogerontology is actually nowhere near to making a breakthrough in convincing policy-makers to fund this field at the level all gerontologists know to be appropriate. It is hard to reconcile these two statements. Rather, the political failure for so many decades of what is still widely touted as politically the most palatable message (emphasising compression of morbidity, for example) strongly suggests that a change of message may be overdue. A message that truly lacked scientific legitimacy would indeed be a retrograde step, but SENS seems, by contrast, to be a step forward, successfully igniting public interest and debate about the importance of working hard to combat aging. It seems set to continue to do so while it survives scientific scrutiny, especially when the lack of such scrutiny cannot credibly be explained as experts being too busy to dissect something so absurd.

Implementation of SENS, even in mice, is a substantial project that I have suggested will require at least $1 billion over 10 years, and others feel that this is an underestimate. Thus, it is emphatically not my objective to antagonise or alienate scientists who might contribute to that project; rather, a broad collaboration is required, involving not only science but also efforts to accelerate public understanding of and enthusiasm for our work. However, the expertise that I believe must be brought cooperatively to bear on the research and development of therapies to defeat aging includes fields that lie well beyond the conventional definition of biogerontology (and, incidentally, whose leaders have often viewed their respective components of SENS much more positively than most biogerontologists have). Thus, barriers already exist that must be dismantled, and after some years of attempting a more collegial approach to achieving this I have reluctantly concluded that a modicum of plain speaking in the short term is the only way.

The history of science abounds with examples of good new ideas that took unduly long to be accepted by the senior members of the field. Warner et al. concluded: “Modern biogerontology is blessed with exciting new results, new ideas and new hopes for progress ... It is time to draw public attention to these accomplishments and prospects, and to develop public support for this research area ... Helping the public discriminate between science and science fiction is an important step towards this objective.” Indeed it is. Helping the public discriminate between knowledge and dogma is another one, in which I am – and shall remain – vigorously engaged.

References

1. de Grey ADNJ. Resistance to debate on how to postpone ageing is delaying progress and costing lives. EMBO Rep 2005;6(S1):S49-S53.
3. de Grey ADNJ. Like it or not, life extension research extends beyond biogerontology. EMBO Rep 2005;6(11):1000.


