Rebuttal of Estep et al. Submission by Aubrey de Grey

Abstract

Estep et al.'s Challenge tactics centre on repeating the word "unscientific" as often as possible in the apparent hope that this will render the judges oblivious to the complete absence of substance in their submission. Particularly incongruous is their accusation that I use the media to skirt expert criticism, when the SENS Challenge itself is my most conspicuous effort to do just the reverse, exposing the public reticence of SENS's off-the-record detractors and thereby forcing them to make their supposed case in print. Their summary consists entirely of claims of their own scientific infallibility, aspersions on my methods and credentials, and blurrings of the distinctions between the methods of science and of technology. Not wishing to descend to such tactics, I will ignore Estep et al.'s invective and instead summarise here my detailed enumeration [posted on the *TR* website] of the flaws in the specific criticisms given in their supplementary material [also posted there].

Estep et al. state that: "Any claim regarding extreme extension of life span in higher organisms must be regarded with extreme skepticism, and the evidentiary and logical support for such a claim must be as extraordinary as the claim itself." This is correct for claims that such extension **has** been achieved, but not for claims that a particular **plan** for achieving it **might** (not would) succeed. Since human aging causes immense suffering and death, any plan that might dramatically postpone it merits detailed expert review; only if its chance of success can be evaluated as negligible should we ignore it. Similarly, their statement: "human aging is not well understood, and any prospective therapy or cure must be regarded as pure speculation… any claim of a cure for human aging prior to evidence of therapeutic efficacy, or prior to a scientifically supported mechanistic model of human aging, must be pseudoscience" forgets that, whereas science is about reducing our ignorance, technology is about **sidestepping** our ignorance.

Estep et al. highlight the three most challenging of my seven categories of aging "damage" and scorn my preferred approaches to combating them. One such approach, allotopic expression (AE), has been pursued experimentally for 20 years.[1] The others were each the focus of a full-day workshop, one of them NIA-sponsored, involving eight eminent experimentalists spanning all relevant disciplines, whose enthusiasm for the approach was demonstrated by coauthorship of the article arising from the respective workshop[2,3] – 14 of 16 attendees signed and the others declined for reasons unrelated to their evaluation of the approach (see ref. 3's acknowledgements). Faced with this evidence – rather stronger than mere attendance at conferences – that my proposals are wholly legitimate, Estep et al. simply omit it from their critique. The section of one of these articles[2] that they deride as "pseudoscientific pretense" was contributed by Prof. Bruce Rittmann, who, as shown by his biography,[4] cannot easily be dismissed for lacking relevant experimental expertise (as Estep et al. so blithely dismiss me). I reject experimentalists' criticisms only when I have detailed, robust scientific arguments and the support of more appropriately specialised experimentalists. Estep et al. evidently overlook how thoroughly their diatribe fits their own definition of pseudoscience.

In my interactions with experimentalists exemplified above, I always provide all the facts known to me that might help them to evaluate my proposals reliably. By contrast, Estep et al. repeatedly omit key facts that Estep certainly knows (though his coauthors may not). They lampoon my prediction from 2000 concerning AE, without mentioning that I made it assuming that Zullo et al.'s seminal breakthrough (which I presented at the time I made the bet[5]) would be published imminently in *Science* (where it was then in review), stimulating effort to perfect this approach; in fact, followup effort remained negligible until it was finally published in 2005.[6] Thus, it is grossly misleading to suggest that my overoptimism arose from underestimating how hard AE is – and I fully explained this recently in a reply to Estep on a well-known mailing list.[7] Similarly, Estep et

al. accuse me of selectivity in presenting my view that nuclear mutations and epimutations irrelevant to cancer do not contribute to age-related decline within a currently normal lifetime, even though Estep has been invited to respond to my paper in press in *Mechanisms of Ageing and Development*, which was invited and accepted by the world leader in that field (Jan Vijg) and in which I justify this conclusion in great detail and with abundant references.[8] It is thus Estep et al., not I, who attempt to mislead readers by selectivity.

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Rebuttal

As in my summary rebuttal above, I shall not stoop here to the level of invective preferred by Estep et al. but will restrict myself to scientific rebuttals of the specific scientific criticisms that they could, and should, have presented honestly and directly, unlaced by such impassioned and content-free rhetoric. This set of rebuttals, if considered robust, of course suffices to invalidate that rhetoric and, thus, to dispose of Estep et al.'s bid to win the SENS Challenge. Thus, I have no need to address the rhetoric directly.

I will take the three SENS strands that Estep et al. critique in detail in reverse order:

Example 3: Mitochondrial engineering

The shallowness of Estep et al.'s analysis is revealed especially starkly by their contradictory statements concerning allotopic expression in cell culture, which midway through their analysis they call an example of "assumptions and technologies that reside firmly in the realm of fantasy" but, in their summary, they call an example of "routine biology experiments." They fail to cite work published over recent years[1-3] that flatly contradicts their statement that "virtually no progress on this problem has been reported," even though such work has been extensively cited in my publications[4,5] and on my website, sources with which they elsewhere reveal themselves to be very familiar. This selectivity is one of the main criticisms they level at me, but they, not I, are abundantly guilty of it.

The remainder of Estep et al.'s analysis of allotopic expression is a shining example of what I criticise when I contrast the scientist's modus operandi with the engineer's. It is absolutely true that allotopic expression **might** be much harder than the experimentalists currently pursuing it believe, and also that lifespan **might** turn out to be greatly extensible without addressing mitochondrial mutations. However, these facts are only reasons to be cautious in expending great effort in developing allotopic expression if one is solely interested in discovering the contribution (if any) of mtDNA mutations in aging, i.e. not in combating that contribution if it exists. They do not constitute reasons for caution if the goal is to postpone aging as much as possible as soon as possible, because the uncertainty concerning mtDNA mutations' role in aging despite over 30 years of intense investigation suggests that we may never determine that role other than by the definitive experiment of making such mutations superfluous, something that is most directly achieved by allotopic expression of all mtDNA-encoded proteins. Thus, the downside of developing a technology that we may ultimately not need is less than the downside of perpetuating a focus on determining whether we will need it to the exclusion of developing it.

Example 2: Microbial hydrolases

Estep et al.'s analysis of this SENS strand is littered with ex cathedra statements presented as if they were trivial proofs that it cannot work. Who says that "it is likely that the regulation and specificity of microbial hydrolases must be extraordinarily high" or that the enzymes in question would be "relatively non-specific"? This arbitrariness is again revealed by internal contradictions in Estep et al.'s assertions, this time within a single paragraph [the second paragraph of this section]: in the first sentence they dismiss the ability of encoding these enzymes as proenzymes (activated by cleavage only on arrival at the lysosome) to minimise the probability of toxicity, and in the very next sentence they mention that this is precisely how the body naturally protects against toxicity of enzymes we already encode. [Note that this sort of approach is an extremely powerful defence against the potential toxicity of xenoenzymes in compartments other than the lysosome, which I have always accepted[6] is a significant risk. Toxicity within the lysosome is, as I have also pointed out in print,[7] only a remote possibility, because all proteins, including catabolic enzymes, are quite rapidly degraded by those same enzymes once they reach the lysosome.] They focus on lipofuscin as the target of interest and claim that many enzymes would probably be required to break it down. However, this ignores my published argument[7] that just one enzyme would probably unlock lipofuscin granules and render their internal structure accessible to our existing enzymes, as is the rule for treatment of lysosomal storage diseases. They then allude to the likely need for "several independent genome engineering events," completely ignoring the past four decades of success in enzyme replacement therapy for lysosomal storage diseases, in which recombinant enzyme is simply injected – again a topic that my publicaions on this SENS strand discuss in detail. They additionally ignore the relevance of this therapy to the elimination of age-related aggregates such as arterial oxysterols, neuronal protein fibrils and retinal photoreceptor-derived compounds – materials whose molecular composition is much more homogeneous than lipofuscin (and whose contribution to age-related disease and decline is better supported) – despite the extensive discussion of these targets in my publications on this SENS strand.[6-8] Most importantly of all, they pretend that their complaints are conclusive to anyone who understands how hard experimental biology really is, when in fact it is well known that this approach has attracted great interest and enthusiasm from gerontologists and other biologists alike, not least Huber Warner, who, in his erstwhile capacity as head of the Biology of Aging program at NIA, sponsored me to run a full-day workshop on it in 2004. Interestingly, Warner was the communicating author of a recent denunciation of SENS that I discuss in more detail below. Thus, even extreme skepticism about SENS overall evidently does not translate into skepticism about this strand of it.

Finally, they suggest that the method my coauthors and I outlined[7] for isolating such hydrolases is "obvious pseudoscientific pretense and technological window dressing." This is a most revealing

statement, unlikely to have been made by a scientist who had checked the credentials of the coauthors most likely to have contributed the material, namely the bioremediation specialists. The passage in question was in fact contributed by Prof. Bruce Rittmann, who, as Estep et al. could have discovered by consulting his online CV,[9] is a universally acknowledged world leader in bioremediation. Perhaps Estep et al. simply regard the whole field of bioremediation as pseudoscience? That would be a surprising opinion for a biologist to hold of a field that has a 30-year history of outstanding scientific, technological and commercial success.

Example 1: WILT

WILT is, as I have always acknowledged, the most ambitious SENS strand. Some of my more PR-conscious colleagues have from time to time suggested that I downplay it when discussing SENS, but my view is that to do so would be unscientific, because WILT – just like SENS overall – recognises the difficulty of the problem to be solved without being daunted by it. Historically, and to some extent even today,[10] cancer has been described in terms that I feel underestimate the power that it derives from its genomic instability and consequent access to the ingenuity of natural selection. I contend that we will do well to explore anti-cancer avenues that recognise that power, even if those avenues seem implausibly fraught at first sight.

Rather than recognising and applauding this, Estep et al. make a litany of crass errors in their description of WILT, which underpin their complaints about its feasibility. They begin by asserting that it relies on "extraordinarily efficient and specific" somatic gene therapy, when in fact the large majority of age-related cancers arise in continuously renewing (epithelial or haematopoietic) tissues, in which WILT proposes stem cell replacement by cells whose genetic modification has been performed ex vivo followed by selection for cells that had the desired modification. This selection step means that even today's relatively low-efficiency gene targeting technology suffices, now that recent advances in culturing stem cells in vitro allow them to be expanded to arbitrary numbers without losing their stemness.[11] Somatic gene targeting will be needed in order to extend WILT to mesenchymal tissues, but even a treatment that lacked this facet and only eliminated death from epithelial and haematopoietic cancers would be decidedly welcome. Moreover, in vivo gene targeting is seeing rapid progress;[12] with this in mind, Estep et al.'s scorn at my claim that it could be sufficiently advanced for WILT's purposes in mice in ten years and in humans in 25 years rings decidedly hollow.

A similarly egregious misinterpretation of WILT underpins all the specific objections to it that Estep et al. list. WILT was devised in full knowledge that critically short telomeres are mutagenic, that a telomerase-independent mechanism of telomere extension exists in a minority of cancers, and that stem cells would be rendered dysfunctional as their telomeres became critically short; both my published articles on WILT[13,14] – including one[13] co-authored by six experimentalists with indisputably impressive credentials, who would hardly risk that reputation by endorsing fantasy – describe in considerable detail why these phenomena can be expected to be rendered harmless by the combination of gene targeting and stem cell therapy that WILT proposes. Thus, as elsewhere in their submission, Estep et al. are flagrantly seeking to mislead the Challenge panel by providing them with only partial information.

Estep et al.'s next complaint about SENS (their "example 4") concerns its reliance on stem cell therapy and further mischaracterises my position. I certainly do not claim that biomedical engineering is outside the domain of all biologists, only that many biologists (especially biogerontologists) are unduly inclined to an exclusively curiosity-driven, rather than partly goal-oriented, mindset. To ramify their accusation, Estep et al. then switch "[a]s one example" to an aspect of SENS that has nothing to do with stem cell therapy, namely the harmlessness of non-oncogenic nuclear DNA (nDNA) mutations: thus, they give no evidence whatsoever to support their criticism of my incorporation of stem cell therapy into SENS. It is tempting to speculate that the reason why Estep et al. consider that "the line of demarcation between the legitimate

discoveries and therapies proposed by others and the scientifically unsupported speculations of SENS is often unclear" is because they have decided in advance which of my statements are and are not legitimate and are then unable to distinguish between those two categories in terms of their evidentiary support in the work I cite.

The harmlessness of non-oncogenic nDNA mutations is indeed a key plank of SENS in its current form. Estep et al. seek to challenge this by reference to the work of Vijg's group, who have over the past decade developed a highly informative assay for mutation accumulation over the lifespan of mice, and by claiming that I have inappropriately cited this work in support of my view. This is a false accusation, because I have always been absolutely clear when citing that work that I am challenging the authors' interpretation of their own data. Vijg's group have indeed presented their data as provisionally supporting a role for such mutations in aging, but, as I have explained in outline in various fora and in detail in a manuscript in press[15] that Dr. Estep has seen (since he has been invited to reply to it), their data do not support this conclusion and in fact support the opposite conclusion. This manuscript was invited and accepted by Dr. Vijg in his capacity as co-editor of *Mechanisms of Ageing and Development* – hardly a course that he would have taken had he regarded my interpretation of his and others' data with the disdain expressed by Estep et al., biologists indisputably less expert in the area than Dr. Vijg. The same manuscript[15] also addresses, in similar detail, the other topics that Estep et al. refer to in this passage, namely the relevance of epimutations in all cell types and mutations in postmitotic cells. For example, I note there that epimutations have indeed been found to accumulate with age but that this accumulation has not been shown to be associated with any functional deficit, nor to maintain its rate throughout life: indeed, the data in the only publication[16] cited by Estep et al. that explored three or more timepoints suggests a deceleration (see figures 3 and 4 in that article). Thus, Estep et al.'s accusation that "a large body of scientific evidence on various pathologies and their possible contributions to aging is ignored" by me (in reaching my "nuclear mutations: only cancer matters" conclusion) is utterly baseless.

Estep et al. then commit the basic error of claiming that the *possibility* that SENS as currently described will fail to extend human lifespan much is a reason to discard it right now. In medical research, the appropriate goal is to maximise the *probability* of a patient's positive health trajectory. The suggestion that the *possibility* of failure constitutes a conclusive reason not to pursue a given avenue of biomedical endeavour, even though success would provide absolutely unprecedented health benefits, is a particularly clear demonstration of Estep et al.'s abandonment of accepted biomedical thinking. Of course, that is not the only problem with their logic: they also ignore the possibilities that SENS will be improved during its development and that it will deliver great health benefits even if it fails to extend lifespan.

Their next accusation is that I have suggested that the participation of eminent scientists in my SENS conferences legitimises SENS: "Many journalists, and even some scientists, are not aware that the SENS conferences are attended by many scientists who are not supportive of the SENS plan. This confusion has been used by de Grey to imply that attendance at SENS conferences by legitimate scientists somehow serves to validate the SENS plan." I have never done any such thing. Rather, in the article[17] that they cite in this regard, which was a response to a 28-author viewpoint denouncing SENS,[18] I noted simply that none of that viewpoint's authors attended SENS 2 and that this, together with their evident failure to consult my relevant publications or the key experimental work cited therein, may have deprived them of information necessary to evaluate SENS reliably. (It may be of interest that neither Estep nor any of his coauthors attended that conference either.) Similarly, the endorsement of SENS by the Methuselah Foundation is not because I am its chair but because most of the Methuselah Foundation principals attended the recent SENS conference and were impressed by the science presented and the support that it gave to the overall SENS program. To insinuate otherwise is unfounded and disingenuous.

SENS is not Science or Engineering

Estep et al. assert that not only is SENS not science, it is also not engineering. In introducing their case they make one cogent point, namely that what matters is not the terminology (whether SENS is science or engineering) but who has the most relevant expertise. Unfortunately for them, however, all they can point to in moving from this fact to a denunciation of SENS is *my* lack of experimental biology expertise – something I have never disguised – whereas what is necessary, and wholly lacking, is any evidence that their expertise exceeds that of the experimentalists who have publicly supported, and in many cases are actively pursuing, the various research avenues that I have brought together within the SENS program. I agree with Estep et al. that there is nothing in SENS that they would be unable to understand and criticise constructively should they choose to study it adequately; where I differ from them is that I claim – with the extensive justification outlined in this document – that they have so far failed to study SENS adequately.

Concerning the difference between scientists and engineers in mindset and motivation – as opposed to laboratory expertise – that I have often mentioned, Estep et al. expertly make my point for me by noting that the only reason *they* engineer model organisms is to find things out. To quote them: "If we could easily predict the outcome, why bother going through all the trouble of actually doing the engineering?". I wonder if Estep et al. think the Wright brothers built their airplane in order to discover whether it would fly? I personally suspect that they built it because they were confident that it would fly and they wanted to build something that would fly. Estep et al.'s oversight of this motivation is quite breathtaking to anyone who understands that, since aging causes immense suffering and death, it is something to be explored not for the sake of curiosity alone but with the goal of actually doing something about it.

Estep et al.'s next claim is that SENS does not specify intermediate goals to validate the effectiveness of its components, making it an "extremely inefficient" way to proceed. This is complete nonsense: each SENS component has extremely well-defined molecular and/or cellular goals that can clearly be assayed in isolation. Further. if those goals are achieved we will have learned a great deal, with great conequent benefits to medical science, whether or not the overall SENS panel succeeds in extending mouse lifespan. Moreover, it will actually take only one or two years to test whether the overall SENS panel will greatly extend mouse lifespan, because the interventions are to be begun on mice that are already middle-aged.

Gerontology, SENS, and Opposition to SENS are Misrepresented

After another paragraph of content-free invective, Estep et al. critique my perennial assertion that there has been too much focus within gerontology on "cleaning up metabolism" – pre-emptively minimising the occurrence of initially inert molecular and cellular damage as side-effects of essential metabolic processes – and not enough on cleaning up that damage after it occurs but before it spirals out of control. Here again they betray confusion concerning SENS in every sentence. AGEs were discovered by non-gerontologists[19] decades before Monnier and Cerami proposed their role in aging,[20] and work on AGE breakers[21] has in fact been largely dismissed by those gerontologists working on glycation[22] (for reasons that I have argued[23] are far from conclusive). Estep et al. err again when they suggest that AGE breakers are the only SENS strand that exists: removal of extracellular junk (amyloid) by vaccination is even further advanced[24] (and not principally as a result of work by gerontologists). They then proceed to mischaracterise WILT and allotopic expression as preventative rather than curative: this is again backwards, as both those interventions actually seek to act further *downstream* in the chain of events leading from metabolism to pathology than the other SENS strands do, allowing the intermediate damage to occur but heading off its pathological consequences.

Estep et al. then seek to reinforce their rejection of SENS by suggesting that the more deeply scientists study it, the more they see that it is fantasy. Given the enormities that I have enumerated

above, however, it is perfectly clear that the study of SENS that Estep et al. have conducted thus far has merely been an attempt to identify features of it that can be presented in a negative light in isolation to those who have not studied SENS at all – which, they presumably hope, includes the SENS Challenge judges. Any objective and even remotely wide-ranging perusal of my publications and other output on SENS, however, will reveal all too plainly the extraordinary selectivity to which Estep et al. have had to resort in order to construct their critique. Estep et al.'s accusation that I have engaged in irresponsible or dangerously inflammatory rhetoric to ignite a proper debate over SENS is equally unfounded: since it was first published in 2002 (without any such rhetoric),[25,26] they and others within the biogerontology establishment have had ample time and opportunity to give SENS the constructive evaluation that it deserves. Thus, my adoption of somewhat more provocative tactics since 2005 is merely a necessary response to my colleagues' refusal to discuss a biomedical avenue that may save so many lives. The suggestion that "the extreme deficiencies of SENS … have been pointed out to [me] on numerous occasions" is also transparently disingenuous, since these alleged deficiencies are merely the features that Estep et al. discuss in their Challenge submission, with criticisms whose worthlessness I have explained above.

Summary

Estep et al. surpass themselves here in their demonstration of how accurate are my criticisms of mainstream gerontology's mindset in relation to combating aging. They imply that SENS is worthless while it is "not even testable" – a view unlikely to be shared by those for whom it may be the only chance to avoid the suffering and death that aging so inevitably brings today. They suggest that it is a deficiency of SENS that I have not published "sensible developmental guidance for the scientific testing or implementation of SENS" – which can only mean either that they have not noticed that each SENS strand has its own clearly defined and assayable molecular and cellular endpoints or that they are asking me to tell them what they boast that they already know, i.e. how to conduct standard biological experiments. They repeat the embarrassingly ad hominem argument that my own lack of experimental training invalidates SENS, implicitly rejecting the relevance of the experimental expertise of those biologists (many of them coauthors on my relevant papers, many of them not) who are actively pursuing the technologies of which SENS is composed.

A concluding argument given by Estep et al. is that I am not entitled to ask my critics to prove me wrong: they describe this as "a classic attempt to subvert the scientific process." While some may wonder why, in that case, they submitted an entry to the Challenge at all, there is a deeper flaw in this argument. It is based on the generalisation that one doesn't advance scientific knowledge by debate or voting, but by experiment. This generalisation is true at one level, but it oversimplifies the scientific process, because "thought experiments" are precisely what scientists routinely and necessarily do all the time in order to decide which real experiments are and are not worth performing. Most scientists would not dream of questioning this fact, which is absolutely fundamental to the conduct of science. That Estep et al. so blithely contradict it is a particularly clear demonstration of the knee-jerk nature of their evaluation of SENS.

In closing, I draw readers' attention to Estep et al.'s remark in their second paragraph: "extraordinary claims require extraordinary evidentiary support." I would humbly submit that extraordinarily emphatic denunciations of a colleague's work also require extraordinary evidentiary support – support which Estep et al. have signally failed to deliver.

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