Rebuttal of Mobbs Submission by Aubrey de Grey

Mobbs's critique of SENS comprises the following assertions, each revealing gross misinterpretations of it:

1) SENS treats symptoms, not causes (stated both directly and using the analogy of diabetes)

On the contrary, the symptoms of aging (age-related diseases and debility) are *not* targets of SENS: rather, SENS targets their accumulating and initially inert *precursors* ("damage"), including indigestible molecules, mutations and changes of cell number.[1] Those are in turn caused by metabolism itself, but that does not mean metabolism should be our sole target: just like a car, the human body needs maintenance (repair of ongoing damage) as well as a robust design (to resist such damage), and improving the design after manufacture is far harder than maintenance. Similarly, in type I diabetes, Mobbs says that beta cell replacement would be best and "will be developed" – but, contrary to his assertion, that is precisely the SENS approach to cell loss or any downstream consequences thereof.

2) SENS omits oxidative damage to proteins

No – that is included, under intracellular and extracellular indigestible molecules ('junk').[2,3] Oxidatively damaged proteins that do not fall under those headings are, by definition, broken down and their constituent amino acids reused if undamaged and excreted otherwise, so SENS correctly omits them. The level of oxidised protein rises with age even excluding junk, but that is because oxidation rates rise and/or degradation rates fall, and that in turn is because of changes addressed by SENS, such as impaired lysosomal acidification secondary to accumulation of indigestible molecules.[4]

3) SENS omits changes in gene expression

No: gene expression changes either are compensatory responses to other, non-genetic changes – and thus will typically revert when the latter are reversed as SENS proposes[5] – or are caused by epimutations (random, stochastic changes in DNA methylation or histone modification), whose incidence is kept low by our endogenous chromosomal maintenance machinery needed to avoid cancer. [Like *bona fide* mutations, epimutations can cause cancer at so much lower a level than that which could cause any non-cancer dysfunction that genes not relevant to the cell cycle are "unnecessarily" well protected.[6] Cancer itself is an explicit SENS target.[7]]

4) Some age-related changes may be benign

Indeed, but determining *which* are benign has defeated biogerontologists for decades. Thus, it is likely to be faster to develop treatments for all changes that *might* be pathogenic than to defer such work pending conclusive evidence of which are pathogenic and which not. Some age-related changes may be actively beneficial, compensating for harmful ones – but those will be rendered benign, hence benignly reversible, when, as SENS proposes, the harmful changes for which they compensate are also reversed. These points are trivial corollaries of the observation that restoring the structure of an elderly body to that of a younger one will reliably restore youthful function too.

5) SENS involves impractically many individual therapies

Impractically many today, but my timeframe for SENS is long: I give it only a 50% chance of succeeding in 25 years (ten in mice) even assuming ample funding.[8] Also, this underscores why SENS focuses on initially inert "damage" rather than metabolism: when the targets of therapies are

metabolically inactive, risks of unforeseen interactions between those therapies are minimised. Finally, the SENS targets are far fewer than either their causes (the components of metabolism) or their consequences (the aspects of age-related debilitation). Thus, even if my timeframe for SENS is overoptimistic, SENS is still probably closer to fruition than any alternative.

6) SENS requires safe, comprehensive gene therapy

Yes, but many experts believe that safe and comprehensive gene therapy is only a decade or two away. Thus, now is the time to develop the life-extension genes that we will want to deliver at that time – especially since gene therapy in mice is already well advanced.[9] (Even gene targeting is seeing rapid progress.[10])

7) No SENS therapy can be implemented with available technology

Incorrect on at least two counts: immune-mediated removal of neural amyloid (extracellular junk) and pharmacological un-stiffening of the artery wall (extracellular crosslinks) were demonstrated in rodents several years ago[11,12] and are in clinical trials.[13,14]

In conclusion, SENS is undoubtedly a highly ambitious approach to combating aging. This might condemn it if aging affected only a small minority of the population; or if other, more straightforward strategies seemed likely to postpone aging similarly well if successfully implemented; or if SENS were shown to be flatly unimplementable without several major breakthroughs in our understanding of aging. Since none of these criteria obtains, however, SENS should be both discussed and pursued without delay.

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