Response by Estep et al. to de Grey's Rebuttal

Abtract

In our critique of SENS non-experts relied on us to assess SENS and Aubrey de Grey's claims. Now, with his response, they can see for themselves that even when under the microscope of public scrutiny, his response—like SENS itself—is a tangled mixture of fact and fantasy that cannot be believed, and it conforms to our list of features of pseudoscience. On the TR web site we detail some of the falsities of his response but they are diversions from the important points in our critique. The most important point is this: SENS is an elaborate deception propelled to notoriety through its emotional appeal; its facade is built from the real science of others, but at its core, SENS is simply a collection of naïve hypotheses dressed up by misrepresentations of science and engineering research. As yet another example, de Grey's submitted paper referenced in his response misrepresents a minuscule amount of non-representative selected evidence. He falsely concludes "that all presently available evidence is consistent" with his theory that mutations and epimutations do not contribute to senescence; this, without providing any evidence whatever regarding the role of epimutation. None. Consider the consequences of portraying any daunting problem so incompletely and inaccurately that focus is diverted away from actual causes and possible solutions. We have no doubt that SENS is exactly such a diversion.

Response

Aubrey de Grey's response to our critique of SENS is like SENS itself: a hopelessly tangled mixture of fact and fantasy that cannot be believed. It doesn't address some of the most serious deficiencies of SENS highlighted in our critique, and it is heavily over-weighted with argumentative diversion, as predicted by our list of identifying features of pseudoscience. Aubrey de Grey's response contains so many obviously false and highly misleading claims that we won't bother with many of them; however, we think it best to straighten out at least some of the misinformation. Below, we will simply state Aubrey de Grey's claim, follow it with the truth that refutes the claim, and in a few cases make a prediction related to his claim.

For the reader who simply wants our bottom line assessment of Aubrey de Grey's claims we offer this perspective: the debate between Aubrey de Grey on one side, and many critical scientists on the other, is not just about the scientific validity of SENS or its underlying technologies; it is also about legitimate versus illegitimate approaches to the presentation and evaluation of evidence. The ascent of SENS to its current level of visibility has been accomplished through the use of stereotypical pseudoscientific tactics including argumentative diversion, emotionally charged rhetoric and "special pleading," and distorted—and at times, overtly false—depictions of science and engineering research. We don't believe these distortions and falsifications are the result of unbiased carelessness since they uniformly support the SENS agenda. His response to our critique is no exception and key elements of SENS remain unsupported by a legitimate presentation of any evidence, and much evidence is available to refute them.

Most scientists and engineers probably don't ever encounter overt pseudoscience in close proximity to their own work. It has taken some time for scientists to see the clear pattern of Aubrey de Grey's increasingly egregious misrepresentations, and to respond. This situation brings to mind a quote attributed to Mark Twain "A lie can travel halfway around the world while the truth is putting on its shoes." This might have been true in Twain's time, but in our time of instant global communication, false claims can reach even remote areas of our world many months, or even years, before the truth has its shoes on. Our list of "General Features of Pseudoscientific Plans for Extension of Human Life Span" won't prevent Aubrey de Grey and others from making outrageous and unsupported claims since they can gain so much attention and financial reward for making them—especially when aided by a small minority of irresponsible scientists and members of the media. However, responsible people are now aware of the new wave of pseudoscientific opportunism inevitably brought on by recent scientific successes in aging research, and the truth now has its shoes on. We hope our list of features will help to clarify important scientific issues, and to reduce intrusions from increasingly sophisticated pseudoscience, in this important area of research.

Claim: "…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…"

Response: TR Editor Jason Pontin claims this challenge was initiated by him and all available evidence supports this claim. Furthermore, we have evaluated only a few of SENS' weaknesses, as did Warner and colleagues (Warner et al. 2005), and Aubrey de Grey's responses demonstrate beyond a shadow of a doubt that he is completely insincere in his wish for scientists to critique SENS.

Prediction: His complaints to the media about scientists not giving SENS a fair hearing will continue, in spite of the fact that we have done so and he has not addressed our primary criticisms. SENS is now, and will remain, a public relations ploy.

Claim: We claim to be scientifically infallible.

Response: Where? Nowhere. Like all scientists we are constantly confronted by our own fallibility, and we rely on the rigorous procedures of science to help prevent us from inadvertently deceiving other people and ourselves. We also rely on peer review to help us. We don't like the rejections and occasional misunderstandings of our work by colleagues and editors, but we know this process helps to weed out some of the weaknesses in our work that result from our own fallibility.

Claim: Says in his response he only claims that SENS **might** succeed, not **would** succeed.

Response: de Grey pretends that SENS has been advanced with caution and circumspection; however, in his quoted description he writes that SENS "is not just an idea: it's a very detailed plan to repair all the types of molecular and cellular damage that happen to us over time. And each method to do this is either already working in a

preliminary form (in clinical trials) or is based on technologies that already exist and just need to be combined." "When we get these therapies, we will no longer all get frail and decrepit and dependent as we get older..." SENS is explicitly being claimed to repair **all** types of molecular damage, and "**when**" we get these therapies—not "**if**"—aging will be cured. The cautiousness of his current response is incompatible with the certainty of some of his previous claims, such as the one featured here.

Claim: "…science is about reducing our ignorance, technology is about **sidestepping** our ignorance" and later "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."

Response: de Grey again falsely portrays a stark divide between science and engineering, a divide that does not exist in modern biomedical research. To deride scientists who recognize the extreme deficiencies of SENS, he often falsely and ridiculously claims that we would still be trying to "fly by flapping" if not for rejection of scientific thinking by engineers (de Grey 2005). He uses the Wright Brothers as prime examples of engineers who rejected scientific approaches and sidestepped human ignorance to simply build a powered airplane that flew. Of course, this is another de Grey fairytale, and a few minutes of research will show that the Wright Brothers were meticulous reductionist researchers (call them scientists, engineers, inventors, or any combination you wish) who followed in a direct intellectual lineage from the brilliant aeronautical scientist Sir George Cayley and Otto Lillienthal (Smithsonian 2006a). Cayley is widely regarded as the scientist who first recognized the four primary forces acting on an aircraft: thrust, lift, drag, and weight. Cayley identified these first two as separable, and thereby eliminated the concept that heavier-than-air powered flight was only achievable by flapping.

The Wright Brothers invented ingenious approaches to test and correct important variables of existing equations describing the forces on airplanes; they designed and implemented their own procedures to test individual airplane parts; and they designed and built their own test equipment, including a wind tunnel and various instruments for measuring important variables, so that *every critical component of their aircraft could be rationally designed and repeatedly tested* (Smithsonian 2006b). So, we also think they were somewhat confident their aircraft would fly; however, using similar logic and criteria, we don't think SENS is comparable in any way to the Wright Brothers' meticulous approach to flight. Aubrey de Grey should discontinue this fraudulent and farcical comparison, his fairytales of the history of science and engineering, and his routine defamation of science in general and of aeronautical and other scientists.

Claim: workshop participation and association with credentialed scientists gives credibility to SENS.

Response: we are uninterested in superficiality (credentialism and casual signatures on workshop reports, especially from people with little or no experience in the relevant areas), and instead focus on substance (the merits and deficiencies of science and engineering, and the accurate reporting of published facts).

Claim: as described in our critique, the first SENS publication states "Nuclear mutations other than those leading to cancer, for example, have been compellingly excluded from relevance to mammalian aging within anything approaching a normal life span." He did not justify this claim then and now writes "I justify this conclusion in great detail and with abundant references" and accuses us of trying "to mislead readers by selectivity" because we don't mention his submitted paper on this subject.

Response: Estep did not mention this submitted publication because he was not only asked to respond to this paper, he was an invited reviewer, and at the time of this writing the paper is still going through the editorial process. Since de Grey has referenced this paper in his response, and has made it accessible to the public on the internet, we will respond to its claims.

In the abstract of this paper he claims to consider "a selection of recent data on the rate of accumulation of nDNA [nuclear DNA] damage in the context of this hypothesis, and conclude that all presently available evidence is consistent" with his theory that mutations and epimutations do not contribute to senescence. To reach this unwarranted conclusion he misrepresents a minuscule amount of non-representative selected evidence. He writes "An increase in mutant load during adulthood is undetectable in some tissues, including the brain, and is a factor of at most three in any tissue yet examined." He fails to mention that the "factor of at most three" is an extremely large and previously unsuspected mutational burden. In the words of Vijg and Dolle, "Surprisingly, the total number of rearrangements in the heart and liver at old age was found to be very high, that is, up to almost 40 events per cell in old heart" (Dolle and Vijg 2002). Not only is this high number conveniently omitted by de Grey, so is the compelling model put forth by Vijg and Dolle to show how such rearrangements might plausibly contribute to aging (see Figure 4 of (Vijg and Dolle 2002)). He also fails to consider research that shows extensive and increasing damage in critical regions of nDNA of the brain with advancing age (Lu et al. 2004) (as one selected example). This publication from Bruce Yankner's lab shows that damage is spread heterogeneously in the genome and is highly concentrated in promoters of critical and highly active genes in the frontal cortex of the brain. In old age, damage is present in these promoters in about 100% of cortical cells, and damage is correlated with aberrant gene expression.

He also writes "the only cell type exhibiting steadily accumulating rearrangements is the postmitotic cardiomyocyte" and cites one paper by Vijg and Dolle (Vijg and Dolle 2002). However, the text and Table 1 of this publication clearly show this is false, and all three organs—brain, liver, and heart—show increased frequencies of rearrangements. Although results of statistical tests are not provided in this review the authors claim that both heart and liver rearrangements are increased. Furthermore, in a subsequent paper, Table 1 (Mutant Frequencies and Genome Rearrangements in Organs of Young and Old Mice) does show *P*-values from a Wilcoxon rank sum test for rearrangements for these three tissues, and for small intestine. All four assayed organs show increased rearrangements with age, but only liver and heart show statistically significant increases due to small sample sizes and large standard deviations for rearrangements in brain and small intestine (Dolle and Vijg 2002). Even if de Grey's presentation of these data were accurate, his conclusions about them would be wrong, since a large and increasing

number of rearrangements in any single organ is probably sufficient to declare that genome instability might well contribute to senescence and mortality. This is especially true of the heart, whose failure is responsible for a large fraction of age-dependent disabilities and deaths.

de Grey also continues to claim that epimutation doesn't contribute to aging, but, once again, he provides no evidence whatever in this paper to support this claim. Yet, he pretends this paper addresses epimutation by first introducing it, then by lumping it together with nDNA mutation as "SMT damage" without any explanation for why this is done, and then by falsely presenting a few bits of evidence regarding damage to nDNA as described above. No evidence regarding epimutation is introduced or discussed but he concludes that all presently available evidence is consistent with his theory that epimutation does not contribute to senescence. This paper is only the most recent one in a series of such publications by de Grey that feature his ideologically-driven tortuous portrayal of data to fit a theory—the opposite of the accepted scientific approach: adjustment of theories to fit existing data.

Prediction: Very soon it will be apparent to all reasonable scientists that SENS is not simply a creative mixture of fact and fantasy, it is also presented in a manner that constitutes overt scientific misconduct.

Example 3: Mitochondrial engineering

Claim: "lifespan **might** turn out to be greatly extensible without addressing mitochondrial mutations"

Response: this is a straw man (as is the rest of this section) and doesn't address our main point at all. We wrote "even if accomplished, there is insufficient evidence to conclude that mitochondrial genome decay limits cellular or organismal life span more than other molecular pathologies within these same cells, e.g. non-oncogenic decay of the nuclear genome or epigenome." We don't claim that life span might be extended without somehow reducing or remediating mitochondrial damage and mutations and we fully support mitochondrial research in this area.

Claim: "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."

Response: successful allotopic expression of all 13 mitochondrial coding regions while maintaining mitochondrial and cellular function is a technology that resides in the realm of fantasy. Nevertheless, attempts to achieve these things are without a doubt routine biology experiments. It is de Grey's apparent expectation that routine biology experiments always work as hoped or predicted that seems to confuse him on this point.

Prediction: his expected date of completion of allotopic expression of all 13 coding regions of the mitochondria has passed *and the clock is still ticking*. We believe that this

problem is much more complicated than he does and it will remain unsolved for a very long time—if it is ever solved. Aubrey de Grey will continue to make excuses as to why his expected date of completion was so unrealistic and to explain the lack of progress in this area. The most tempting excuse will be a shortage of funding, and critics of SENS likely will be blamed, even though these excuses already appear ridiculous to experienced scientists.

Example 2: Microbial hydrolases

Claim: "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"?" and, later "this ignores my published argument 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."

Response: experienced scientists and engineers understand that certain types of problems separate fantasy from practical reality. The engineering or selection of a microbial protein to function in long lived cells and animals is possible in principle, but describing how to do it is the crux. Our points about specificity will be obvious to most readers. Lipofuscin is extremely heterogeneous, and de Grey's "arguments" that accumulation of heterogeneous waste products in lysosomes can be dealt with in a manner similar to therapies for lysosomal storage diseases, do not constitute proof in the least. Lysosomal storage diseases result from a deficiency in a naturally-occurring endogenous enzyme, which causes the accumulation of specific molecules in the lysosome. A primary treatment approach is administration of a working version of the defective enzyme, one specific for the accumulated molecules and that has evolved to work for this purpose; but even this has proven to be extremely problematic. (NOTE: de Grey's claim here and elsewhere in his response, and also in his response to Warner and colleagues (Warner et al. 2005), is that SENS is being rejected because we are unfamiliar with key points or arguments. He presents "arguments" from his papers as if they are irrefutable evidence. We don't reject these arguments because we are unaware of the specifics, we reject them because they are mostly like the one comparing the treatment of lipofuscin to treatments of lysosomal storage diseases: they are ridiculously simplistic and almost certainly wrong).

In producing an exogenous therapeutic enzyme for certain substrates, it is not only important to ensure the enzyme cleaves them, it is obviously important to make sure it doesn't cleave the millions of other biologically important chemical bonds available to it inside the body. In engineering language this is the "signal to noise" ratio. A proenzyme is conditionally cleaved into an active form and its inactivity can only be described probabilistically; it is not a perfect switch that is 100% off when inappropriate. In the use proposed by de Grey, the enzyme in question has to be highly specific over many decades of life so as to cleave the intended product(s) with appreciable frequency, and cleave unintended ones infrequently. How can we be sure that the hydrolytic potentials of endogenous enzymes are directed properly over many decades of human life? Because,

as a result of natural selection over many millennia, they simply do—but even these display dysfunction with age. According to a currently favored evolutionary theory advanced by G.C. Williams in 1957, antagonistic pleiotropy, endogenous enzymes can perform admirably to ensure the organisms' successful reproduction, and then actually do harm at some later stage (Williams 1957). How can exogenous enzymes be selected or designed to function properly over many decades, a property likely not even possessed by all endogenous enzymes? In theory, a proenzyme can be engineered to function just as well as one that has evolved in long-lived organisms, but how? Nobody knows how, including Aubrey de Grey, and from his response, he doesn't even seem to understand that this is the type of difficult problem separating fantasy from practical reality.

Example 1: WILT

Claim: "…historically, and to some extent even today, 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… "

Response: But this is simply the conventional view in cancer research and treatment. To a reasonable approximation *everyone* believes that genome instability and selection are the crux of the problem with cancer and its treatment, and to pretend this view is somehow unique is bizarre. de Grey believes he is owed recognition and applause for making a simplistic guess as to how to cure cancer? Instead, we thank our colleagues who make far more educated guesses in the formulation of theories that are consistent with available data, who plan rationally designed, difficult, and sometimes elaborate experiments, who begin to test these theories in preliminary experiments to secure funding in order to further test these theories, who hire highly trained people capable of performing these experiments, who actually get the experiments done and then interpret and report the results of these non-trivial experiments to their colleagues so that others can build on this work. Some of them are racing quickly to do all this because they are caring for patients who are dying of cancer. Once again, it is difficult to tell if Aubrey de Grey simply doesn't have a clue, or if he knowingly misrepresents science to such a degree that it is unrecognizable to scientists themselves.

Claim: "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."

Response: de Grey creates multiple diversions from our essential points. First, as clearly described in our critique, TERT appears to posses a function that is independent of telomere extension, and is essential for stem cell mobilization. Second, he never answers our question "why do this since current data suggest that ridding the soma of telomere extension capacity simply shifts the incidence of different types of cancer, reducing some

and increasing others, with increased frequencies in highly proliferative tissues?" We ask again. Why do this?

Prediction: While pharmacological inhibition and modification of certain activities of telomerase will continue to be discussed as possible ways to treat cancer (just as they were prior to Aubrey de Grey's interest in this field), his only contribution to this area, therapeutic deletion of the entire telomerase gene and related genes from the genome, will be recognized to be a crude biomedical fantasy. It will be abandoned by all sensible people—if it hasn't been already—and even de Grey's co-authors will cease to write about it or discuss it publicly—if they haven't already.

SENS is not Science or Engineering

Claim: "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."

Response: we actually wrote that we engineer organisms "because we cannot predict the outcome." Our purpose was not only to show our own inability to do this, but to make clear that this applies to everyone. We can't accurately predict the outcomes of these experiments *and neither can Aubrey de Grey, or anyone else*.

Gerontology, SENS, and Opposition to SENS are Misrepresented

Claims: Advanced Glycosylation Endproducts (AGEs) were discovered by scientists (Maillard) "decades before Monnier and Cerami proposed their role in aging" and "work on AGE breakers has in fact been largely dismissed by those gerontologists working on glycation."

Responses: Maillard described the chemical structures that formed in heated foods (protein and sugar mixtures) and while he did predict they would occur *in vivo*, it seems he never suggested they would *persist and accumulate with age* as intermolecular crosslinks, as Cerami and colleagues did. Persistence and accumulation are the key concepts that differentiate the work of Cerami and colleagues from what came before. This is the problem that AGE breakers were developed to reduce and these therapies were pioneered by Cerami and associated gerontologists. It is *completely irrelevant* to our point that *some* gerontologists working on glycation disagree with specific therapies or approaches, as suggested by de Grey.

Claim: "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".

Response: de Grey's points are highly debatable and the letter referenced by him is not evidence of his claim that anti-amyloid vaccination is further advanced than AGE breakers. Its purpose is to correct a news story and suggest that the negative effects of the

vaccine AN-1792 reported in the story were not quite as bad as depicted. The clinical trial of this vaccine was halted in early 2002 because it caused life-threatening complications in test subjects. Elan Pharmaceuticals is again enrolling patients in trials for a new vaccine; however, it is far too early to say that this or any other anti-amyloid vaccine will work. The simple fact is that neither anti-amyloid vaccines nor AGE breakers has reproducibly shown clear efficacy in human or animal trials, or an absence of serious side effects, and by these measures, neither is an "existing" therapy.

Claim: "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."

Response: "Heading off" is synonymous with preventing. The claimed purpose of allotopic expression of mitochondrial coding regions in the nucleus is to distance them from the source of damage, thereby *preventing* damage to them, to reduce mitochondrial dysfunction. Of course, this was only half of our point. The other half is that gerontologists are not obsessed with the prevention of damage as falsely claimed by de Grey. They are working on many things including prevention *and* regeneration and repair. Even the study of calorie restriction, a topic of wide interest in gerontological research, is not exclusively limited to the study of prevention of aging, since mechanisms of repair and regeneration are obviously inextricably linked to CR.

Summary

Claim: "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."

Response: This is the sort of emotional rhetoric that motivates any interest in SENS. We wrote "Some of these technologies might never exist and until all of them—or functional equivalents—do exist, the overarching hypothesis of SENS is not even testable." Emotional states are irrelevant to whether or not SENS is testable.

Claim: "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."

Response: This passage clearly demonstrates an ignorance of essential life extension issues. All therapies carry side effects. In life extension, criteria of success must extend beyond the simplistic molecular and cellular endpoints referred to by de Grey, e.g. prevention of telomere extension by a therapy designed for this purpose, to ultimate consequences. What unintended consequences (such as increased genome instability or the shift of cancer types in telomerase-deficient mice) might result from not just SENS'

specified therapies, but any therapy, that would undermine the ultimate goal of extending life span? How are these to be discovered and minimized in people? Any legitimate science or engineering plan would consider these issues in detail, and regard them as unsolved problems until data support bolder claims.

Claim: "…"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."

Response: hypotheses are a "dime a dozen" in biology and the ones presented by Aubrey de Grey don't take into account much contradictory evidence or common knowledge among experts in these fields, and supporting data are tortuously presented. We believe it is in our best interests personally, and in the best interests of science generally, to focus on ideas and challenges presented by experienced researchers who produce challenging data—and who adjust theories to fit these new and challenging data—and to not waste time on the naïve claims of someone who has demonstrated repeatedly the tendency to misrepresent data in order to fit an almost certainly incorrect theory.

Claim: "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."

Response: again, de Grey attempts to mislead by using the real science of other people to camouflage the pseudoscience of SENS. Almost everyone working on science related to SENS was doing so prior to SENS' existence, including de Grey's coauthors. Legitimate science does exist within the SENS plan, but this is the work of other people, and any real science is separable from Aubrey de Grey's contributions.

None of our criticisms of de Grey can be rightly considered *ad hominem*. We aren't criticizing his dress, appearance, friends or family, his way of walking or speaking, or any other of his personal traits. These are none of our business. We are focused solely on his conduct in the presentation of science, which is an essential part of the exchange of scientific ideas, and this aspect of people's behavior *is* our business. We don't even know if he is consciously aware of his deceptions since he so obviously does not understand the relevant science. de Grey's ongoing misconduct wouldn't be tolerated in any other branch of scientific research. In fact, it probably couldn't even occur in any other branch of science since it is completely dependent upon a pseudoscientific promise of enormous emotional power.

REFERENCES

de Grey, A. D. (2005). "Like it or not, life-extension research extends beyond biogerontology." EMBO Rep **6**(11): 1000.

Dolle, M. E. and J. Vijg (2002). "Genome dynamics in aging mice." Genome Res **12**(11): 1732-8.

Lu, T., Y. Pan, et al. (2004). "Gene regulation and DNA damage in the ageing human brain." Nature **429**(6994): 883-91.

Smithsonian National Air and Space Museum, Wright Brothers web site, Forefathers of flight http://www.nasm.si.edu/exhibitions/gal209/fly/1899/forefathers.cfm

Smithsonian National Air and Space Museum, Wright Brothers web site http://www.nasm.edu/wrightbrothers/fly/1901/apparatus.cfm, http://www.nasm.edu/wrightbrothers/fly/1901/smeaton.cfm, http://www.nasm.edu/wrightbrothers/fly/1901/wind.cfm

Vijg, J. and M. E. Dolle (2002). "Large genome rearrangements as a primary cause of aging." Mech Ageing Dev **123**(8): 907-15.

Warner, H., J. Anderson, et al. (2005). "Science fact and the SENS agenda." EMBO Rep **6**(11): 1006-8.

Williams, G. C. (1957). "Pleitropy, natural selection, and the evolution of senescence." Evolution **11**: 398-411.