Life Extension Pseudoscience and the SENS Plan

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Abstract

Recent scientific advances have taken gerontological research to challenging and exciting new frontiers, and have given many scientists increased confidence that human aging is to some degree controllable. We have been on the front lines of some of these developments and the speculative discussions they have engendered, and we are proud to be part of the increasingly productive biomedical effort to reduce the pathologies of

aging, and age-associated diseases, to the greatest degree possible—and to extend healthy human life span to the greatest degree possible.

In contrast to clearly justifiable speculations regarding future advances in human longevity a few have made claims that biological immortality is within reach. One, Aubrey de Grey, claims to have developed a "detailed plan to cure human aging" called Strategies for Engineered Negligible Senescence (SENS) [1, 2]. This is an extraordinary claim, and we believe that extraordinary claims require extraordinary evidentiary support.

In supplementary material posted on the Technology Review web site we evaluate SENS in detail. Briefly, here are our conclusions: 1) SENS is based on the scientifically unsupported speculations of Aubrey de Grey, which are camouflaged by the legitimate science of others; 2) SENS bears only a superficial resemblance to science or engineering; 3) SENS and de Grey's writings in support of it are riddled with jargon-filled misunderstandings and misrepresentations; 4) SENS' notoriety is due almost entirely to its emotional appeal; 5) SENS is pseudoscience. We base these conclusions on our extensive training and individual and collective hands-on experience in the areas covered by SENS, including the engineering of biological organisms for the purpose of extending life span.

Most scientists believe pseudoscience poses a real danger to the integrity and public image of science. Since experts recognize SENS is pseudoscience, but it nevertheless has been featured widely and uncritically by popular media, we devote the rest of this short note and the first section of our web supplement to a more general response to this troubling aspect of SENS.

We believe the future will bring advances that are today almost unimaginable. How will the non-expert separate the false promises of pseudoscience from the likely outcomes of rigorously applied biomedical science and engineering? The long history of pseudoscientific claims shows us there are obvious identifying features of pseudoscience that are rarely or never associated with real science or engineering—but what exactly is pseudoscience?

The prefix "pseudo" means "false" and pseudoscience is generally accepted to mean practices that only superficially appear to be science, but violate central scientific precepts. One of the most clearly illustrative definitions of pseudoscience—particularly in the context of this SENS Challenge—was given by Richard Feynman, a widely respected physicist and staunch defender of science. He called some kinds of pseudoscience "cargo cult science," a reference to practices of certain South Sea Islanders during World War II (pp. 310-311, [3]). Upon seeing the building of airports which brought in military cargo planes loaded with assorted material goods, the cargo cults built their own crude airport reproductions to lure in these inexplicably airborne behemoths loaded with fabulous cargo. Their simulated airports were complete with torch-lit runways, a "control" hut complete with bamboo antennas, and even a "controller" wearing wooden pieces over his ears as mock headphones. Feynman rightly

thought that these elaborate but obviously superficial simulacra collectively made a powerful metaphor for pseudoscience camouflaged by superficial aspects of real science.

One can easily imagine why the cargo cults went through these rituals since rich rewards appeared to descend miraculously from the heavens for others who did—but the planes never landed for the cargo cults. Most of us know through experience that there are several missing ingredients preventing the cargo cults from succeeding. But what if we weren't familiar with airplanes and airports, and the elaborate and technologically advanced civilization that produces and supports them?
Are there general principles that can help people to avoid this type of wasted effort, this wishful thinking that results in a focus away from real problems and real solutions?

We agree with Feynman that an important ingredient missing from cargo cult rituals and pseudoscience is a certain kind of integrity, a skeptical unwillingness to settle for convenient but superficial explanations no matter how dearly or desperately we wish them to be true. There are other important differences between science and pseudoscience, and a primary feature of our web supplement is a list of "General Features of Pseudoscientific Plans for Extension of Human Life Span" that we assembled with the help of some of our colleagues. This list is modeled after other published lists concerning pseudoscience [4], and it is designed to help non-experts distinguish life extension pseudoscience from legitimate science and engineering—including challenging but legitimate new developments. Not surprisingly, most or all of the points on our list clearly apply to the SENS plan and Aubrey de Grey.

However, given the recent successes and highly emotional nature of life extension research, Aubrey de Grey is not the first, nor will he be the last, to promote a hopelessly insufficient but ably camouflaged pipe-dream to the hopeful many. With this in mind, we hope our list provides a general line of demarcation between increasingly sophisticated life extension pretense, and real science and engineering, so that we can focus honestly on the significant challenges before us.

REFERENCES

1. de Grey, A.D., et al., /Time to talk SENS: critiquing the immutability of human aging./ Ann N Y Acad Sci, 2002. *959*: pp. 452-62; discussion 463-5.

2. de Grey, A.D./Strategies for Engineered Negligible Senescence (SENS): A practical way to cure human aging/. 2006: http://www.gen.cam.ac.uk/sens/.

3. Feynman, R.P. and R. Leighton, /"Surely You're Joking, Mr. Feynman!"/ 1985, New York: W.W. Norton and Co.

4. Friedlander, M.W., /At the Fringes of Science/. 1998: Westview Press.

Introduction

Recent scientific advances have taken gerontological research to challenging and exciting new frontiers, and have given gerontologists increased confidence that human aging is to some degree controllable. These successes have also led to a great degree of speculation and excitement among both scientists and non-scientists, on internet chat groups, and in popular media. Several people—both scientists and non-scientists—have claimed that science is on the verge of one or more breakthroughs that could significantly extend human life span. None of these claims is scientifically rigorous, but most of these speculations are reasonable and defensible; they are part of the normal optimistic and progressive nature of scientific discourse. In most cases, claims are not made regarding the precise nature or timing of these breakthroughs, nor do most claimants say they have a way or plan to cure aging.

In contrast to clearly justifiable speculations regarding future advances in human longevity, a few have made claims that biological immortality is within reach, and at least one "detailed plan to cure human aging" [1] has been presented. We therefore set out to scientifically evaluate the validity of claims of this sort, with particular emphasis on Strategies for Engineered Negligible Senescence (SENS), as put forth by de Grey and colleagues [1, 2]. de Grey's own description of SENS is as follows: "It 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. This means that all parts of the project should be fully working in mice within just 10 years and we might take only another 10 years to get them all working in humans. When we get these therapies, we will no longer all get frail and decrepit and dependent as we get older, and eventually succumb to the innumerable ghastly progressive diseases of old age" [3].

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. Of course, there is a long history of pseudoscientific claims of miracle cures, and fountains and elixirs of youth. Nevertheless, we believe the future will bring biomedical advances that are today almost unimaginable. How will the non-expert separate the false promises of pseudoscience from the likely outcomes of rigorously applied science and engineering? The long history of pseudoscientific claims shows us there are obvious identifying features of pseudoscience that are rarely or never associated with real science or engineering.

Identifying features of life extension pseudoscience

The prefix "pseudo" means "false" and pseudoscience is generally accepted to mean practices that only superficially appear to be science, but violate central scientific precepts. Pseudoscientific claims have been described as follows: "they appear to be scientific, make assertions that they are scientific, but on closer examination turn out to be fatally flawed in content, in method, or in both". This basic definition by Friedlander [4] is concordant with the definitions of several others, including Park [5] and Sagan [6].

Pseudoscience isn't limited to the reporting of questionable experimental results; it can be a philosophy, dogma, or plan, based on a misrepresentation of scientific evidence, often driven by a profit motive, or ideology, as in the case of Lysenkoist genetics and agricultural practices in the former Soviet Union [4, 6]. There is no simple formula for demarcating the dividing line between real science and pseudoscience; but many scientists, philosophers, mathematicians, and assorted skeptics have contributed to the relevant body of knowledge, and some have listed qualities that tend to identify pseudoscience [4-7].

We have borrowed from these prior observations to craft a set of distinguishing features of pseudoscientific plans to extend human life span (**Table 1**). We have assembled this list because we hope to elevate the scientific basis of current dialogue regarding aging and life span extension, and to demonstrate to the public that there are stereotypical traits of pseudoscience that tend to distinguish it from legitimate science—including radical and challenging new ideas. We also wish to give the public fair warning that surely one of the oldest false promises of humankind is with us today and is being peddled as science. We believe that none of the features listed in Table 1 is essential to real science. The list explicitly applies to plans for proposed cures, interventions, or therapies, for either model organisms or humans, for the eventual purpose of extreme extension of human life span. Drugs, dietary supplements, and other regimens, such as exercise or dietary regimens, might influence human aging by a significant amount, but the amount is very small compared to claims of biological immortality. Naturally, we object to any "anti-aging" claim absent sufficient supporting evidence, but we are even more concerned about unscientific claims of extreme life span extension, such as those made in support of SENS.

To make the list easier to read, and to model other published lists [4], we have broken the list into three parts: The Problem of Aging, The Plan, and The Proposer. Naturally, we are aware of legitimate exceptions to certain aspects of some of these features. For example, there are people who change fields and develop expertise in the new field, and legitimate science is occasionally first announced and discussed in popular media. For this reason we have tried to include important qualifiers. We don't wish to impugn the good names of individual journalists or popular media organizations, but some members of popular media have supported numerous pseudoscientific causes [4-7]. Judging the technical merits of cutting-edge science and engineering can only be done by people with many years of specialized training and experience. Therefore, use of popular media is only objectionable when it is used in opposition to, or as an attempt to skirt, expert opinion. When reviewing this list one should keep in mind that aside from the first three features, any one feature—or even a few—does not identify a plan as pseudoscience, but if many elements of a given plan are similar to those on the list, a red flag should be raised.

Table 1. General Features of Pseudoscientific Plans for Extension of Human Life Span

The Problem of Aging

1. Unscientifically simplified; diffuse and undiscovered damage/pathologies excluded as causes of aging without compelling evidence
2. Unscientifically claimed to be curable to some degree by specific therapies

The Plan

3. Hypothetical and untested approaches are strongly implied or claimed to be "cures" for aging, e.g. the use of stem cells to provide life extension or indefinite regeneration
4. Scientific references are misrepresented as supportive and many that refute key aspects of the plan are ignored
5. Dependent upon at least one non-existent/fantasy therapy or technology
6. Aggressive timeline (increases recognition and financial reward)
7. Popular media are used to promote the plan, and skirt or oppose expert opinion
8. Asserted to be outside the domains of experts with relevant training and experience
9. Heavily relies on the science of experts, but casually dismisses expert criticisms
10. Proposer's contributions are highly speculative and camouflaged by real science
11. It is "big picture"; lacks valid science/engineering developmental guidance
12. Claimed to result in, or be a first step toward, biological immortality
13. Support base generally consists of non-experts, including celebrities; it grows and then wanes in the protracted absence of progress

The Proposer

14. Claims to be unjustly opposed by a monolithic "mainstream" or conspiracy
15. Presents extraordinary claims absent sufficient scientific evidence, and challenges opponents to prove the claims wrong
16. Generally, a non-expert; lacks training in relevant science/engineering and betrays obvious lack of understanding of relevant areas
17. Belittles, defames, and caricatures science in general and/or opponents of the plan in particular; misrepresents opponents views; boasts of own abilities
18. Frequently engages in argumentative diversion and misrepresentation
19. Unable to predict the outcome or timeline of routine biology experiments, but predicts the outcome and timeline of untested "therapies": life span extension in the near future
20. Uses emotionally charged propaganda; accuses opponents of costing lives by delaying implementation of the plan

Most of these features are self-explanatory and many of them are typical features of pseudoscience in general [4, 5]. A few features are unique to plans for life span extension. Of these, the first three are the most important. These highlight the fact that human aging is not well understood, and any prospective therapy or cure must be regarded as pure speculation. This is in fact the crux of this list, and 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. Even after the existence of a scientifically supported mechanistic model of human aging, any prospective therapy should be considered experimental until efficacy is tested. In other words, for now, and for the foreseeable future, all explicit and implicit claims of cures for human aging are pseudoscience. Since this is a list of general features of pseudoscience of life span extension, not every feature in this list necessarily applies to SENS, or to any particular pseudoscientific plan to "cure" human aging. Nevertheless, it will be immediately apparent to those familiar with SENS that a large number of them do apply.

A few of our colleagues have privately raised concerns about publicly criticizing the pseudoscientific features of SENS and its primary architect and proponent Aubrey de Grey; not because they support the scientific claims made within SENS or by de Grey, but because they think the Methuselah Foundation's Mprize is a worthwhile idea, or because some SENS conference participants are legitimate scientists. These objections highlight a serious problem with the perception of SENS (the plan): it has been so intermixed with legitimate science that it has taken on a small degree of respectability through confusion. In the following section we intend to disentangle science fact from science fiction.

SENS Mixes the Legitimate Science of Others with Scientifically Unsupported Speculation

The SENS plan addresses seven pathologies that increase in severity with advancing age and proposes a solution for each [2, 3, 8, 9]. We agree that the some of the pathologies grouped together by SENS are causes of death in some individuals (this is obviously true of cancer, for example). In fact, all of these pathologies were discovered in the routine performance of science and medicine, and have been previously suggested to cause progressive dysfunction or death. Beyond grouping these pathologies together—and unscientifically excluding others—SENS is simply a collection of prospective therapies, some simple and mundane (e.g. exercise) and some best described as fantasy.

To address certain of these seven pathologies de Grey has adapted others' experimental work and has suggested extreme and scientifically unsupported versions of these as therapies. These include proposals for somatic telomerase deletion, somatic mitochondrial genome engineering, and the use of transgenic microbial hydrolases to degrade intracellular aggregates, such as lipofuscin [8, 10, 11]. All three of these proposed therapies are to be accomplished by gene therapy in large fractions of somatic cells. The first two are simply extrapolations of experimental work being done by others [12-17]; however the extrapolations are so extremely speculative, and the basic ideas so naïve and flawed, they simply cannot be considered to be legitimate science or engineering. In the following examples we consider certain aspects of SENS that are inconsistent with science and engineering, but are completely consistent with pseudoscience.

Example 1: WILT

One of the proposed therapies of SENS is "Whole Body Interdiction of Lengthening of Telomeres" (WILT) [18]. The goal of WILT is to delete from a large fraction of somatic cells several individual genes involved in telomere extension in order to prevent cancer for an extended period beyond a normal life span. This requires multiple independent gene deletion events for each of several trillion cells of many different types. To accomplish this in such a large number of cells without causing serious side effects, these deletion events must be extraordinarily efficient and specific. Any expert in gene therapy or genome engineering can attest to the fact that, for even one such event in such a large number of cells, the most specific and efficient methods currently available for allelic deletion or replacement fall many orders of magnitude short of this requirement, even *in vitro*. To propose that technology allowing *in vivo* somatic genome manipulations of this sort will be available in the near future is completely outside the realm of responsible speculation. For those with sufficient knowledge and training, it is difficult to contemplate an enzyme or method with suitable specificity and efficiency to safely

accomplish such a task. Finding enzymes or vectors with greater specificity and efficiency for DNA manipulation or delivery does not follow the predictable developmental schedules of other technological advances, such as those described by Moore's Law, and we do not expect to find these several orders of magnitude any time soon—if ever.

The pseudoscientific nature of WILT (and SENS by extension) becomes even more apparent, however, when we consider that even if a method magically became available to accomplish the technical goals of WILT, there is no evidence WILT would be beneficial. In fact, there is substantial evidence it would cause serious problems. The reader should bear in mind that the following analysis does not apply to the use of telomerase inhibitors in the treatment of cancer to keep a cancer patient alive, possibly for a normal lifetime. It is limited to the elimination of telomere extension for the purpose of extreme life span extension, as proposed by de Grey.

To test the relevance of telomere shortening in carcinogenesis DePinho and colleagues produced mice deficient for the telomerase RNA component (mTERC) [19]. This approach is important in determining the role of telomere erosion in carcinogenesis, since the only known role of mTERC is in telomere extension. These mice display severe defects, including increased cancer of certain types and shortened life spans, when their telomeres shorten to the length of those in humans [20]. Does this result apply to human cancers? Available data and expert opinion suggest they do. To quote DePinho and colleagues from a review of the role of telomeres in cancer: "With regard to carcinogenesis, telomere erosion has been cited as a potential risk factor for the genesis of certain human tumor types... In line with these predictions, late generation mTERC null mice exhibit an age- and generation-dependent increase in cytogenetic abnormalities and a significant increase in the incidence of spontaneous cancers." [21] These mTERC deletion mice have been used in further studies to show that telomere erosion results in severe defects in chromosome maintenance and DNA repair [22].

An alternative pathway (ALT) exists for telomere maintenance in cancer and de Grey suggests this pathway might also require inactivation to prevent cancer [18]. However, the ALT pathway is only activated in only about 10% of cancers, and even though intact telomerase is responsible for increased proliferation and metastatic potential in the remaining 90%, as discussed above, mTERC deletion actually increases the frequencies of some cancers [19]. The role of ALT in this increase is unclear but there is no reason to believe a similar increase in the frequency of cancer or other serious problems won't occur if mechanisms responsible for ALT are perturbed.

Furthermore, a recent report suggests that stem cell mobilization depends on a function of telomerase reverse transcriptase (TERT) that is independent of its telomere elongation function [23]. This strongly suggests this gene cannot be deleted from stem cells if they are to function properly. Yet de Grey proposes this gene should be deleted in aging, but otherwise healthy, people and in exogenous stem cells used to treat them [18]. The extreme difficulties of developing this approach, and the potential dangers of implementing it, beg a simple 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 [20, 21, 24, 25]? As with many other aspects of SENS, de Grey's description of WILT as a method for "cancer prevention" [11] is unsupported and contradicted by available data.

Example 2: Microbial hydrolases

We have also considered de Grey's proposal to use microbial hydrolases to degrade intracellular aggregates that accumulate with age. For many of the same reasons addressed in our consideration of WILT above, the absence of technology necessary for this "therapy" place it clearly in the realm of fantasy. Below, we discuss a few of the flaws with this approach which are also general flaws that recur throughout SENS, such as claims unsupported by quantitative considerations of specificities, efficiencies, or estimates of probabilities and errors. For example, it is likely that the regulation and specificity of microbial hydrolases must be extraordinarily high, yet de Grey and colleagues description of the use of microbial hydrolases address this very serious problem only superficially [10]. Although lipofuscin is somewhat uncharacterized, it appears to be mostly made of a large variety of common cellular components, including lipids, branched carbohydrates, many protein species containing multiple types of damage, many fluorescent compounds, and other unidentified substances [26, 27]. Thus, several enzymes would likely be required, and several independent genome engineering events likely would be necessary for delivery.

In addition to the problem of getting these hydrolases into the cell, consider the possible outcome of having several relatively non-specific hydrolases diffusing about the interior of the cell, even as engineered pro-enzymes. Digestive enzymes in the stomach and gut, and in organelles such as the lysosome, are highly regulated and inactive as pro-enzymes until they are transported into locations where they can do no harm. Stringent regulation of such destructive potential is essential for life and dysregulation can cause disease and death [28]. Such regulatory processes are present in all living things and have had many millions of years for evolution to select for suitable regulation and specificity, and for appropriate interactions with other cellular components, so that they function properly over lifetimes in long-lived animals such as humans. There is currently no reason to believe that suitably specific enzymes could be isolated having all the properties necessary for specific degradation of lipofuscin, even in cultured cells. Further, even if this works in one or several human cell types in culture, we cannot assume it will be harmless in all cell types, especially over decades of remaining human life span—much less the extremely long period predicted by de Grey. Even enzymes under evolutionary selection frequently behave in undesirable ways over the course of a normal human life span [28]. So much could go wrong with this implementation that the shortening of life span might well be the outcome. de Grey offers no guidance on how such an outcome would be modeled, predicted, or avoided.

Although we have pointed out sufficient reasons why this approach is fatally flawed, we encourage readers to consult de Grey and colleagues' published description (sections 5.2 and 5.3 and Figures 5 and 6 of [10]) of the methods proposed for the first step of this elaborate proposal: isolating such hydrolases . This step is far and away the easy part, it has ample precedent, and any legitimate scientist or engineer working in this area should be able to describe it with clarity and appropriate references. In our view the description provided by de Grey et al. [10] is obvious pseudoscientific pretense and technological window dressing.

Example 3: Mitochondrial engineering

We feel it is important to emphasize that while the motivation of de Grey and others may be well-intentioned, SENS relies on assumptions and technologies that reside firmly in the realm of fantasy. For example, de Grey bet Bruce Ames that all 13 mitochondrial proteins will have been successfully moved to the nucleus in cultured cells by October 2005 [8]. It is now mid-2006, and no such feat has been reported. In fact, virtually no progress on this problem has been reported. However, 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. Therefore, if this achievement ever succeeds it certainly will be of interest to mitochondrial research biologists, and the use of such a development might help determine whether or not mitochondrial genome integrity does limit cellular or organismal life span to any degree; but at this time there is no reason to believe this approach will be a useful therapy for aging or age-associated disease. In summary, this proposed "therapy" isn't currently possible, is unlikely to be possible in the near future, might never be possible, and even if it were possible its therapeutic benefits in aging are uncertain.

Example 4: Misrepresentations of the difficulty of curing aging

The absence of scientific support for SENS is demonstrated further by its treatment of the subject of stem cells. Although the use of stem cells to repair and regenerate the aging soma is arguably the most essential aspect of SENS (and other extreme life-extension theorizing), de Grey has only vaguely described the details of how this is to be accomplished. Instead, the exploration of this largely unknown but exciting area of research is left to others. All scientists rely on the work of others, so what is the problem? In the case of SENS the problem is threefold. First, even though de Grey completely relies on biologists to make the basic discoveries, he rejects their expert criticisms and claims SENS is outside their domains of expertise by calling it "engineering" [8]. This, despite the fact that many such biologists perform the general types of biological engineering specified by SENS, as discussed below. Second, the line of demarcation between the legitimate discoveries and therapies proposed by others and the scientifically unsupported speculations of SENS is often unclear. Of course, we do not claim this is intentional, but it gives a false impression of scientific legitimacy. Third, some scientific references are supplied in de Grey's publications, ostensibly in support of certain generalizations or key speculations, but which are not supportive and sometimes tend to refute the statement(s) which they are cited to support.

As one example, consider the references cited by de Grey to rule out the contributions of non-oncogenic nuclear DNA (nDNA) mutations to aging. One early publication by de Grey and colleagues 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" [2]. de Grey has boiled this down to a succinct statement he has repeated often: "Only cancer matters." One publication by Dolle et al. is the only reference given in support of this extreme conclusion, and a second reference to work by Dolle and colleagues is given elsewhere [8, 29, 30]. However, the authors of these publications have published several papers in which they show supportive data and express belief in the likely importance of nDNA mutations in aging [31-34]. In a later publication on SENS [35], de Grey himself cites one of these publications and the views of these authors as supportive of nDNA mutations contributing

to aging; however, he does not change his earlier opposing conclusion, even though none of the previously cited references support it. In fact, in reviewing the previously cited references, we find that the results from these publications indicate that somatic nuclear DNA damage might contribute to aging, and certainly don't rule it out. Furthermore, in the second of these publications the authors write that their results on nDNA mutation "suggest that distinct mechanisms lead to organ-specific genome deterioration and dysfunction at old age" [29].

de Grey also casually rules out the contributions of non-oncogenic epimutation to aging through "guilt by association" misrepresentation. He groups together nDNA mutation and epimutation, provides grossly insufficient evidence to rule out nDNA mutation as important in aging, and then declares epimutation is ruled out as well without providing any supporting evidence [8, 35]. There is no logical or mechanistic reason for this. In fact, references are available that suggest that epimutation might be common and problematic with advancing age, possibly even more so than nDNA mutation (for example see [36-38]). Furthermore, other known molecular pathologies, such as unrepaired DNA damage in post-mitotic tissues, as well as largely uncharacterized and undiscovered damage and pathologies, are dismissed altogether as contributing to aging (for one example, see [39]). This is baseless and unscientific conjecture.

Overall, a large body of scientific evidence on various pathologies and their possible contributions to aging is ignored, and publications cited, ostensibly in support of a gross generalization—"only cancer matters"—tend more to refute, than to support this position. These are unacceptable and unscholarly practices resulting in misrepresentations of available data, and of the difficulty of curing aging. We are not saying this has been done intentionally, but intent is, to a great degree, irrelevant. Whatever the intent, SENS' bottom line assessment of the difficulty of curing aging is helped greatly by these misrepresentations in two primary ways. First, if certain pathologies underlying aging remain undiscovered, or uncharacterized, then future research must be done just to discover and characterize them. It is uncertain how long this will take and how amenable they will be to therapeutic correction. Second, the known molecular pathologies excluded by SENS are ubiquitous and diffuse, and some are possibly irreversible corruptions to carriers of biological order and information essential for life (e.g. the genome and the epigenome). Even if they are reversible they are likely to be extremely difficult to correct. If any of these excluded pathologies causes significant dysfunction during a normal human life span—which is very likely, as the passage above from Dolle et al. clearly suggests—then correction of only the seven pathologies grouped together by SENS might have no significant effect on life span.

In addition to intermixing the science of others with his own unscientific speculations within the SENS plan, de Grey also has freely intermixed the legitimacy of the SENS conferences with the quite separate, and scientifically illegitimate, SENS plan. 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 [40]. Scientists attending these conferences must be made aware of this and the inherent problems that arise from such confusion. A similar intermixing of SENS with the business of the Methuselah Foundation and the Mprize also is occurring and references to SENS are featured prominently on

their web site, including (currently) at the top center of the home page [41]. It would be a shame to see any positive or notable effort tainted by the pseudoscience of SENS.

SENS is not Science or Engineering

The claim that SENS is a practical, comprehensive, and detailed plan to cure aging is not supported by logic, appropriate scientific references, or data. To overcome the unscientific aspects of SENS de Grey has attempted to promote it as an "engineering plan" [8]. This name game is a clear attempt to place the debate on the merits and deficiencies of SENS outside the reach of experts. Historically, engineering was generally outside the nominal areas of expertise of scientists in aging research, and professional engineers generally worked in "applied science" areas of design, production, and maintenance of mostly or completely defined systems. However, modern biomedical research bridges the divide between pure science and traditional engineering, and there is a continuum of methods and procedures and a clear line of demarcation does not exist.

Whether or not the issues addressed by SENS are more properly considered science or engineering is largely irrelevant; the truly important question is this: who has relevant expertise in these areas? Many biologists, biotechnologists, and medical scientists, are familiar with both aging research and with biological engineering principles. More importantly, the majority of the undersigned have extensive training and experience in the engineering of experimental organisms. We have created cell lines, and cells with gene knockouts, knock-ins, and overexpressers; we have designed and altered plasmids, viral vectors, phage, transposons, and other biological vectors; we have made many types of genome modifications, in vivo "libraries," and we have made transgenic animals. This is but a small selection of such procedures we have performed. Individually, and collectively, we have produced many tangible results from engineering biological systems, while de Grey has never even attempted the engineering of biological systems. There is nothing revolutionary within SENS that informed scientists are unfit to understand and criticize—especially scientists who have far more training and experience than de Grey in the areas covered by SENS.

We agree with de Grey that we don't need to understand everything about a system to engineer it. In fact, we routinely engineer mice and other model organisms to test a variety of theories; however—and this is where we very much differ from de Grey—we engineer these organisms precisely because we cannot predict the outcome. If we could easily predict the outcome, why bother going through all the trouble of actually doing the engineering? de Grey's presentation of SENS is based fundamentally on unsupported predictions of the outcomes of research experiments that have yet to be conducted.

According to de Grey, SENS' seven solutions are to be used in mice and success will be determined by measuring life span; once life span is extended in mice, SENS' same basic solutions are to be applied to humans [1]. This approach reveals unscientific assumptions and several implementation flaws. SENS assumes that one (or some combination) of the pathologies it targets limits life span in mice, and, by inference, that pathologies unaddressed by SENS do not significantly contribute to aging (since life span extension by SENS is asserted to be significant). The same is true for humans, although the specific life span limiting pathologies might not be the same as in mice. This highlights a problem for *any* damage/pathology remediation approach that extends life span in mice: if life span limiting pathologies are different

in mice and humans, approaches that work in mice probably won't work in humans, and might not help identify what pathologies actually do limit human life span.

Furthermore, there is no plan of how to develop each one of SENS' suggested solutions into actual therapies. There is a complete absence of intermediate goals and details on how to measure the effectiveness or deleteriousness of a single proposed therapy. There are no described or suggested experiments that will yield valuable data if the ultimate goal of life span extension is not achieved, and no contingencies are provided for unforeseen consequences. All therapies carry unexpected side effects and biological costs. What new types of damage would occur, or what types of existing damage would be increased, if the therapies of SENS were used? SENS has no answers. If life span extension is the only outcome sought and this is not accomplished what will we have learned? Certainly, we can wait three or four years for a life span experiment in mice to be completed to declare success or failure. However, this approach is extremely inefficient, even in mice, and it is simply not a tenable approach to testing prospective therapies in either mice or humans on the schedule proposed by de Grey [35]. SENS is not science or engineering because it provides grossly insufficient guidance for implementing or testing its proposed solutions, among other obvious deficiencies noted above.

Gerontology, SENS, and Opposition to SENS are Misrepresented

In addition to the misrepresentations described above, de Grey has misrepresented the views of hypothetical "mainstream" gerontologists, and he has confused and misrepresented the fundamental differences of opinion between himself and gerontologists. He often caricatures working gerontologists as blundering fools; he has repeatedly hung the straw gerontologist for failing to understand SENS, for failing to understand the implications of their own research, and for failing to envision progress beyond their nominal domains of expertise, among other things [8, 40, 42]. Do these accusations have merit? There might be some truth somewhere within, but it is so distorted and misrepresented, why bother with it?

As a typical example, we direct the reader's attention to one selected publication. In it de Grey compares the damage of aging to a leaky roof, expressly for the purpose of hanging yet another straw gerontologist from a crude tree of his own making [8]. In this perspective published in SAGE KE, he ridicules the gerontologist for obsessing over the prevention of pathological damage, and claims SENS focuses on repairing damage. This is plainly false. Gerontologists have been central to the discovery of the pathologies listed in SENS, and they have investigated ways to both prevent *and* repair these pathologies. One example is the discovery of Advanced Glycosylation End-products (AGE), and the pioneering work in the development of AGE breakers, a therapy for reducing or repairing an existing pathology [43-45]. This is the work of gerontologists, and is the only one of SENS' suggested solutions that actually exists, albeit in pre-clinical form. Gerontologists are also working on ways to reduce pre-existing amyloid and other intracellular aggregates, to deal with senescent cells, and to develop therapeutic stem cells. The purpose of all of these approaches is to reduce or repair existing problems, not just prevent them. The remaining two solutions of SENS, de Grey's own WILT and allotopic expression of mitochondrial coding regions, are the ones he has written the most about; the purpose of these is not to repair damage—they are fundamentally *preventive*.

The SAGE KE perspective is confused, groundless, unscientific, and defamatory hyperbole. Unfortunately, this one publication is not an anomaly, as the same misrepresentations, and other similar ones, can be found throughout his publications. Furthermore, de Grey has schematized this misrepresentation as arrows following from metabolism to damage to pathology, and the roles of the "engineer" and gerontologist are depicted as in SAGE KE. de Grey calls this schematic diagram the "SENS philosophy," and it is featured on the SENS web site and in his slide shows [9]. Given the information above, thoughtful readers and viewers can now understand this misrepresentation.

Aubrey de Grey also has belittled scientists who disagree with or do not actively debate SENS, and claims they do so because they are "ignorant" [46]. It is our experience that this claim is half true—many scientists are indeed unfamiliar with de Grey's publications on SENS and its details. Unfortunately, as a result, many of them have granted passive acceptance of SENS. In exchanges among legitimate scientists, a few have expressed disbelief that SENS was being claimed as a "cure" for aging whose success only requires combining and refining existing therapeutic technologies. A primary reason we provide de Grey's own description of SENS, why we have used his own words and predictions in our analysis of specific aspects of SENS, and why we direct the reader's attention to certain of de Grey's publications, is so that our colleagues can read his claims and judge for themselves. It is the personal experience of each of us that the more we knew of SENS, the less accepting of it we became. Therefore, the truth is the opposite of de Grey's claim, and the fantasy of 'opposition to SENS through ignorance,' is giving way to the reality of 'opposition to SENS through understanding.' Illogic, false analogies, caricatures, and name-calling are employed in the defense of SENS because SENS cannot be defended logically or scientifically.

Although we believe SENS to be obvious pseudoscience, there is one feature that does separate it from routine pseudoscience: the nature of the irresponsible accusations that de Grey makes against scientists. His assertion that they are costing lives by not debating SENS is a very dangerous tactic with the obvious intent to inflame the passions of prospective supporters. The title of a recent advertisement for SENS, in the guise of a scientific commentary in an otherwise respectable journal, is very clear: "Resistance to debate on how to postpone ageing is delaying progress and costing lives" [47]. He estimates this cost to be 100,000 lives a day and he places responsibility for the loss of these lives directly on gerontologists. Although unusual, even for pseudoscience, this sort of inflammatory rhetoric is not unprecedented. It is a feature of some of the most pernicious historical episodes of pseudoscience and other assorted fanaticism [4] (p 261-263, [6]). The fact that many gerontologists routinely discuss and debate how to postpone aging has not stopped him from publicly proclaiming they are resistant to it. Nor have the extreme deficiencies of SENS—which have been pointed out to de Grey on numerous occasions—prevented him from using such inflammatory rhetoric.

Summary

It is our opinion that SENS is flawed in both method and content and fits commonly used definitions of pseudoscience, including the one proposed by Friedlander [4]. Various means have been used to intermix the highly speculative and unscientific ideas of de Grey with the legitimate science of others, which tends to camouflage the obvious deficiencies of SENS. The value of

SENS lies within the elements of real science that are the product of decades of scientific effort by others, and SENS' scientific value appears to be no greater than the sum of these parts.

Whatever legitimacy there might be to de Grey's own contributions to SENS, they are overwhelmed by his obvious misunderstandings of relevant science and pervasive misrepresentations. SENS depends on several non-existent technologies and de Grey's claims for their availability, or degree of maturity, are extremely naïve or hyperbolic. 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. Even if the necessary technologies do become available at some future date there is no reason to believe the implementation of any or all of these proposed therapies will extend life span. Furthermore, there are unprecedented ethical barriers and safety considerations for the testing of genome augmentation, and the deletion of multiple individual genes, in a large fraction of somatic cells of an aging but otherwise healthy person.

de Grey is unable to predict the outcomes and timelines of routine biology experiments—as with allotopic expression of mitochondrial coding regions in cell culture—but he expresses great confidence in the outcome and timeline of the vastly more speculative and unscientific proposals of SENS: life span extension leading to eventual immortality, in the near future. He fails to provide sensible developmental guidance for the scientific testing or implementation of SENS. He firmly maintains SENS is outside the understanding of recognized experts, and claims it is an "engineering" plan; but he has no training or experience in the engineering of biological organisms, while most of SENS' harshest critics do have such training and experience. He has intermixed the science of such trained and experienced experts with his own science-fiction speculations, while mischaracterizing their views and ideas, as exemplified by—but not limited to—the SAGE-KE perspective. And, he has frequently appealed to popular media to promote his ideas with a sense of urgency, often accompanied by declarations of the inhumanity of allowing the increasing death toll due to aging, and by special pleading for how these deaths can be averted by extremely large quantities of money placed in his control.

We think the evidence overwhelmingly suggests that SENS is not just pseudoscience of life span extension, it is the archetype. We believe that all of the characteristics of "the Proposer" in our list apply to Aubrey de Grey, including the false claim of a monolithic "mainstream" in unjust opposition to SENS, and the challenge to "prove me wrong" in the absence of compelling supporting evidence for the claims of SENS. This "SENS Challenge" is itself part of the pseudoscience archetype, and it is simply a culmination of ongoing challenges made by Aubrey de Grey to opponents of SENS to prove him wrong. This is a classic attempt to subvert the scientific process, it is known to be typical of pseudoscience, and it is described as such in Dr. Friedlander's book, which predates SENS by several years (p.46, [4]).

We submit this critical challenge to pseudoscience in general, and to SENS in particular, as dispassionately as possible. We agree with the 28 respected scientists who recently signed a letter that describes the SENS agenda as "pretense" [48]. We do not suggest that Aubrey de Grey doubts SENS is legitimate science or engineering; we simply state that SENS is not legitimate science or engineering, and Aubrey de Grey's beliefs on the matter are irrelevant. This principle is generally applicable to pseudoscience, and many experts and historians agree that Velikovsky,

Lysenko, and other notable practitioners of agenda/ideology-driven pseudoscience, were, and are, very likely convinced of the soundness of their ideas; furthermore, adherents of such ideas tend to have deep and absolute conviction [4]. However, the scientific endeavor is far more important, and integrity in science more precious, than the ideologies, wishful thinking, or self-deceptions of any individual or group. We apply this principle to all, including Aubrey de Grey, and ourselves.

REFERENCES

1. de Grey, A., *Strategies for Engineered Negligible Senescence (SENS): A practical way to cure human aging*. 2006: http://www.gen.cam.ac.uk/sens/.
2. de Grey, A.D., et al., *Time to talk SENS: critiquing the immutability of human aging.* Ann N Y Acad Sci, 2002. **959**: p. 452-62; discussion 463-5.
3. de Grey, A.D., *'We will be able to live to 1,000'*, *http://news.bbc.co.uk/1/hi/uk/4003063.stm*. 2005.
4. Friedlander, M.W., *At the Fringes of Science*. 1998: Westview Press. 202.
5. Park, R.L., *Voodoo Science*. 2000, New York, NY: Oxford University Press. 230.
6. Sagan, C., *The Demon-Haunted World: Science as a Candle in the Dark*. 1996, New York, NY: Random House. 457.
7. Coker, R., *Distinguishing Science and Pseudoscience*. 2001.
8. de Grey, A.D., *An engineer's approach to the development of real anti-aging medicine.* Sci Aging Knowledge Environ, 2003. **2003**(1): p. VP1.
9. de Grey, A.D., *SENS web site, http://www.gen.cam.ac.uk/sens/just7.htm*. 2005.
10. de Grey, A.D., et al., *Medical bioremediation: prospects for the application of microbial catabolic diversity to aging and several major age-related diseases.* Ageing Res Rev, 2005. **4**(3): p. 315-38.
11. de Grey, A.D., *Whole-body interdiction of lengthening of telomeres: a proposal for cancer prevention.* Front Biosci, 2005. **10**: p. 2420-9.
12. White, L.K., W.E. Wright, and J.W. Shay, *Telomerase inhibitors.* Trends Biotechnol, 2001. **19**(3): p. 114-20.
13. Shay, J.W. and W.E. Wright, *Telomerase: a target for cancer therapeutics.* Cancer Cell, 2002. **2**(4): p. 257-65.
14. Shay, J.W. and W.E. Wright, *Mechanism-based combination telomerase inhibition therapy.* Cancer Cell, 2005. **7**(1): p. 1-2.
15. Gray, R.E., et al., *Allotopic expression of mitochondrial ATP synthase genes in nucleus of Saccharomyces cerevisiae.* Methods Enzymol, 1996. **264**: p. 369-89.
16. Oca-Cossio, J., et al., *Limitations of allotopic expression of mitochondrial genes in mammalian cells.* Genetics, 2003. **165**(2): p. 707-20.
17. Guy, J., et al., *Rescue of a mitochondrial deficiency causing Leber Hereditary Optic Neuropathy.* Ann Neurol, 2002. **52**(5): p. 534-42.
18. de Grey, A.D., et al., *Total deletion of in vivo telomere elongation capacity: an ambitious but possibly ultimate cure for all age-related human cancers.* Ann N Y Acad Sci, 2004. **1019**: p. 147-70.
19. Blasco, M.A., et al., *Telomere shortening and tumor formation by mouse cells lacking telomerase RNA.* Cell, 1997. **91**(1): p. 25-34.
20. Rudolph, K.L., et al., *Longevity, stress response, and cancer in aging telomerase-deficient mice.* Cell, 1999. **96**(5): p. 701-12.

21. Chang, S., C. Khoo, and R.A. DePinho, *Modeling chromosomal instability and epithelial carcinogenesis in the telomerase-deficient mouse.* Semin Cancer Biol, 2001. **11**(3): p. 227-39.
22. Wong, K.K., et al., *Telomere dysfunction impairs DNA repair and enhances sensitivity to ionizing radiation.* Nat Genet, 2000. **26**(1): p. 85-8.
23. Sarin, K.Y., et al., *Conditional telomerase induction causes proliferation of hair follicle stem cells.* Nature, 2005. **436**(7053): p. 1048-52.
24. O'Hagan, R.C., et al., *Telomere dysfunction provokes regional amplification and deletion in cancer genomes.* Cancer Cell, 2002. **2**(2): p. 149-55.
25. Lee, H.W., et al., *Essential role of mouse telomerase in highly proliferative organs.* Nature, 1998. **392**(6676): p. 569-74.
26. Warburton, S., et al., *Examining the proteins of functional retinal lipofuscin using proteomic analysis as a guide for understanding its origin.* Mol Vis, 2005. **11**: p. 1122-34.
27. Porta, E.A., *Pigments in aging: an overview.* Ann N Y Acad Sci, 2002. **959**: p. 57-65.
28. Barrett, A.J., N.D. Rawlings, and J.F. Woessner, *Handbook of Proteolytic Enzymes*. 1998, London: Academic Publishers.
29. Dolle, M.E., et al., *Distinct spectra of somatic mutations accumulated with age in mouse heart and small intestine.* Proc Natl Acad Sci U S A, 2000. **97**(15): p. 8403-8.
30. Dolle, M.E., et al., *Rapid accumulation of genome rearrangements in liver but not in brain of old mice.* Nat Genet, 1997. **17**(4): p. 431-4.
31. Dolle, M.E., et al., *Mutation accumulation in vivo and the importance of genome stability in aging and cancer.* Results Probl Cell Differ, 2000. **29**: p. 165-80.
32. Dolle, M.E., et al., *Mutational fingerprints of aging.* Nucleic Acids Res, 2002. **30**(2): p. 545-9.
33. Vijg, J. and M.E. Dolle, *Large genome rearrangements as a primary cause of aging.* Mech Ageing Dev, 2002. **123**(8): p. 907-15.
34. Hasty, P., et al., *Aging and genome maintenance: lessons from the mouse?* Science, 2003. **299**(5611): p. 1355-9.
35. de Grey, A.D., *Foreseeable and more distant rejuvenation therapies.* Aging Interventions and Therapies, pp. 379-395., ed. S.I.S. Rattan. 2005: World Scientific.
36. Bennett-Baker, P.E., J. Wilkowski, and D.T. Burke, *Age-associated activation of epigenetically repressed genes in the mouse.* Genetics, 2003. **165**(4): p. 2055-62.
37. Fraga, M.F., et al., *Epigenetic differences arise during the lifetime of monozygotic twins.* Proc Natl Acad Sci U S A, 2005. **102**(30): p. 10604-9.
38. Martin, G.M., *Epigenetic drift in aging identical twins.* Proc Natl Acad Sci U S A, 2005. **102**(30): p. 10413-4.
39. Lu, T., et al., *Gene regulation and DNA damage in the ageing human brain.* Nature, 2004. **429**(6994): p. 883-91.
40. de Grey, A.D., *Like it or not, life-extension research extends beyond biogerontology.* EMBO Rep, 2005. **6**(11): p. 1000.
41. *The Institute of Biomedical Gerontology (IBG)*. 2006: http://www.methuselahfoundation.org/.

42. de Grey, A.D., *Biologists abandon Popper at their peril.* Bioessays, 2000. **22**(2): p. 206-7.
43. Brownlee, M., et al., *Aminoguanidine prevents diabetes-induced arterial wall protein cross-linking.* Science, 1986. **232**(4758): p. 1629-32.
44. Makita, Z., et al., *Hemoglobin-AGE: a circulating marker of advanced glycosylation.* Science, 1992. **258**(5082): p. 651-3.
45. Stevens, V.J., et al., *Nonenzymatic glycosylation of hemoglobin.* J Biol Chem, 1977. **252**(9): p. 2998-3002.
46. Nuland, S., *Do You Want to Live Forever?*, in *Technology Review*. 2005. p. 36-45.
47. de Grey, A.D., *Resistance to debate on how to postpone ageing is delaying progress and costing lives. Open discussions in the biogerontology community would attract public interest and influence funding policy.* EMBO Rep, 2005. **6 Spec No**: p. S49-53.
48. Warner, H., et al., *Science fact and the SENS agenda.* EMBO Rep, 2005. **6**(11): p. 1006-8.