The Impracticality of Biomedical Rejuvenation Therapies: Translational and Pharmacological Barriers

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Abstract

Editor's Note: A response to this article from Aubrey de Grey, Editor-in-Chief, can be found on pages 397–400 in this issue.

The notion that it is possible to eradicate age-related degeneration and live a life with a negligible rate of senescence solely by using a physical “repair-oriented” approach is flawed on a number of fronts. Here, I will argue that there are so many unknown variables embedded in this line of thinking that make the final result impossible to predict. Two relatively easy-to-research areas are the search for successful cross-link breakers and an effective lysosomal degradation therapy. A more complex and speculative strategy is whole-body interdiction of lengthening of telomeres (WILT). Highlighting these as examples, I argue that it is unlikely that such rejuvenation biotechnologies will be used meaningfully by the general public. The discussion assumes that although such therapies may in theory one day be developed in the laboratory, and even possibly be formulated as physical clinical therapies, these will be unusable in practical terms when applied upon humans at large. Due to inherent characteristics of our biological, evolutionary, and psychological heritage, it is implausible that curing aging will occur by using physical interventions alone.

Introduction

“REPAIR-ONLY” STRATEGIES ARE EXEMPLIFIED by the SENS (Strategies for Engineered Negligible Senescence) model.¹ This concept proposes that, as we age, we accumulate seven different types of tissue damage that result in degeneration and age-related dysfunction. The notion crucially suggests that it may be possible to devise biotechnological (artificial) regenerative therapies that can repair this damage and thus significantly reduce the risk of degeneration and chronic disease.²

I have informally outlined elsewhere why I think that an effective therapy aiming to reverse or eliminate the deleterious effects of aging will not be a physical one.^{3,4} Physical repair-only therapies fail to address the human body as a complex adaptive system, ignore emergent phenomena and self-organizational properties, and take no account of entropy or the “direction” of evolution. These types of interventions are bounded by Newtonian mechanics and suffer all the shortcomings of a reductionist philosophy. However, for the sake of argument I am willing to theoretically accept that one day it may be possible to develop repair-only therapies for use by humans, and I will examine the practicalities of administering such treatments in clinical settings.

Clinical physicians are very aware of the risks, side effects, and shortcomings of the medications currently in use. With respect to developing rejuvenating therapies against age-related degeneration, it appears that, while there is ongoing research aiming at identifying specific agents that may have an effect on each and every one of the seven types of damages involved in the repair-only rationale, there is no consideration of the pharmacological or clinical consequences of this research. The SENS approach refers to seven types of damage, and thus it implies at least seven types of separate treatments. In reality, it is certain that there would be a much higher number of such hypothetical distinct treatments, perhaps 20 or 30 (taking into account secondary therapies used to address the adverse effects of the proposed primary therapies). It is well recognized that individual drugs have certain effects that cannot easily be predicted when these drugs interact with other therapeutic agents. For instance, it is known that the pharmacodynamics of complex therapies follow nonlinear rules.⁵ The concentration, elimination rate, and dosage of drugs obey the laws of dynamical systems, and in the case of the Concentration and Effect, the loop plot can be given by⁵:

$$E = \frac{D \cdot E_{\max}(e^{-k_{10}t} - e^{-kEt})}{CE_{50} \cdot V(k_{10} - kE) + D(e^{-k_{10}t} - e^{-kEt})}$$

$$\text{and } C = \frac{D}{V} \cdot e^{-k_{10}t}$$

where E =effect, $E_{\max}$ =maximum effect, C =concentration, D =dose, V =volume of distribution, k_{10} =elimination rate constant, kE =effect side dissipation constant, t =time, and $CE50$ =the concentration at which the 50% of the maximum effect is observed.

This loop plot describes the reciprocal nonlinear relationships involved in the increases of the drug concentration and its expected effect. Considering that in the repair-only approach there is reference to many (certainly more than seven) different therapeutic strategies, the final therapeutic effect (Ef) of all the strategies taken together is given by:

$$Ef = E^n$$

where n is at least seven, and probably nearer to 20–30.

Nonlinearity implies that the output of a system is not necessarily proportional to the input, and systems may display classical chaotic behavior that is impossible to calculate.⁶ The complete lack of knowledge regarding these interactions makes the entire repair-only concept vulnerable to further criticism. There is no discussion, not even in tentative theoretical terms, about the frequency of the intervention and its duration. It is most likely that these putative interventions will have to be repeated regularly, but the regularity and timings remain unknown variables. By definition, the duration of the treatment must be indefinite, but the periodicity of its application is poorly described. If the time intervals of this periodicity are short (perhaps a matter of hours or days), then this will make the therapy impractical to administer. If such a therapy exists but it is impractical for the general public to use, then the therapy is essentially useless. I will further highlight these concerns through three representative examples.

The Lysosomal Degradation Example

One repair methodology is to use enzymes to degrade intracellular material that cannot be eliminated by the aging lysosomes.⁷ Such a therapy would involve identifying enzymes that can break down and digest waste material (such as lipofuscin, for example), with the ultimate aim of administering these enzymes to humans. Examples of proof-of-principle include the existing "enzyme replacement therapy" in the case of lysosomal storage disorders such as Gaucher's disease.⁸ However, the practical applications of this treatment remain highly problematic. For instance, the use of enzyme replacement therapy with Imiglucerase as a therapy for Gaucher's disease involves 2-hr sessions of intravenous administration of the compound, which need to be repeated every 2 weeks, at a cost of \$200,000 per patient per year.^{9,10} Even so, the treatment is a replacement of a missing enzyme and not a total repair of the defective gene. Furthermore, the case of Gaucher's disease implicates just one gene mutation, a recessive gene on chromosome 1, whereas in the case of aging there are several mutations that need to be addressed, on many chromosomes, and this makes enzyme replacement therapy even more complicated.

In any case, another problem with regard to this particular example is the consideration of the need to eliminate "junk" material such as lipofuscin. It has been suggested that lipofuscin can help express lysosome-stabilizing factors and im-

prove the viability of the lysosome under stress, acting like a hermetically useful agent.¹¹ A complete elimination of lipofuscin through a putative future pharmacological agent would have negative repercussions upon the function of the lysosome.

Regarding the duration and frequency of administration, a broad-comparison counter argument could be made with people who are, for example, on dialysis and have to endure protracted intravenous interventions several times a month. Statistics show that 260,000 people are in this position in Europe and approximately 400,000 in the United States,¹² perhaps a total of 4 million worldwide or 0.05% of the Earth's population. This is a relatively small percentage, and the logistics of the treatment are easy to assimilate by the health system. But if we assume that a theoretical 10% of humanity would need have access to the rejuvenating treatments to make these worthwhile, the logistical and practical difficulties would be multiplied by a factor of 200 compared to the dialysis example, and will thus result in significantly more problems with the administration of the treatment.

The Example of Cross-Link Breaker

Another area of research based on the repair-only methodology is the identification and administration of substances that can remove cross-links. A typical example is the case of ALT-711 (Alagebrium) developed by the Alteon Corporation. Although this compound initially showed effective reduction of systolic blood pressure through cleavage of the cross-links between carbohydrates and collagen, the therapeutic effect was *a priori* destined to fail due to the fact that the reaction was based upon an autocatalytic principle. In other words, as the methyl groups of 4,5-dimethyl-3-(2-oxo-2-phenylethyl)-thiazolium chloride (ALT-711) were made available to cleave the carbohydrate-protein bond, the resulting adduct compound was then released and was free to re-interact with other free carbohydrate molecules, so the cross-links were again reformed.¹³ This is was a typical repair-only example that dealt with one type of damage, without ensuring long-term cure (*i.e.*, the elimination of the cause of the damage). The fact that economic factors were mentioned as the main reason for the discontinuation of this product is another testament to the weakness of the repair-based rationale.

Another target for cross-link cleavage is glucosepan. In this case, development of an enzyme or similar compound sounds a promising way forward. However, on the whole, there is little clinical information on this product,¹⁴ making it difficult to suggest concrete therapies that can deal with this particular compound. This is confounded further by the fact that there are other cross-link compounds that will have to be eliminated,¹⁵ and it is evident that a wide range of cross-link breaker therapies need to be developed.

More Speculative Therapies

If one examines the case of more speculative therapies such as WILT and stem cell therapies, which play an integral part in the repair-only paradigm, more problems become evident. I will not provide a full criticism of these proposed therapies, but it may be useful to examine some typical examples. To induce elimination of cells (so that these can subsequently be replaced with stem cells), there would be a need to use chemotherapeutic agents such as:

1. Temozolomide-type therapies.¹⁶ These are currently administered in a highly complicated manner both orally and intravenously, depending on a wide number of variables.¹⁷
2. Prochymal-type therapies (Remestemcel-L). These are given by intravenous infusion at weekly intervals. Initial reports indicate that this is safe, but the long-term effects are unknown.¹⁸

Even if the therapy proves technically successful, it is pharmacologically and practically difficult. How likely is it that the public at large will visit a clinic for regular weekly infusions, in addition to the weekly infusion required for the lysosomal therapy mentioned above? It can be argued that these infusions can be administered together in the same solution, which opens new questions about possible interactions, destabilization of the components, increased risk of side effects, etc. In addition, WILT-type therapies can only be effective if used in association with other treatments that address age-associated decline.¹⁶ In other words, each proposed treatment may work efficiently only if the other treatments are also effective. In these examples, I highlight the difficulties in dealing with nonlinear systems, where dependence on the initial conditions can make the system entirely unpredictable.

Even if softer modalities of administration are developed, such as nanoparticle inhalation deliveries or transdermal motifs, the risk of toxicity or side effects will remain. Nanoparticles could translocate from the lung into the blood, resulting in systemic exposure and toxicity of internal organs. In addition, nanoparticles may employ the neuronal uptake route, and this too can result in systemic exposure. Vascular toxicity and thrombosis were observed.¹⁹ Inflammatory biomarkers such as interleukin-1 α and tumor necrosis factor- α were increased in the brain of mice that were exposed to therapeutic nanoparticles.²⁰

Oberdörster et al.²¹ demonstrated a significant increase of neuronal lipid peroxidation and mild glutathione depletion in fish after exposure for 48 hr to fullerene nanoparticles. These unknown variables remain a problem, although not an insurmountable one. However, translational research can add extra decades onto the current predictive time scales. Furthermore, issues of noncompliance are likely to remain as described below, and we are not in any position to provide answers about the safety profile. According to De Jong and Borm²²:

Up to recently it was not realized that these carrier systems themselves may impose risks to the patient. The type of hazards that are introduced by using nanoparticles for drug delivery are beyond that posed by conventional hazards imposed by chemicals in delivery matrices. However, so far, the scientific paradigm for the possible (adverse) reactivity of nanoparticles is lacking and we have little understanding of the basics of the interaction of nanoparticles with living cells, organs and organisms. A conceptual understanding of biological responses to nanomaterials is needed to develop and apply safe nanomaterials in drug delivery in the future.

Noncompliance Issues

The fact that an effective therapy against aging may theoretically be developed in the laboratory does not necessarily align with the actual use of this therapy by the public. It is well known that noncompliance is a widespread

problem in medicine²³ and, even in life-threatening conditions, the use of life-saving therapies can be suboptimal.²⁴ For example, it was shown that only 75% of coronary heart disease patients take sufficient medicine for it to be effective.²⁵ An example comparable to therapies for aging rejuvenation is that of antiretroviral medication that can save a patient from certain death from acquired immunodeficiency syndrome (AIDS). In this case, it was found that up to 37% of patients may be noncompliant.²⁶ Another study shows that suboptimal adherence may be a problem in 50% of patients.²⁷

Worsening compliance is proportional to the number of drugs taken.²⁸ It is also inversely proportional to the number of times a patient has to take the therapy each day. If a patient has to take the medication once a day, the average compliance rate is 80%. This drops to 50% for those who have to take their medication four times a day.²⁹ However, there are several other predictors of noncompliance, all of which add unknown variables to the problem (Table 1).

Devising strategies for improving adherence to medication is a complex issue in itself. Steiner³⁷ quotes:

Adherence is a set of interacting behaviors influenced by individual, social, and environmental forces; adherence interventions must be broadly based, rather than targeted to specific population subgroups; and counseling with a trusted clinician needs to be complemented by outreach interventions and removal of structural and organizational barriers. To achieve the adherence goals, front-line clinicians, interdisciplinary teams, organizational leaders, and policymakers will need to coordinate efforts...

The deeper reasons for nonadherence to life-saving medication are difficult to understand. We are bound by Darwinian constraints that assure the survival of the species. Subconsciously, we may downgrade the significance of our own death as long as the survival of the species is assured. Therefore, we are less motivated to take medication, even when this medication is going to keep us alive for longer. It is a primeval instinct hardwired in our genome. This counterintuitive *Todestrieb* or "death-drive"³⁸ is rooted in the Freudian *id* and buried under several layers of evolutionary psychological defense mechanisms. It is not

TABLE 1. MAJOR PREDICTORS OF NONADHERENCE³⁰

Psychological problems , particularly depression, and also cognitive impairment which is common in older people who would be candidates for treatment with rejuvenation biotechnologies ³¹
Asymptomatic disease , which would be an issue in younger healthy people who enroll for the treatment ³²
Side effects of the medication , likely to be several, as a wide range of therapeutic interventions will be deployed ³³
Administrative issues , such as inadequate follow-up or discharge planning, poor relationship between patient and provider, missed appointments, lack of health insurance, and cost ³⁴
Complexity of the treatment , ³⁵ another significant problem, as the suite of rejuvenation treatments is likely to be substantial, in addition to the complicated frequency of the dispensation of the regime.
Length of treatment , ³⁶ likely, by definition, to be several centuries!

intentional or based on a conscious decision, and it does not depend on logic. Both the desire to live and create and the desire to die and decompose coexist within our subconscious³⁹ and can manifest in different ways, one of which may explain the nonadherence to life-saving medication.⁴⁰ Finding ways to deal with this aspect of death-drive (*i.e.*, in this case, noncompliance) is likely to be as difficult as finding ways to diminish human aggression, which is another fundamental characteristic of the death-drive.⁴¹

Other Significant Obstacles

Polypharmacy and interactions

Co-morbidities would create a complex problem with the expected effects of the therapy. What would be the impact of any given pre-existing illness upon the effectiveness of any (or all) of the therapies proposed by the repair-only methodology? A pre-existing illness such as, for example, liver or renal disease, may interfere with the pharmacodynamics of the therapy in any specific individual, and the coexistence of depression, dementia, or other age-related degeneration will impact upon the therapeutic application. Age-related molecular changes cause biological and pharmacological effects that not only cannot easily be predicted, but have not even yet been studied sufficiently.⁴² The fact that several discrete rejuvenation therapies need to be co-administered at repeated intervals would exacerbate all the known problems associated with polypharmacy.⁴³

If we assume that an effective therapy suite based on engineered negligible senescence is available, it will need to be tested repeatedly in two separate broad groups. The first would be the "younger" healthy group, arbitrarily defined up to the age of 60. The intervention would, on the whole, aim to prevent future degeneration, and it will not be therapeutic. The second group would be the over 60s age group likely to have several co-morbidities, such as existing age-related illnesses that need "curing." Extrapolating risk-benefit ratios is notoriously difficult when we compare young/healthy individuals with older/ill ones.⁴⁴ The effectiveness and adverse effects of the putative treatment would need to be assessed both in a preventative setting and a curative one. In theory, this would not be a difficult endeavor, but it would certainly involve additional years, perhaps decades, to the time scale before it can be released for public use.

Tolerance and adaptation

In medicine, we consider three aspects of a condition: The primary cause, the damage resulting from this cause, and the final consequences resulting for this damage. In the case of an infection, for instance, the cause is the bacterium, the damage is the immunological and microanatomical changes, and the consequences are the clinical symptoms, such as sore throat or cough. In aging, the cause is the evolutionary necessity for sexual reproduction and hence the imbalance of resource allocated for repairs.⁴⁵ The damage is the actual organismal changes broadly described by the seven areas of SENS, and the consequences are all the clinical manifestations of age-related degeneration such as dementia, arthritis, etc. Clearly, the elimination of the primary cause is the gold standard of medicine, and repair of the damage or of its consequences are only of secondary importance. Without

eliminating the primary cause, the organism attempts to adapt to the extraneous repair therapies and, through mainly epigenetic mechanisms, it may develop tolerance to these external therapies. An example here is levodopa, in the case of Parkinson's disease, where this rejuvenating compound, which essentially replenishes dopamine/repairs the dopaminergic neurons, can have initial positive effects but, with prolonged use, the effects wane.⁴⁶ The mechanisms of tolerance are poorly understood but remain a problem and need to be addressed, otherwise the intended therapy may gradually become less effective.

Persistence of background damage and network dysfunction

As mentioned above, the repair-only methodology, by definition, is concerned with the repair of the age-related damage and ignores the cause. It also assumes that after the repair, the clinical consequences will be positive. However, this approach does not take into consideration any effects at the interface between the cause and the damage. By repairing the damage, the cause remains untouched and it continues to generate more damage.⁴⁷ If the primary cause of aging remains untreated, it will continue to fuel the damage, a fact that necessitates repetitive (and uninterrupted) therapeutic interventions. The ongoing anatomical, morphological, and structural alterations to the human body resulting from a repeated and ongoing repair therapy are not known. The background evolutionary forces that cause the age-related damage will continue to affect the body indefinitely, and the putative pharmacological therapy will need to be applied perpetually.

What would be the consequences of this repeated and protracted onslaught of damage-repair agents upon the fundamental structure of the body? Engineered modification of groups of molecules or cells is bound to have an effect upon the collective three-dimensional spatial configuration (and, thus, function) of other cell groups.⁴⁸ Random errors and unforeseen new damage can be multiplied with each treatment session and may accumulate, resulting in alteration of the entire network dynamics and eventual dysfunction. Cells and macromolecules are part of complex networks that are tightly regulated. Signaling cascades are fine-tuned and depend on the topology of the network; therefore, the coordination of control mechanisms can be difficult, particularly (for example) with initiation and control of apoptosis.⁴⁹ The nested hierarchies with respect to macromolecules, cells, organs, and organisms are governed by network rules that are not easy to foresee, and compensatory activation or deactivation of system components can be triggered even by trivial perturbations.⁵⁰

Discussion

Because the human organism is a complex adaptive system,⁵¹ the repair-only concept that relates to it is governed by the cybernetic principle of downward causation, which states that: "all processes at the lower level of a hierarchy are restrained by and act in conformity to the laws of the higher level."⁵² Therefore, the repair of the individual components is constrained by laws originating at higher, organismic, or global levels. It will be difficult to calculate the effects of artificial agents upon the body by just

considering the individual components of the organism. The properties of any therapeutic agent will not always be additive because new rules emerge at each higher level (from macromolecules to cells, organism, and society). Due to the inherent complexity and nonlinearity of biological systems, a minor manipulation of a macromolecule can have profound effects on the entire organism, and the dynamics of this are intricate.⁵³ That is why the rate of success of drugs in clinical trials is just 19%.⁵⁴ Furthermore, the initial damage caused by an age-associated mechanism may result into cascading effects which cannot be reversed simply by repairing this initial damage.⁵⁵ Campbell and Albert⁵⁶ highlight these difficulties very succinctly:

... Reversing the damage and returning the network to its original state clearly obviates the need for additional repair. However, these approaches are often unrealistic in a practical sense. One alternative approach involves compensating for network damage by fixing the state of one or more initially unaffected nodes...e.g. through gene manipulations, constitutive activation, or pharmacological interventions. However, these modifications have an effect on every signalling component with which the targeted component interacts; in many cases, the deleterious effects of an intervention supersedes the intended benefit...Clearly, directly inducing widespread modifications to expression levels of many regulatory components, or of the interactions between many such components, can be problematic.

When research is being undertaken to identify a repair factor, there must be some consideration about the translational issues and future practicalities associated with this treatment. Otherwise the basic research remains unusable. Not only that, but the applied clinical and pharmacological considerations will add several decades to the original estimates of the realization of a putative publicly available treatment.

In practical terms, there are so many variables, each with a set of nested subvariables, which render the system to behave in a chaotic (nonlinear, nondeterministic) fashion, whose outcome cannot be predicted because it depends on the initial condition of a large number of parameters. A system must be viewed as a whole entity and not a simple combination of its individual parts. The worldview that solutions to the aging problem are simply a matter of damage repair depends on a highly complex group of a large number of open and unsolvable equations. Even if a treatment is indeed discovered, it is unlikely that this will be of any useful practical application to large sections of humanity.

Despite the belief that the introduction of therapies for negligible senescence will be incremental, it is tempting to follow an idealistic stance and expect that a sudden breakthrough in technology will accelerate the pace and provide hitherto unknown therapeutic benefits. After all, for example, until September, 1928, people were dying helplessly from bacterial infections and no one could have predicted that a certain Alexander Fleming would have made such an important discovery that changed the face of medicine. However, it is unlikely that a similar scenario will be repeated with regard to aging. In the example of the antibiotics, the action was effective because it was directed at the actual cause of the problem, *i.e.*, the destruction of the bacterium. It was not directed at repairing the damage caused by it. By contrast, in the case of aging, rejuvenating biomedical therapies are directed at the consequences and not the cause of the damage

itself. In a repair-only approach, such a root cause will remain an uncontrolled perpetual problem, as mentioned above.

Conclusion

It is legitimate to accept that a certain degree of speculation should be involved in our search for a cure of age-related degeneration. Nevertheless, this speculation must be informed and realistic. It must be based upon models of our existing knowledge, and be extrapolated from these models in a constructive, practical, and feasible manner. Over-optimistic speculation has no practical value in clinical sciences. This is not to say that aging is untreatable. However, our method must match the enormity of our task, and as this enormity is very complex, we must deploy a vastly complex approach.

When considering the best-case scenario, the repair-only methodology involves the *de novo* discovery of at least seven different types of therapeutic agents and at least seven different vehicles of administration of these therapeutic agents. It needs to address at least 823,543 (*i.e.*, 7⁷) possible interactions with each and every such agent, deal with issues of cost, noncompliance, the impact of the therapies upon the fundamental network structure of the organism, the perpetual duration of the treatment, inherent psychological barriers, and evolutionary complexity/emergent concerns. Bearing in mind that after many decades of research we have not yet solved even one of these obstacles, the suggestion that we will soon be able to use practical strategies for engineered rejuvenation in humans is dangerously close to the level of science fiction.

The search for physical biomedical technologies that are effective in annulling the process of senescence in humans in a clinical setting is unlikely to become reality. Negligible senescence will not be achieved through something physical. Believing otherwise is more an idealistic alchemist's dream than pragmatic cold reality. This search suffers from an observational bias and is typical of the "streetlight effect."⁵⁷ It is analogous to the parable, where Nasreddin Hodja lost his front door key while walking home on a very dark night.⁵⁸ He went under a street light and started looking for it with great tenacity and determination. "Are you sure you dropped it here?" a neighbor asked. "No," said the Hodja, "I didn't drop it here." "So why are you looking for it here?" exclaimed the neighbor. The Hodja replied, "Don't be silly! I am not going to look for it in the dark. I am looking for it here where there is more light!"

In our effort to defy aging, the repair-only paradigm looks for answers where it is conceptually easy to look. Perhaps, it may now be the time to acknowledge that the answer lies elsewhere.^{59–61}

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