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The machine-like repair of aging. Disentangling the key assumptions of the SENS agenda

(Reparar el envejecimiento como una máquina. Desenredando las asunciones clave de la agenda SENS)

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ABSTRACT: The possibility of curing aging is currently generating hopes and concerns among entrepreneurs, experts, and the general public. This article aims to clarify some of the key assumptions of the Strategies for Engineered Negligible Senescence agenda, one of the most prominent paradigms for rejuvenation. To do this, we present the three fundamental claims of this research program: (1) aging can be repaired; (2) rejuvenation is possible through the reversal of all molecular damage; (3) and the human organism is a sophisticated machine. Secondly, we argue that this agenda fits with a machine conception of the organism (described by Daniel Nicholson); we show that, if aging is understood from this philosophical approach, there is an internal confusion in the research program between what is repair and what is rejuvenation. Finally, we state that this theoretical viewpoint connects with scientific criticism and reinforces the idea that there are limits to the aspirations to live indefinitely young.

KEYWORDS: aging, machine, repair, rejuvenation, Strategies for Engineered Negligible Senescence.

RESUMEN: *La posibilidad de curar el envejecimiento está suscitando actualmente tanto esperanzas como reservas entre los emprendedores, expertos y el público general. Este artículo se propone clarificar algunas de las asunciones clave de la agenda de las Estrategias para la Ingeniería de la Senectud Inapreciable (Strategies for Engineered Negligible Senescence, SENS). Con este fin, presentamos las tres tesis principales de este programa de investigación: (1) el envejecimiento puede ser reparado; (2) el rejuvenecimiento es posible mediante la reversión del daño molecular; (3) y el organismo humano es una máquina sofisticada. En segundo lugar, argumentamos que esta agenda se ajusta a la concepción de los organismos como máquinas (descrita por Daniel Nicholson). Mostramos que, si el envejecimiento se entiende desde este enfoque, hay una confusión interna en este programa de investigación entre la noción de reparación y la de rejuvenecimiento. Finalmente, señalamos que esta perspectiva teórica conecta con objeciones científicas a SENS y refuerza la idea de que hay límites a las aspiraciones de vivir jóvenes indefinidamente.*

PALABRAS CLAVE: envejecimiento, máquina, reparación, rejuvenecimiento, Estrategias para la Ingeniería de la Senectud Inapreciable.

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1. Introduction

The desire for a healthier, longer, and more vigorous life is a dream as old as the Epic of Gilgamesh. Modern scientific-technical advances changed this scenario by making the dream seem achievable. Molecular biology discoveries and new biotechnology innovations have replaced magic and miracles, and they now apparently guide research directly toward well-established goals. The scientific discussion on the possibility of curing aging—developed by authors such as Aubrey de Grey or David Sinclair, among others—has increased exponentially in the last twenty years, raising hopes and concerns among entrepreneurs, experts, and the general public. The search for the Fountain of Youth has become the biomedical paradigm to defeat aging (Sinclair & LePlante, 2019). The leaders of this crusade promise that it is just the beginning of radical life extension and the end of (many) diseases. The mantra is that "the first person to live to be 1,000 years old is alive today" (de Grey & Rae, 2007, p. 325).

According to de Grey, we have a 50% chance of bringing human aging[1]—a percentage that he bases on the hopes of geroscience, but also on the scientific-technological limits of this discipline—under what he calls a decisive level of biomedical control within the next three decades. This research program is well-known as the Strategies for Engineered Negligible Senescence (SENS) (de Grey *et al.,* 2002). Having developed this paradigm over many years, de Grey and colleagues are now trying to transfer the new discoveries to the clinical practice setting. They consider it a challenge, but not an impossible one, given the rate of scientific progress in understanding how we age. Just two centuries ago, the average life expectancy was 40 years in the most developed countries. Improvements such as antibiotics, balanced diets, cleaner drinking water, low child and maternal mortality rates, and vaccines, among others, have lead the way toward a new age of health and longevity (Vijg & de Grey, 2014, p. 374; Oeppen & Vaupel, 2002). We have added years to life, and we die much later—besides adding years to life we have achieved greater vigor and vitality. However, today, we still suffer from aging and death finally comes sooner or later to everyone.[2] In the past, all these milestones influenced the trajectory of our expectations from life. The advocates of SENS believe that in the not-too-distant future, we will have broken the limits of the maximum lifespan. We will all live a millennium if that is what we wish for.

Given this scenario, it is significant to examine to what extent the promises of this research program are philosophically and scientifically justified. We need to analyze the key assumptions of the SENS agenda. An objective here is, therefore, to provide the reader with a philosophical evaluation of the claim that we can live young much longer than now, al-

[1] As Maël Lemoine (2020a) rightly point out, the fundamental philosophical question is knowing whether aging is a disease. For reasons of time and space, we will not discuss this topic in this paper. In short, we show that de Grey (2008a, 2013) conceptualizes aging as such and we should medically fight against this problem. Aging is the germ of many age-related diseases and pathologies typically associated with old age. Therefore, we will simultaneously address all of them if we directly address aging. One of us is committed to a more general extension of this sort (Saborido & García-Barranquero, 2022). For a broader theoretical literature see, Bostrom, 2005; Caplan, 2005; de Winter, 2015; Hayflick, 2007; Schramme, 2013.

[2] For further reflection on this matter, see García-Barranquero (2022).

most indefinitely. To achieve this, the paper is divided in three sections. In section 1, we will introduce three fundamental claims of these authors, influenced by the ideas of de Grey: (1) aging can be repaired; (2) rejuvenation is possible through the reversal of all molecular damage; and (3) the human organism is a sophisticated machine. To continue, in section 2, we will shed light on some of the weaknesses of this agenda. We will compare this research program with Daniel Nicholson's description (2013) of machine conception of the organism. From our point of view, the most crucial criticism of this promise is that it fluctuates between two different research goals with internal confusion in its research program. We will discuss this confusion by showing that, on the one hand, its research goal is impossible within its set of proposed interventions, while, or, on the other hand, even if the SENS plan worked, the result would not be as expected. That is, if they conceptualize the human organism as a sophisticated machine, it is philosophically very debatable that one can live young and almost indefinitely. Finally, in section 3, we will confront our conclusions with the skepticism that SENS generates in the rest of the scientific community on aging studies. Notably, there are widespread doubts due to the lack of empirical evidence and contrasted data offered by this agenda. This skepticism connects with Jeremy Howick and collaborators' analysis (2013) of the limits of mechanisms. Following this framework, we will focus on the current knowledge we have of a particular hallmark— telomeric shortening. The limits we will discuss are: first, our understanding of mechanism A may be incomplete or erroneous. Second, mechanism A may have favorable results when manipulated under particular conditions in a laboratory, but may not be extrapolated to this success in clinical practice. Third, mechanism A may behave paradoxically and have adverse and unknown side effects. Therefore, this paper provides a new critique of those promises of rejuvenation.

2. A scientific model for repairing aging

Nowadays, in the 21st century, a large percentage of the population of the most developed countries suffer the ravages of aging—age-related diseases as arthritis, cancer, dementia, osteoporosis, or other pathologies and processes that reduce physical and mental capacities. Many of us forget, that even with the improvements in vigor and vitality reviewed above, most people's last years of life are often marked by fragility, sickness, and vulnerability. Some geroscientists insist that we must stop this "horror show" whereby our health declines over time, and our longevity is greatly limited in order to develop the type of life we want (Grey & Rae, 2007, p. 10). According to advocates of extended life, there are no logical reasons why we should accept this, and we must realize that this is a bad thing for us—and for those around us. Aging is one of the most important problem of our time and, they claim, it is no longer a total "mystery" (cf. Medawar, 1952). With biotechnology trying to liberate us from our own chains, we ask ourselves the following question: how should we address aging now?

Two decades ago, de Grey and colleagues (2002) published the first systematic research program to defeat aging: SENS is a pioneering project that defends the maintenance-repair of the human organism as the best possible approach to promote rejuvenation. For them, a healthy old age for current people in their 80s is not enough. These authors claim that somehow mid-life has to be indefinitely extended through biotechnological interventions.

We should turn back the hands of the molecular clock to the stage of life in which we are in our optimal conditions. SENS understands rejuvenation as recovering the youth's cognitive and physical characteristics in an ad infinitum process.[3] For instance, Michael Hauskeller (2014, p. 100) puts it this way: "rejuvenate the body and bring it back to that stage, in which we are supposed to be at the height of our powers". With other words, Nicholas Agar (2010, p. 86) points out that "the SENS agenda means getting people to stay in the mid-life almost indefinitely and letting them develop the type of life they want in a radically different way than if they did not enjoy this opportunity that (bio)medicine offers them". People can die, but they are not suffering from the same ravages of aging. Therefore, SENS is comprised of two interconnected goals: living healthier and longer than now, almost indefinite.

This research program includes different levels of analysis and intervention. Firstly, it identifies and describes the molecular damage that causes us to age (de Grey *et al.,* 2002, p. 456). The list of hallmarks of aging is composed of: (d1) extracellular aggregates; (d2) cell senescence; (d3) mitochondrial mutations; (d4) diverse lysosomal aggregates; (d5) extracellular aggregates; (d6) extracellular cross-links; (d7) cell loss; (d8) immune system decline; and (d9) hormone secretion decline. Secondly, it proposes some treatments to repair molecular damage (de Grey *et al.,* 2002, p. 456). The list of interventions would depend on the previous damages which would be reversed by: (i1) telomerase gene deletion in quiescent cell types; angio-stasis; autologous vaccines; (i2) ablation of senescent cells; (i3) allotopic expression of normally mtDNA-encoded proteins; (i4) addition of bacterial hydrolase genes; (i5) phagocytosis via immune stimulation; (i6) AGE-breaking small molecules; (i7) stimulated phagocytosis of aggregates; exercise combined with gene therapy; stem cell therapy; growth factor–induced cell replacement; (i8) IL-7-stimulated thymopoiesis; and (i9) genetically engineered muscle. What follows is a general classification of these specific interventions of reversal: (a) replacing cells loss and cell atrophy; (b) reinforcing division-obsessed cells and mitochondrial mutations; (c) removing death-resistance cells and, intracellular and extracellular waste products; and (d) repairing extracellular matrix stiffening. These four R's—replace, reinforce, remove, and repair—are the scientific way to maintain the human organism in optimal conditions.

Last but not least, SENS aims to go back and perform the previous steps again whenever there is molecular damage to the human organism. Its background assumption seems to be that the human organism cannot persist in time by itself—neither precision nor speed is sufficient for the goal of rejuvenation. Ultimately, the human organism wears out over time, and diseases and death appear quickly. The need for rejuvenating interventions suggests that the human organism cannot do this naturally, it is only possible with the achievements of biotechnology. In this vein, de Grey proposes the idea of "longevity escape velocity" (LEV), that is, how the progress of science in reversing the effects of aging in an individual is occurring faster than the aging process itself, which means that the individual could potentially undergo successive rejuvenation interventions almost forever. In short:

> Since we are already so long lived, even a 30% increase in healthy life span will give the first beneficiaries of rejuvenation therapies another 20 years—an eternity in science—to benefit from

[3] For a somewhat different interpretation (Juengst *et al.,* 2003; Wareham, 2016).

> second-generation therapies that would give another 30%, and so on ad infinitum. (de Grey, 2004, p. 725)

SENS thus exposes the possibility of living healthier and longer through its set of proposed interventions. At the same time, it shows how this process can be constantly repeated and developed as soon as better biotechnological innovations and molecular discoveries are available. SENS follows a research program towards what it claims to be (apparently) well-established research goals. The optimism that motivates this attitude relies upon two reasons: (1) the moderate increase in life expectancy during the last centuries, which suggests that life extension is possible; and (2) more developed scientific-technological advances for addressing aging itself (Vijg & de Grey, 2014).[4] For SENS, the scientific progress of the agenda is undeniable, and the advances in its new techniques and treatments are proof of this.

Given the above-mentioned features of the SENS agenda, it seems clear that, while avoiding any attempts to define aging in the first place, SENS seems to be a biotechnology-driven research program to defeat aging. SENS is an engineering approach that seeks a solution to the puzzle of aging. Such a mechanistic viewpoint[5] drives the language its advocates use, such as the four R's we highlighted above (replace, reinforce, remove, and repair). Degenerative processes will only be, therefore, reversed by the list of the proposed nine treatments. Despite the acknowledged extraordinary complexity of aging, such complexity is just perceived in terms of complication and potential waste of time trying to disentangle the dynamics of the aging process in order to explain it. What matters is not studying "why" we age but "how" it happens in molecular terms in order to solve it at this same molecular level (de Grey, 2013).[6] A scientific question such as aging ends up being fundamentally an engineering puzzle. That is why they persistently use an analogy between the human organism and a sophisticated machine to describe their "crusade" to defeat aging, which makes explicit their background assumption in understanding aging as a mechanistic problem. We have only one biological body and it is out obligation to protect it:

> The human body is a machine. As such, we should at least consider the possibility that we could extend the healthy lifespan of a human being in the same ways that we already, successfully use to extend the healthy (i.e., fully functional) lifespan of a man-made machine, such as a car. (de Grey, 2008b, p. 277)

This maintenance-repair approach restores everything that is not working well in the human organism indefinitely in order to stay young. LEV shows how interventions will be

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[4] As we have shown previously, there are decisive improvements in increasing life expectancy. We note that one of the key factors has been the decrease in infant mortality. That is why our population's life expectancy may stagnate for many scientists, among other reasons (see Dong *et al.,* 2016; Milholland & Vijg, 2022). Therefore, we here show the reasons SENS has for its optimism. We value the comments from one of the referees on this issue.

[5] This question will be the core of the article in section 2. We use the term mechanistic in a preliminary way until we analyze its different meanings in biology.

[6] Scientists seeking a cure finally explicitly define aging from their therapeutic interventions (Lemonie, 2020a, pp. 2-3).

more effective than their first versions over the decades. As our healthy life expectancy increases, we will be able to improve geroscience much more than expected. We will not just be buying time but will live indefinitely. We will only die from external causes, such as accidents or homicides.

As this idea of understanding the human organism as a sophisticated machine is quite old and well-known in the history and philosophy of science, we will disentangle the key assumptions (and internal confusions) of this agenda and further address the implications of the mechanistic program of SENS in the next section. We will show that the convergence of the four R's with the intention of rewinding the pathological process of aging is badly grounded from a philosophical viewpoint. This lack of clarity is one of the reasons why the search for a cure in the SENS agenda oscillates between a goal that seems to fit a scientific program and another one that perpetuates a narrative about future expectations that might eventually be fulfilled only by means of mere biotechnological advancements.

3. Machines, rejuvenation, and failures of the SENS agenda

In the previous section, we have presented that the SENS agenda rests on three fundamental claims: (1) aging can be repaired; (2) rejuvenation is possible through the reversal of all molecular damage; and (3) the human organism is a sophisticated machine. We have also noted that the SENS agenda aims to defeat aging and promote rejuvenation. In this section, we will show some of the weaknesses of this research program from a philosophical viewpoint. We take a theoretical step in our attempt to disentangle certain confusions in the SENS agenda. As John Dupré (2020) says, if SENS conceptualizes the human organism as a sophisticated machine, it is possible to protect it against all sources of molecular damage, to repair and gradually replace what does not work correctly, and maintain it in an optimal state. What we discuss here is the underlying framework of the research program. Some authors show that the SENS agenda carries implicit mechanistic assumptions. From a general perspective, Christopher Wareham (2016, p. 525) states that "the SENS program targets 'seven deadly things', including nuclear and mitochondrial mutations, which, if corrected, would undermine the aging process. In this way, the human body could be engineered to last longer". From a narrower focus, Suresh Rattan (2020, p. 415) says that "remaining stuck to the body-as-a-machine viewpoint reduces ageing and its associated health challenges to a mere problem of engineering and design".[7] However, we will provide reasons why this framing is less than obvious. To do that, we will clarify means by using the language of the organism as a sophisticated machine and we will explain why this research program has certain assumptions that fit with a mechanistic approach. Later, we will argue that SENS needs to be clearer in its agenda if it follows this approach.

[7] Other authors have implicitly pointed to this conceptualization of the human organism by SENS, even if they have not literally written the label "mechanistic body", "mechanism", or "sophisticated machine" (Agar, 2010; Davis, 2018; Diéguez, 2021; Hauskeller, 2014). On the other hand, de Grey's approach is inspiring for authors with similar scientific goals (Kurzweil, 2005; Sinclair & LePlante, 2019; Wood, 2016).

Firstly, we present Nicholson's (2013) description of the different meanings of the concept of "mechanism" in biology's past and present history. For the purpose of this article, we think the following idea from Nicholson (2013, p. 670) fits with the SENS agenda: "organisms are themselves machines (MCO)—just machines of far more intricate design than any machine created by man". We argue why SENS can be associated to the human organism as a machine understanding of mechanicism, we will reject other dimensions of the concept that are well-known in the literature. On the one hand, mechanicism is understood as "the philosophical thesis that conceives of living organisms as machines that can be fully explained in terms of the structure and interactions of their component parts". On the other hand, machine mechanicism is understood as "the inner workings of a structure" and causal mechanism as "a step-by-step explanation of the mode of operation of a causal process that gives rise to a phenomenon of interest" (Nicholson, 2012, p. 153).[8]

We will instead avoid a critical analysis of SENS' view in the light of the ideas of mechanism put forward by Peter Machamer, Lindley Darden, and Carl Craver (2000, p. 3), who define a mechanism as "entities and activities organized in such a way as to produce regular changes from initiation or configuration conditions to termination or completion conditions". It does not seem in fact that the SENS agenda can be usefully analyzed from the perspective of the new mechanical philosophy, in which, as Stuart Glennan (2002, p. 344) for example says, the organism is defined as "a complex system that produces that behavior by the interaction of a number of parts, where the interactions between the parts can be characterized by direct, invariant, change-related generalizations". What seem lacking here is an epistemological and ontological assumption that the human organism is a machine, while focusing on how its specific behaviors are performed in terms of parts and their interactions.

This "new mechanisms" perspective, analyzed from the integrative approach of Saúl Pérez (2019, p. 78-80), differs on several accounts from the MCO: (1) they consider that mechanism is an organized compound that is of the real world, and exist independently of the models we make of them; (2) they defend that a component part of a mechanism is often a mechanism itself; (3) they reject reductionism regarding mechanisms, i.e., the possibility to reduce higher level mechanism to lower level mechanism; (4) they show that a mechanism is always a mechanism for a phenomenon; and (5) mechanisms are not machines. Notably, we will focus on the first, third, and fifth characteristics as fundamental to the distinction we are making in this article regarding the SENS agenda.

To explain the correspondence between SENS and the MCO, we design the following table (Fig. 1) in which we indicate the characteristics of the MCO that fit the SENS agenda description of the human organism and of the plausible/identified goals and methods to be adopted to solve/cure aging.

[8] A complementary interpretation is Andersen (2014).

The MCO (Nicholson, 2012, 2013)	The SENS agenda (de Grey *et al.,* 2002)
Speficic language and terminology.	Expressions such as the conquest of aging or the end of aging. Words such as agenda, machine, maintenance, plan, program, repair, replacement, solution.
Use of the machine metaphor with explanatory power.	Example of the car as a way to understand the human organism as easily fixable with a set of proposed interventions.
Machines are organized in such a way that the operation of each part depends on its proper arrangement with respect to every other part, and to the system as a whole.	The human organism is constituted by cells, molecules, organs, and tissues that have activities and functions, and are interconnected with each other.
Machines are extrinsically purposive because they lack an autonomous self: their causal means of production reside lie outside of them-selves, demanding outside intervention not just for their construction and assembly but also for their maintenance.	The problems of the human organism and its solutions are identified with an external efficacy to carry out an extrinsic purpose. Aging limits life, and therefore, maintenance-repair of the human organism is necessary. Since the body does not persist forever, biotechnology is needed for this purpose.
Machines have functions because their operation is good for something.	The simple fact of aging and the appearance of age-related diseases prevents us from developing the type of life that we wish for.
Characterized its focus on effective causes, but not on final causes.	The ontology of the part is the same as the ontology of the whole. In this way, if something breaks, you can fix it, and the human organism continues to live indefinitely (in an ad infinitum process).
A machine always consists of the same components.	We are a single human organism and there is nothing outside of it.
Commited to reductionism in its research and explanation of living systems.	Maintenance-repair is successful if all molecular damage is reversed. It is sufficient if we successfully intervene in the 9 hallmarks of aging.

Figure 1

Comparative table between the basic notions of the MCO (left column) and the main characteristics of the SENS agenda (right column)

From figure 1 showing the similarities between the MCO and the SENS agenda, it is quite obvious that the best way to achieve rejuvenation is to conceptualize the human organism as a machine, mechanically structured and mantained. If the body can be reparied, as if it were a car whose parts are changed or transformed, SENS may be feasible. For proponents of the SENS agenda, if LEV worked, this process would lead to an indefinite life in

which we could be in the mid-life almost forever if that is what we wish for. Following Nicholson (2013, p. 674), the MCO is the most intuitive and simple way to understand the complexity of an organism such as ours. This approach, when applied to to aging, fits with a position according to which "how" is the only thing that matters. As many other contemporary mechanistic agendas, it loses its raison d'être by wanting to transform a methodology (fair as it is, like the molecular one) into an ontology, that is, a unique and comprehensive way of understanding living systems. For a SENS agenda, it makes no sense to ask "what?" or "why?", becasue this could only slow down the development of this set of interventions (de Grey, 2003). In the words of Nicholson (2012, p. 674): "biologists have not needed to worry about the thorny question". We have already given the reasons why SENS does not explicitly define: (1) What is the nature of aging?; or (2) Why we age? But the problem is not only here. This approach generates more difficulties than its defenders can pretend to admit just simply because it is not being conceptually clear. Those who defend the SENS agenda are focusing on trying to keep human organism in an optimal state indefinitely. Yet how is it possible to stay young forever? This idea does not make sense if one follows the MCO: nothing is known to last forever, so it doesn't seem likely that an organism can either.[9] So, SENS fluctuates between two scientifically different goals and this internal confusion raises a crucial theoretical distinction: repair and rejuvenation of the human organism".[10] Our thesis is as follows:

1. If the human organism can be understood as a sophisticated machine, the SENS agenda will fail, and the results will not be as expected. If the MCO is valid and the plan is fulfilled, we will slow down aging, but we will not be young indefinitely. At this level, the problem lies in the research goal. It would only be possible to live delaying aging from one point forward but not to constantly turn back the hands of the molecular clock. Therefore, SENS is generating expectations that are not justified by the core of its program.
2. If the human organism is something other than a sophisticated machine, SENS makes a methodological mistake and the research program has to be revised sooner or later. If the goal is rejuvenation, both the understanding and the intervention of aging are unsatisfactory. At this level, the problem lies in the set of proposed interventions. The therapies, hypothetically, could work, but the result would not be as expected. So, the problem of aging cannot be solved through the mere maintenance-repair approach if the goal is rejuvenation. Perhaps biotechnology is needed for this objective that goes beyond what SENS proposed or that will never really be possible.

SENS suggests that the same state of health would remain constant over time. From the current biomedicine, we can imagine what would become of us and our health if we delay aging and the appearance of age-related diseases. We can also easily imagine a better old age than the current one, as it happened in the past with our great grandparents. Now,

[9] Our point of view is also justified by the idea, increasingly accepted in the scientific community, that there is a limit to maximum human lifespan. For a recent study, see Milholland & Vijg, 2022.

[10] Hauskeller (2014, p. 100) also shares this opinion that goes to the core of the SENS agenda: "the aim is not the preservation of life as such, but rather the preservation or restoration of youthful life".

it is difficult to close your eyes and try to imagine an endless youth. This scenario is something that far exceeds what biology can currently do—as we will see in the next section when analyzing what is being said in the scientific community about SENS. Dupré (2020) notes that the way SENS wants rejuvenation is quite similar to capturing a static and timeless essence which can be potentially indefinite.[11] Even if we could remain in the best conditions as long as possible, we would gradually fail beyond a certain point. Nor does it seem philosophically easy to defend that a human being could continue to have a 30-year condition ad infinitum without entering into other problems that are difficult to solve (see the dilemma of personal identity, among others). Treating aging, even satisfactorily, is quite different from aspiring to live a virtual sort of immortality (García-Barranquero, 2021, p. 181).

According to what was mentioned above, the SENS agenda shows its lack of clarity when quantifying life extension possibilities. Generally speaking, they affirm that we will live much longer than we currently do now. Of course, this statement makes sense, and such a purpose seems scientifically plausible. A longer life expectancy or a healthier life at different stages is easily understandable. The problem lies in answering the following question: how many years can we live if aging is arrested once and for all? It is here that we argue that there is an internal inconsistency in its plan. SENS proponents put forward three different milestones: the first human being to live 1.000 years has already been born, we will live an indefinitely life as long as we do not die of external causes, and we will live practically as long as possible we want (cf. de Grey & Rae, 2007). At first glance, these milestones appear to be interconnected, and their similarities are more than obvious. But delving into each of the options, we realize that SENS fails again in the same direction as with the repair and rejuvenation distinction. Only a scenario where a fixed amount of life can be added, which is in line with what we know about the human organism and biology, would make sense (and be viable).

SENS wants to show how there is something like a magic bullet to reverse all the molecular damage of the human organism as if we were 30 years old indefinitely, and purportedly offers a solution to this puzzle by intervening in the hallmarks of aging. After we have analyzed the key assumptions of SENS philosophically, we will argue that the criticisms of the scientific community justify our viewpoint and reinforce the limitations of this research program.

4. *What does the geroscience say about SENS? Criticisms and limitations of the research program*

What does geroscience say about rejuvenation? In the previous section, we have shown that SENS fits with the MCO and that it confuses between what is repair and what is rejuvenation. However, we think that our perspective is complementary to the criticisms and limitations that scientifics have noted to the SENS agenda. The extraordinary claim that

[11] These questions,which prompt a revision of the SENS agenda, fit with Dupré and Nicholson's (2018, p. 24) arguments against mechanistic programs in biology: "[t]hat it is extraordinarily difficult to specify any such change-exempt descriptive properties that permanently characterize the essence of things".

aging might be cured with increased funding, sophisticated biotechnology, and sufficient time, requires scientific evidence. A project as complex as SENS needs a detailed roadmap that explains each step on the way to the research goal in sufficient detail. Although the SENS agenda has a very desirable aim, since practically everyone wishes to live a substantially healthier and longer life, geroscientists emphasize the importance of distinguishing between what is biologically feasible and what is practically impossible. In other words, SENS' effort seems to be driven by what many want to do and not by what the science can do, at least today. Science is not legitimated by individual and social desires and expectations but by specific criteria and evaluation methods that have to be rigorous and empirically tested. In light of this, some geroscientists have questioned the key assumptions of the SENS agenda and have categorically stated that there is another way of understanding aging and the future of (bio)medicine. Against the search for the rejuvenation, as de Grey and his collaborators pursue, Eric Le Bourg says that:

> [I]n science, the burden of the proof lies with those stating a claim, i.e. with the supporters of a theory, but not with its opponents (...). Therefore, it is not incumbent upon opponents to de Grey's ideas to show for instance that, very probably, it will not be possible between 2025 and 2040 to extend the life expectancy of 55-year-old people from 25 to 75 years or to live for 5,000 years (de Grey 2005). If supporters of de Grey's ideas would show they are able to strongly increase lifespan of mammals and particularly of human beings, every biogerontologist would be eager to read their articles. (2013, p. 25)

Similarly, Rattan (2020, p. 416) also notes that: "when one makes a deeper analysis of those claims, by actually reading any published papers behind those stories, it is almost always a case of overhyped claims and empty promises". Other geroscientists—Leonard Hayflick (2004), Robin Holliday (2009), or Stuart Olshansky (*et al.,* 2001)— have shown how SENS has proposed such over ambitious goals addressing aging that its roadmap is increasingly fading into the present. A magic bullet to cure aging is beyond what is reasonably expected from this field of research. Instead, these geroscientists have defended, instead, with strong arguments, the possibility of developing treatments to slow down aging while firmly rejecting the reasons that SENS has given for a long-awaited—rejuvenation complementary to the vision that SENS has of the human organism and that we have explained in the previous section. Le Bourg (2002) affirms that the best strategy to increase the visibility and acceptance of geroscience cannot be based on this approach but on more realistic proposals. SENS has not been shown to extend healthy life in animals, much less in humans. The years are passing and the results are not as expected, far from it. SENS always says that the "crusade" to defeat aging will be achieved in the next 25 years, and it does not matter when you read this because the date will always be extended by a couple of decades (cf. Diéguez, 2020, ch. 3). Huber Warner (2006) discusses the scientific weaknesses of SENS from three perspectives. First, the effectiveness of this research program is highly questionable because none of the treatments is available yet, and it does not seem that these can be developed soon. Success is only possible if all the molecular damage is reversed. Second, the safety of this research program generates great uncertainty because it does not evaluate the side effects of its treatments in detail. The human organism may respond adversely to preventing or treating a particular disease or pathology. Third, the feasibility of this project is highly debatable as there are no human experiments available. As in all biomedical research, transferring results from other animals is not an easy task.

These comments reflect the difficulties of achieving the goal of defeating aging. As Lemoine (2020b) warns, for SENS to succeed the nine interventions must fix the nine damages. Only in this way will it be possible to stop aging. Besides, it is a risky research project because the interventions are radical, and the consequences are unknown and can be very dangerous. These ideas by Lemoine are reminiscent of the limits of mechanisms pointed out by Howick and collaborators (2013, p. 275). Following this framework, we focus on the current knowledge we have of a particular hallmark—telomeric shortening. The limits we discuss are: first, our understanding of mechanism A may be incomplete or erroneous; second, mechanism A may have favorable results when manipulated under particular conditions in a laboratory, but may not be extrapolated to this success in clinical practice. Third, mechanism A may behave paradoxically and have adverse and unknown side effects. We will focus on one of the best-known hallmarks to reinforce what Lemoine, and Howick and collaborators argue.[12]

Telomeric shortening, in fact, is one of the fundamental mechanisms of aging. Telomeres are the ends of chromosomes. A common analogy is to imagine that they are like plastic sheaths at the end of shoelaces, which prevent shoelaces from fraying. Telomeres are made up of tandem repeats of a DNA sequence and associated proteins. The cellular problem occurs when the shortening of the telomeres is such that during the replication process, they cannot preserve the DNA of the chromosomes, producing inconsistency in the genetic material. Telomerase, an enzyme that allows the regeneration of telomeres and, therefore, maintains the replicative capacity of cells, is found in the organism.

María Blasco and her team were able to significantly extend the lifespan of chimeric mice carrying stem cells with extra-long telomeres introduced into their bodies in the embryonic phase (Varela *et al.,* 2016). The artificial lengthening of telomeres by the action of the enzyme telomerase can stop and even reverse this process, although it is not without risks. Blasco's team obtained mice with a greater amount of telomerase in previous experiments. But to overcome these risks they used stem cells that, when cultured in vitro, present long telomeres spontaneously, thus avoiding any genetic manipulation to increase the activity of telomerase. However, several studies have shown that there is no clear correlation between telomere length and lifespan, which is not surprising (Müezzinler *et al.,* 2013). Mice, for example, have telomeres ten times longer than humans, but they do not live ten times longer than humans. There is also the controversy about whether telomere lengthening can automatically cause an increased risk of cancer. This is so because cancer cells are immortal cells that can continue to divide thanks to their ability to lengthen their telomeres with the help telomerase. Thus, studies have shown that in mice with up-regulated telomerase, there is an increased risk of cancer (Han *et al.,* 2009; McNally *et al.,* 2019). However, other studies by Blasco's team show that if telomerase is upregulated in adult mice only occasionally, the mice live longer and do not have an increased risk of cancer (Bernardes de Jesus *et al.,* 2012; Donate & Blasco, 2011). Liz Parrish is the only person in the world who has artificially lengthened her telomeres, with the scientific community and any bioethics committee against her. She has received gene therapy on her body, in-

[12] We warn that we will not follow the numbering of Howick (*et al.,* 2013), although we will outline each of the limitations in our case study.

tending to turn back the hands of her molecular clock. We do not know if she is rejuvenating, but we know that many risks are being overlooked (for another, similar controversy, see Koplin *et al.,* 2020; for more information, see Blackburn & Epel, 2017; Blasco & Salomone, 2016).

This example of telomere lengthening, one of the most promising interventions against aging itself, shows us the limitations of what we know about biological mechanisms. Aging is perhaps no longer a "mystery", but it is still a problem for which we do not have a solution (Rattan, 2020). We need to continue to learn more about what aging is, from when we age, how we age, and why we age if we are to develop successful interventions so that we can live perhaps a little longer, but most importantly live healthier than we do now.

5. Concluding remarks

In this article, we have first explored the key assumptions of the SENS agenda and illustrated many of their weakness. Then, starting from the evaluation of these ideas from a theoretical viewpoint, we have argued that the cure of aging remains a goal to be further explored beyond the mechanistic assumptions, although our understanding of the biological process might seem to shed more lights than shadows. We have expanded on how and why it fits with the MCO in biology—and many of the difficulties that this way of thinking entails (see, Nicholson 2012, 2013). In this sense, there are strong reasons why a research program like SENS can lead to repairing the human organism but not to rejuvenation. SENS demonstrates an internal confusion between its methodology and research goal—this is the main reason why we have said it is conceptually debatable. If SENS is flawed, shouldn't it be replaced by a different model of "how" to understand and, if possible, alter aging? We have defended that the "why" we age is important if we want to develop successful interventions to live healthier.

To sum up, the main driving idea of SENS is that scientific knowledge is increasingly based on biotechnology and our understanding of the mechanisms underlying aging is in any case greater than that of the middle of the last century. SENS' goal of seeking a way to live as in our optimal stage of vigor and vitality forever is only legitimated by how they conceptualize and want to intervene in the process of aging itself. Nevertheless, as we have discussed, there are weaknesses concerning the possibility of rejuvenation by just targeting molecular elements to reverse this process (Rattan, 2020). This fails to considering the complexity of the organic development and potential comorbidities—in addition to its particular way of looking at scientific solutionism (cf. Diéguez, 2020). Our knowledge of a mechanism such as a telomere shortening shows us that we are still far from having effective and safe treatments in humans. And as we have indicated throughout the article, this is only one of the many molecular damages we suffer with time. What about the other eight hallmarks? Can aging be reduced to its molecular approach? The promise of curing aging and staying indefinitely young must be reviewed in the light of philosophy and science.

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