Frequently Asked Questions on Longevity and Rejuvenation

How will this work in detail?

The SENS approach divides the damage that needs to be repaired into seven categories:

- too few cells (cell loss, the main cause of Parkinson's)
- too many cells (death-resistant cells - senescent cells25 make up the majority)
- mitochondrial mutations (i.e. in the DNA of the mitochondria)
- Chromosomal mutations (in the DNA stored in the cell nucleus, whereby only the mutations that cause cancer are relevant here for the time being)
- Intracellular aggregates (rubbish in the cells, e.g. lipofuscin26)
- Extracellular aggregates (waste outside cells, such as beta-amyloid,27 which plays a central role in Alzheimer's disease, or transthyretin28)
- Protein crosslinks (extracellular crosslinks29).

These seven categories are all ones that can be identified through a systematic study of our biology. However, there is another reason to believe that this list is complete: all categories were discovered between 1907 and 1982. Cellular and molecular biology has made great strides since 1982 but has not come across an eighth class.2

The categories represent the forms of damage in aging. Within the categories, there are again different types of damage, but the type of damage is the same.

This classification is useful because the different types of damage each require different types of intervention to repair them, but the type of intervention is also the same for each damage within a damage class.

To take the proteins beta-amyloid and transthyretin mentioned above as an example: Both belong to the same damage class, namely extracellular debris. Therefore, they also have the same associated intervention class, namely endocytosis30 through stimulation of the immune system - simply put, a vaccination that ensures that immune cells engulf the junk. Admittedly, the

intervention itself is also different; for the removal of beta-amyloid, which accumulates mainly in the brain, we need to develop a different antibody than for transthyretin, which accumulates in the heart. But: it is an antibody in both cases and once we have developed the first antibody, the next one is much easier and faster to develop, because we can fall back on the know-how we acquired in developing the first one. This is also a key principle in engineering: Reusing skills developed in earlier steps of the same project.

The approaches currently being pursued to address each type of damage are:

- cell loss mainly cell therapy
- death-resistant cells senolytics31/"suicide genes "32
- mitochondrial mutations allotopic expression33 of 13 proteins
- Mutations in the cell nucleus (only cancer counts) WILT/immunotherapy + THIO
- Rubbish inside the cells transgenic microbial hydrolases34
- Rubbish outside the cells Endocytosis through immune stimulation
- Protein cross-links Molecules that cleave glycation products

Note: "WILT" is the abbreviation for "whole-body interdiction of lengthening of telomeres", a rather radical therapy designed to "starve" cancer cells by (as the name suggests)

- preventing the lengthening of their telomeres35. "THIO" is short for

- 6-thio-2′-deoxyguanosine, a promising anti-cancer drug,36 which is already being tested in clinical trials. It does not starve cancer cells but destroys them selectively by damaging their telomeres.

Since a more in-depth description is beyond the scope here, we recommend an excellent introduction to SENS-related research on the homepage of the SENS Research Foundation.37

Can such fundamental interventions not have unforeseeable consequences?

Again, we benefit from not interfering with the causal network of metabolism: conventional drugs have side effects because they affect the very metabolic processes that keep us alive. Damage repair therapies, on the other hand, remove the structural damage of the aged organism and restore it to the structural state of its youth (i.e. the state in which it is at the peak of health), while the metabolism can work unhindered. Therefore, massive side effects are not to be expected for the time being.

Of course, corresponding therapies can still have side effects, as we will sometimes intervene very deeply in the body. However, it must always be weighed up whether the risks or side effects of therapy are likely to be worse than the indication that is being treated. For example, it may well be that it is much more dangerous for very old people not to use a somewhat immature rejuvenation therapy because they have a high risk of dying in the next few months due to their biological age. Medical ethics today are still dominated by the "first do not harm" principle, which is part of the Hippocrates oath and states that unsafe treatments should not be used under any circumstances.

This principle dates back to a time when we had almost no knowledge at all regarding our bodies and diseases. We still know little today, but so much that doctors need to adopt a new moral perspective: one that weighs up how likely a treatment is to succeed and how likely it is to cause harm (and how great the benefit would be and how great the harm).

If the harms of a particular therapy outweigh its benefits, it will not continue to be used - as with any other form of medicine.

Example: What about the brain? Will consciousness and personality be affected?

We often hear the statement that repairing damage and replacing parts of the body will fail the brain. Generally speaking, however, the brain is made of the same substances as the rest of the body. Therefore, first of all, it is logical to assume that the same therapeutic strategies will work here.

Many people assume that the brain, because of its function of gradually accumulating information (facts, skills, preferences), is not per se rejuvenate because restoring its structure at an earlier age would erase the memories stored in the current structure. But we do not have to change this aspect of its structure. To be precise, we can leave the strength of the synaptic connections38 completely intact and instead remove the plaques39, tangles40, and all senescent glial cells41, replace the lost neurons42, and so on.

The concern that replacing brain cells might alter the consciousness or identity of the person being treated deserves a little more attention. While the complete replacement of the brain in one step would almost certainly indeed destroy the identity, we can be fairly certain, however, that the cell replacement therapies discussed above will have no such effect, provided they are done slowly enough.

After all, similar processes already happen naturally - without such an effect occurring. The brain, like the rest of us, is constantly destroying and regenerating components of cells, from the smallest molecule to enormously complex organelles43 such as mitochondria.44 The same is true of cross-cellular structures such as synaptic connections between neurons and even the loss of neurons. Processes of this kind allow us to evolve throughout our lives in terms of our attitudes, behavior, and other areas and are also the cause of our inability, for example, to remember facts that we could recall perfectly 20 years ago. None of these changes in our cognitive state give us the slightest cause for hesitation when we are asked if we are the same person we were then.

Our brain is essentially - just like the rest of our body - a pattern of information in constant change. Only the change must be slow enough, i.e. not too many parts of the pattern must be changed too quickly. The continuity in the structure is ultimate, as already discussed in the old philosophical problem of the "Ship of Theseus "45, decisive for the continuity of identity.

Applied to our medical example, this means that since gradual replacement of the brain is indeed a threat to identity, but replacement of a molecule or cell component all at once is not, there must be a threshold for the granularity (the degree of dissection) of the replacement below which identity is

fully preserved. Is this threshold exceeded by the cell therapy currently being pursued for the treatment of Parkinson's and other diseases affecting the brain?46 Probably not, because there are no reports in the literature that there have been any problems with identity preservation in the studies to date.

Isn't there a limit set by nature on how long people can live?

There is a limit in that our self-repair mechanisms, which we talk about in the first answer, can only keep us functioning for a limited period (the maximum human life expectancy). This period comes about because, due to the genetically determined imperfection of our self-repair, too much damage has accumulated by the end of this period at the latest. So, as you can read in the next answer, humans are not programmed to die after 120 years at the latest, but are programmed to have enough self-repair to be able to live up to 120 years, but no longer.47

Biotechnologies for rejuvenation would supplement our self-repair and thus help us to exceed our "biological guarantee period".
Studies that examine past trends in life expectancy are not relevant to the question of whether this will be possible - and not because this medicine has not yet been developed and the groups of people studied have therefore naturally not made use of it.

Doesn't aging fulfill an evolutionary purpose? Is it not pre-programmed?

Through natural selection,48 i.e. the natural selection of living beings based on their characteristics, the individual of a species that is better adapted to its environmental conditions always prevails by passing on its genetic information to offspring more often than less well-adapted living beings, because the latter die more often before they can reproduce. Is aging now perhaps a useful trait that has therefore prevailed evolutionarily? Would abolishing aging possibly create problems for the treated human being because aging fulfills an important function?

Until a few decades ago, the assumption that aging is "programmed", i.e. a selected trait, because the aging of individuals represents a certain advantage for the survival of the species, has been held in biogerontological circles. This would mean that we carry genes in which an acceleration of the aging process (which already takes place due to physical laws) is encoded. (Genes in which it is coded that we age at all could not prevail because the aging process already happens in this way and these genes would therefore not offer an individual a selection advantage).

In the last 60 years, however, the consensus within aging research has now largely shifted from the theory of programmed aging to the theory of non-programmed aging.47 The latter says that aging is not a program but - as stated in our first answer - the result of gaps in our built-in anti-aging machinery. There are types of damage that the body accumulates over a lifetime because we don't have genes that let the body repair that damage. If there were no such damage, we would not age. The reason we do not have the genes referred to is that there has not been sufficient selection pressure to allow a comprehensive "self-preservation arsenal" to emerge for our bodies.49 Indeed, the formation of such an arsenal would have required a great deal of evolutionary effort - more genetic signaling pathways, more highly developed genes, and so on,

and there has been no need from the point of view of evolution to put up with this effort. Thus, aging is not the result of evolutionary intention, but of evolutionary neglect.

This concept has been challenged more often in recent years due to new evidence, but detailed analysis shows that the conditions that a program to accelerate aging would have to meet to survive in natural selection do not exist, and NPA theories, therefore, remain the best explanation for the evolutionary basis of aging.50, 51

This means, translated into everyday language, that aging serves no purpose, but only occurs because the effort to eliminate it would not have been worthwhile from an evolutionary perspective. In short, the genes don't care, but we do.

Is there a danger that this will turn us back into babies?

No, there is no such danger at all. Here it is important to understand the difference between aging and development.

Development is a program encoded in our genes that begins at conception and ends in adulthood. It allows us to grow from an egg into an adult human being and to go through all the intermediate steps necessary for this. The self-preservation of our body (i.e. the repair mechanisms in us that already repair aging damage) is also a program encoded in our genes that begins at conception and never ends, but functions less and less well due to aging. aging, as explained in the last answer, is not a program but the result of gaps in the self-preservation programme.49

Rejuvenation therapies can and should only eliminate the molecular and cellular damage that occurs as a side effect of normal metabolic processes and "escapes" the self-preservation program. They do not influence the developmental process. So if we define biological age as the amount of damage in the body, an adult person - given sufficiently thorough therapies - could have the biological age of a 10-year-old or even younger person and still be as adult as ever.

Who is researching something like this?

There are now too many people and organizations dedicated to the fight against aging to list them all, so we will list only the most important ones here and not claim completeness.

<u>Important people in the fight against aging include:</u>

- Aubrey de Grey
- David Gobel
- George Church
- Greg Fahy
- Steve Horvath
- Maria Blasco
- Alex Zhavoronkov
- David Sinclair
- Peter Diamandis

- Nir Barzilai
- José Luis Cordeiro
- Ray Kurzweil
- Bill Fallon
- Michael Fossel
- Bill Andrews
- Liz Parrish
- Judith Campisi
- Michael West

Important organizations include:

- SENS Research Foundation
- Methuselah Foundation
- Unity Biotechnology
- AgeX Therapeutics
- Oisin Biotechnologies
- Cyclarity Therapeutics
- Forever Healthy Foundation
- Buck Institute for Research on Aging
- Altos Labs
- Harvard Medical School (Sinclair Lab)
- Insilico Medicine
- Calico
- Sierra Sciences
- Foresight Institute
- International Longevity Alliance (ILA)
- Life Extension Advocacy Foundation (LEAF)

I won't live to see that anyway, will I?

Encouraging progress is being made and therefore it is not unlikely that a large proportion of the population alive today will benefit from rejuvenation therapies - this is true even for those who are already at a relatively advanced age, see the answers to the two questions below.

The objection that people have been trying in vain for millennia to find a fountain of youth or immortality is correct. But the same is true of flight, access to space, the ability to restore paralyzed limbs, and freedom from smallpox, polio, and tuberculosis: All these things have been impossible for hundreds of thousands of years until the technology needed has been available and used. Now they are already possible for most of the human population and are being extended to the rest.

If we do nothing today to accelerate rejuvenation research, we run the risk of spending our last days wondering if we could have saved ourselves and millions of other people years of unnecessary suffering if only we had decided to act sooner.

And even if these treatments may come too late for some of us: It is still our moral duty to enable our descendants to live without age-related diseases and suffering, and that can only be done if we get to work today.

How close are we?

According to US inventor and futurist Ray Kurzweil, we will reach LEV (longevity escape velocity) in ten to twelve years (as of 2018).52

Bioinformatician and theoretical biogerontologist Aubrey de Grey predict that we have a 50% chance of reaching LEV around the year 2036.53 This would mean that people who are healthy enough at that time and henceforth regularly take advantage of the latest rejuvenation therapies will never die from age-related causes.

This prediction is based, among other things, on de Grey's estimate that we will realize RMR (robust mouse rejuvenation) with a 50% probability in three to five years. According to de Grey, this estimate is based on an assessment of the following factors:

- how far along in development are the individual SENS areas currently are
- how fast the individual sub-areas are progressing
- how much research funding will be available in the future
- how often do we find out something surprising about aging
- how often do we develop new technologies that make the work we need to do easier
- how difficult it will be to combine therapies when they work individually
- how much do we need to rejuvenate people to give scientists time to rejuvenate them better and stay one step ahead of the damage?

Regardless of these predictions, rejuvenation is a rapidly growing field of research that, as you can read under the next question, has already seen some breakthroughs. The first components of a comprehensive anti-aging therapy, such as senolytics, are already being tested in clinical trials.54 Others are on the verge. This should give us confidence that we are in for a revolution in biomedical research - and subsequently in human life - in the next few decades.

Are there already successes?

Yes. The SENS Research Foundation, the leading research institution in the field of the SENS approach to rejuvenation, has a list on its homepage of all publications in scientific journals that originate either from its in-house laboratory or from research projects funded by the foundation.55

This Wikipedia article 56 is very helpful in tracing the history of the research field so far.

Here57 is a roadmap showing which stages of development the individual components of the targeted therapies are in.

This article58 also summarises well not only the scientific but also the organizational, public, and political progress.

27: https://de.wikipedia.org/wiki/Beta-Amyloid

28: https://de.wikipedia.org/wiki/Transthyretin

29: https://en.wikipedia.org/wiki/Cross-link#In_biology

30: https://de.wikipedia.org/wiki/Endozytose

31: https://de.wikipedia.org/wiki/Senolytika

32: https://en.wikipedia.org/wiki/Suicide_gene

33: https://en.wikipedia.org/wiki/Allotopic_expression

34: https://de.wikipedia.org/wiki/Hydrolasen

35: https://de.wikipedia.org/wiki/Telomer

37: https://www.sens.org/our-research/intro-to-sens-research/

38: https://de.wikipedia.org/wiki/Synapse

39: https://de.wikipedia.org/wiki/Senile_Plaques

40: https://en.wikipedia.org/wiki/Neurofibrillary_tangle

41: https://de.wikipedia.org/wiki/Gliazelle

42: https://de.wikipedia.org/wiki/Nervenzelle

43: https://de.wikipedia.org/wiki/Organell

44: https://de.wikipedia.org/wiki/Mitochondrium

45: https://de.wikipedia.org/wiki/Schiff_des_Theseus

46: Björklund A, Lindvall O. Cell replacement therapies for central nervous system disorders. Nat Neurosci 2000 Jun; 3(6): 537-44. doi: 10.1038/75705. PMID: 10816308.

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48: https://de.wikipedia.org/wiki/Selektion_(Evolution)

49: Kirkwood TB. Time of our lives. What controls the length of life? EMBO Rep 2005 Jul; 6 Spec No (Suppl 1): S4-8. doi: 10.1038/sj.embor.7400419. PMID: 15995661; PMCID: PMC1369269.

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52: https://singularityhub.com/2017/11/10/3-dangerous-ideas-from-ray-kurzweil/

53: https://longevity.technology/longevity-escape-velocity-by-2035-and-it-will-be-free/

54: Wissler Gerdes EO, Misra A, Netto JME, Tchkonia T, Kirkland JL. Strategies for late phase preclinical and early clinical trials of senolytics. Mech aging Dev 2021 Dec; 200: 111591. doi: 10.1016/j.mad.2021.111591. Epub 2021 Oct 23. PMID: 34699859; PMCID: PMC8627448.

55: https://www.sens.org/srf-publications/

56: https://en.m.wikipedia.org/wiki/Timeline_of_senescence_research

57: https://www.lifespan.io/road-maps/the-rejuvenation-roadmap/

58: https://www.fightaging.org/faq/#progress-in-sens