

Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

AAV-hTERT

Evidence Summary

The approach could protect against cell aging based on the target, however, there is virtually no experimental evidence for how and whether it will work, particularly for the brain.

Neuroprotective Benefit: hTERT is a reasonable therapeutic target, but no evidence exists for AAV-hTERT to show that it can slow disease or successfully transfect the intended cells.

Aging and related health concerns: Evidence for lifespan extension in mice, but possible concerns for long-term cancer risk.

Safety: Possible risks include cancer and a targeted immune response to transfected cells that might lead to cell loss.

What is it? This therapy would be gene therapy mediated by some form of adeno-associated viral (AAV) vector to induce expression of hTERT, the human version of telomerase reverse transcriptase. Many different types of AAV vectors are available that transfect different types of cells.

Neuroprotective Benefit: hTERT is a reasonable therapeutic target, but no evidence exists for AAV-hTERT to show that it can slow disease or successfully transfect the intended cells.

Types of evidence:

- No clinical trials, epidemiology, or laboratory studies on AAV-hTERT
- Indirect evidence for the target hTERT and/or telomere length
 - 1 Mendelian randomization study
 - Various animal/cell culture studies

Human research on AAV-hTERT to suggest prevention or treatment of dementia and cognitive aging:
None.

Mechanisms of action for neuroprotection identified from laboratory and clinical research.

The success of the approach will depend on separate questions. 1) Can hTERT induction protect against aging and/or Alzheimer's disease? 2) Which cells and how many would need to be successfully transfected? 3) Would an intravenous or intrathecal injection with an AAV-hTERT successfully transfect those cells? 4) Is the treatment safe?

The first question – has not yet been addressed by any laboratory or clinical studies. TERT and/or telomere length has been linked to Alzheimer's disease but remain untested therapeutic targets.

The second question – Michael Fossel and Liz Parrish argue that the hTERT should be targeted to microglia because those cells may be vulnerable to telomere shortening. However, no published studies in either humans or laboratory models have directly examined the therapeutic response to increased hTERT expression in microglia. Michael Fossel states in *The Telomerase Revolution* that telomere shortening in microglia cells occurs in advance of the plaques and tangles of Alzheimer's disease, but there is insufficient evidence to support this claim. According to a review by [Mark Mattson \(Eitan 2014\)](#), telomere length in the human brain is not linked to neurodegenerative disease in general or even consistently to aging. Activated microglia are one of the few types of brain cells that do express TERT, raising the additional question of whether more TERT expression will succeed in reducing activation ([Spilsbury 2015](#)). Telomere shortening in microglial cells might contribute to neurodegeneration, for



example leading to chronic overactivation of microglia and subsequent exhaustion of the cells (reviewed in [Eitan Mattson 2014](#)).

The third question – would an injection with AAV-hTERT transfect the necessary cells – is also uncertain. As of 2011, clinical trials attempting AAV-gene therapy broadly in the brain have not done well due to problems in global delivery to the brain and with the blood-brain barrier (reviewed in [Mingozzi 2011](#)). The ability of an AAV vector to broadly transfect the brain after intrathecal injection (as suggested by Liz Parrish) has been tested in pigs and monkeys to varying degrees of success. An intrathecal injection of AAV9 to monkeys did transfect a variety of cells in the brain and spinal cord, including the hippocampus when the animals were tilted 15-30 degrees head-down during drug infusion (the Trendelenburg position) ([Meyer 2015](#)). Other studies have had less success transfecting brain cells (e.g. [Bevan 2011](#)) and some AAV injections will have difficulty penetrating past the meningeal surface of the brain (e.g. [Driesse 1999](#)).

The patterns of transfection vary depending on the type of AAV and animals' age and species (e.g. AAV9, AAV5, AAV2.5). Few studies have looked in detail at which specific cells become transfected. Maria Blasco's lifespan extension study with AAV9-hTERT in mice reported that the motor neurons appeared to be preferentially transfected. AAV vectors may also work more efficiently in mice than humans (quote from [E Tuddenham](#)).

Even if the appropriate cells are transfected with the gene, many may not express the protein. In one patient treated with an AAV gene therapy in a clinical trial (for a disease other than AD), 60% of his targeted cells at autopsy had the transfected gene but less than 10% expressed the protein.

Despite the complete lack of evidence that AAV-hTERT can protect from neurodegeneration and brain aging, the therapeutic target of TERT expression and/or increased telomere length has some reasonable albeit inconsistent evidence that is worth exploration. The most convincing evidence is a Mendelian randomization study that reported a causative relationship between shortened telomeres and Alzheimer's risk in humans ([Zhan 2015](#)). Whether Alzheimer's can be treated or prevented through an increased TERT expression in a handful of cells in the adult brain remains to be determined.

In mice, a genetic manipulation to cause telomere shortening had opposing effects in wildtype mice versus an Alzheimer's transgenic mouse model. It worsened brain health in wildtype animals, but improved brain health in a transgenic mouse model of Alzheimer's disease, for example with reduced microglia activation and reduced beta-amyloid pathology ([Rolyan 2011](#)). This study indirectly implies that gene therapy to increase hTERT expression may help some patients but harm others, particularly



those at risk of Alzheimer's. Another study on artificial telomere shortening in microglia suggests that, while it can impair brain function, it does not truly replicate age-related changes to microglia structure and function ([Khan 2015](#)).

Research in laboratory models have identified several mechanisms of action of TERT. Telomere lengthening is an obvious one but TERT also interacts with many proteins like NF-kappaB, DNA methyltransferase, BRG1/SMARCA4, and GNL. It is also reported to interact with beta-catenin although this may be an experimental artifact (reviewed in [Larrick & Mendelsohn 2015](#))

A related but distinct therapy was explored in one study in rats. Co-transfection with both TERT and NGF to bone-marrow-derived stem cells (BMSCs) was reported to improve the therapeutic potential of BMSCs in a rat model of vascular dementia ([Wang 2014](#)).

Aging and related health concerns: Evidence for lifespan extension in mice, but possible concerns for long-term cancer risk.

Types of evidence:

- no human research on AAV-TERT
- 1 mouse study on AAV9-TERT
- indirect evidence for the target of TERT and/or telomere length

Maria Blasco's lab in Spain has spearheaded the testing of gene therapy to increase TERT expression in mice. Using an AAV9 that has a broad tropism (it transfects a wide variety of cells and can penetrate the brain), they showed that increased TERT expression could extend lifespan when treated in adult (1-year-old) and elderly (2-year-old) mice, with 24% and 13% increased lifespan, respectively. Health benefits were observed in insulin sensitivity, osteoporosis, neuromuscular coordination, and molecular biomarkers of aging ([Bernardes de Jesus 2012](#)) with no increased risk of cancer. A different AAV-TERT gene therapy targeted to the heart led to improved outcomes and lower mortality in mice that went through an acute myocardial infarction ([Bar 2014](#)). She has also reported that transgenic overexpression of TERT can extend lifespan in cancer-resistant mice by up to 40% although it raises the cancer risk in other mice and presumably would raise the risk in humans (reviewed in [Mendelsohn Larrick 2012](#)).



Telomere shortening has been one of the cornerstones of aging biology theories for many years. Most recently, polymorphisms in hTERT were associated with a 1.8-3 years longer lifespan in women over the age of 75. No association was seen in men or in women aged 60-72 ([Kalpouzos 2014](#)).

Safety: Possible risks include cancer and a targeted immune response to transfected cells that might lead to cell loss.

Types of evidence:

- *no human research on AAV-TERT*
- *1 mouse study on AAV-TERT delivery*
- *clinical research on AAV delivery itself*

Cancer: AAV9-tert treatment in adult or old mice led to lifespan extension without an increased risk of cancer ([Bernardes de Jesus 2012](#)). However, long-term transgenic overexpression of TERT does increase cancer risk in mice and it is possible that the short lifespan of mice protected them from the increased risk of cancer that longer-lived species like humans might experience. A logical step is to test the AAV-TERT transfection in another long-lived species ([Boccardi Herbig 2012](#) editorial). Also, the risk of cancer may depend on the viral vector used to deliver TERT. AAV-vectors do not integrate into DNA so their delivered genes are expected to be lost over time in highly proliferative cells which might lower the concern over cancer ([Bernardes de Jesus 2012](#)).

AAV treatment risks: AAV in general is considered one of the most promising vectors for gene therapy but there are some risks.

- 1) In some clinical studies with experimental AAV gene therapy, the transfected cells became targeted by patients' immune system, which reacted to proteins in the AAV capsid. At best, this immune-system targeting could reduce the therapeutic benefit of the AAV treatment. At worst, it could accelerate the loss of important cells in the brain or body. Scientists are working to develop AAV that will not elicit immune responses, but it is a difficult goal. The immune response depends, in part, on the major histocompatibility complex, which is highly polymorphic across humans, making it difficult to create a single type AAV that could evade immune system recognition in many different people. ([Kotterman 2014](#), [Mingozzi 2011](#)).
- 2) When genes are inserted into DNA, they can disrupt the function of existing genes. Although AAV-delivered genes do not typically insert into DNA, so the risk of this mutagenesis is low, long-lived species may be at risk over time.



- 3) Many people have antibodies to AAV that can minimize the effectiveness of a given AAV dose and even cause some inflammation in response to the treatment. ([Kotterman 2014](#)).

Sources and dosing:

No therapies are yet available. A variety of AAV serotypes exist that can target different cells and organs of the body. AAV9 is the best able to penetrate the brain following peripheral injection. AAV2 transfects neurons rather than glia. AAV injected intrathecally rather than intravenously will transfect different tissues although it may still overlap, as intrathecal injections can still transfect peripheral organs. When injected into the blood stream, almost all AAV goes directly to the liver which will be important to guide dosing.

Bioviva: Liz Parrish, the CEO of BioViva, claims to have been treated with an intramuscular injection of a gene therapy to induce follistatin and an intravenous injection of some kind of hTERT gene therapy. Whether the company will pursue intrathecal versus intravenous injection is unclear.

According to [MIT Technology Review](#), her treatment came as a surprise to several on their scientific advisory board (SAB). Michael Fossell was one of the 2 MDs working with Liz but, according to his [blog](#), he will be pursuing hTERT gene therapy through his company, Telocyte, and he does not think her actions will lead to effective treatments.

Future research: Much additional research is needed before AAV-TERT can become a clinically viable therapy. It will be necessary to: Perform adult-onset genetic manipulations of microglia telomere length in animals to separately confirm microglia as the cellular target; test intrathecal injection of an AAV-hTERT into aged rats and dogs and possibly transgenic Alzheimer's mice; and perform dose-response curves and test different AAV serotypes and injection paradigms. For aging and lifespan specifically, it needs to be tested in more diverse animal models including longer lived species, looking carefully at cancer biology. Targeting to some specific diseases first should be considered to prove short-term gains that would improve quality-of-life and raise the rationale for a highly experimental long-term treatment. Identify some pharmacodynamic biomarkers should be identified that could be used to track in the short term whether the gene therapy has been remotely successful in people.

Search terms:

Pubmed

- adeno, telomere



- adeno, tert
- aging TERT
- lifespan TERT
- AAV-HTERT
- microglia telomere
- microglia tert
- Alzheimer, telomere
- Alzheimer tert or telomerase
- Alzheimer, adeno, tert
- Alzheimer, adeno, telomere
- Alzheimer, adeno
- Blasco M

Google

- Intrathecal injection, Adeno (google)
- telomere, autopsy, Alzheimer
- telocyte or telocyte with AAV or adeno
- adeno intrathecal injection human
- AAV transfection of human versus mouse
- AAVg astrocyte

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