2026 IMPACT CIRCLE

Project Title: Gene therapy to boost proteostasis and extend brain healthspan

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Unmet Need/Primary Question:
Decades of research have defined the "hallmarks of aging", the biological processes that determine when and how organisms age1, 2. Brain aging is the main risk factor to develop mild cognitive impairment and neurodegenerative diseases such as Alzheimer's disease. At the root of the aging process, it is proposed that the pathways that sustain the health of the proteome (termed "proteostasis") are substantially disrupted in the elderly3 . Proteostasis requires the complex and dynamic integration between all cellular processes involved in the production of healthy proteins4 . One of the main modules of the proteostasis network altered during aging involves the function of a subcellular compartment known as the endoplasmic reticulum (ER) 5 , the main "protein factory" of the cell. When abnormal proteins accumulate inside the ER, a repair and adaptive pathway is activated known as the unfolded protein response (UPR) 6 . How the UPR protect the cell? Evolution had generated specialized surveillance mechanisms mediated by "sensors" that detect toxic proteins to reprogram gene expression and stablish efficient repair responses. In fact, the UPR is governed by the concert action of transcription factors (regulators of gene expression), highlighting ATF6 and XBP1. Our group is among the 4 more cited labs in the field of ER proteostasis in the last 5 years. We have been pioneering in generating gene therapy strategies using adeno-associated viruses (AAVs) to artificially boost the proteostasis capacity of the brain and this year we were recognized as a major player in the area of gene therapy7 . We have shown that our gene therapy strategy was successful in restoring synaptic function and the cognitive capacity of aged animals, correcting around 70% of the molecular alterations observe in brain aging8 . This technology also alleviated age-related diseases in experimental models of models of Alzheimer's disease, and frontotemporal dementia9, 10. The idea of using gene therapy and transcriptional reprogramming to stop aging is not "science fiction" anymore due to the fact that the FDA approved this year the first clinical trial (number NCT07290244) for aging, where a gene therapy known as ER-100 was developed by Life Biosciences to reprogram the cell and rejuvenate

Novel Hypothesis:
Because proteostasis failure is a central pillar of the aging process, we hypothesize that the artificial enhancement of the UPR pathway will delay or reserve normal brain aging, restoring functionality. Here we propose to develop a novel gene therapy to reprogram gene expression and improve neuronal proteostasis. The idea is to develop a state-of-the-art technology for intravenous administration with a single dose ("one and done" intervention).

Project Proposal:

We plan to determine the significance of the UPR pathway as a central component antagonizing brain aging (see Figure 1). Although UPR signaling is generally studied as a linear pathway, ATF6 and XBP1s physically interact to enforce selective gene expression programs. We generated an ATF6/XBP1 fusion protein that behaves as a heterodimer and has stronger neuroprotective activity than single components, a technology we termed UPRplus10. Here we plan to develop a non-invasive strategy to improve brain proteostasis to deliver and compare the efficacy of XBP1, ATF6 and UPRplus to modify the course of brain aging. To this aim, we will use a novel engineered AAV serotype that can be administrated intravenously (PHP.eB) to reach the brain and target neurons. We predict that the enforced expression of an ATF6 and XBP1 heterodimer may drive distinct gene expression patterns that synergize in providing protection against normal aging. Our experimental strategy will include the establishment of a collaborative network with Buck researchers to determine possible improvements in cognitive capacity of aged mice (Lisa Ellerby lab) and synaptic function (collaboration Tara Tracy). We also plan to measure if the "biological age" of the brain (molecular clock, collaboration David Furman) is reversed and if this is associated with reduced content senescent cells.

Description of Potential Impact:

The brain is a complex organ that defines who we are and regulates our body. As we age, the function of our brain decays, having enormous consequences to our quality of life. The progressive loss of proteostasis contributes to the deterioration of the brain and other organs, representing the main risk factors to develop neurodegenerative diseases such as Parkinson and Alzheimer. We have undertaken a non-conventional approach to address a fundamental question where instead of targeting one gene (the classical approach of pharmaceuticals), we plan to engage a full network of processes (gene reprogramming) that as a whole will improve brain function (holistic view). We believe that the concept behind our possible findings is "rejuvenation": we aim to artificially recover a repair capacity that young cells naturally have and that is lost as we age. We predict that UPR-dependent programming will reestablish the production of healthy proteins (i.e. synaptic proteins, neuronal connectivity factors, etc). Importantly, gene therapy is one of the most exiting areas under development in biomedicine, receiving most of the current investments. Gene therapy is simple, safe and feasibly, demonstrated by the progressive approval by the FDA of technologies to cure complex diseases10. Clinical trials in Alzheimer's disease with AAVs have paved the path toward real human applications, demonstrating feasibility11, 12. The field of geroscience needs to advance in this frontier and the current proposal may represent a unique opportunity to foster novel transforming ideas. Now the challenge is to use these new technologies to modify the normal course of aging with the aim of restoring functionality and thus extend healthspan.

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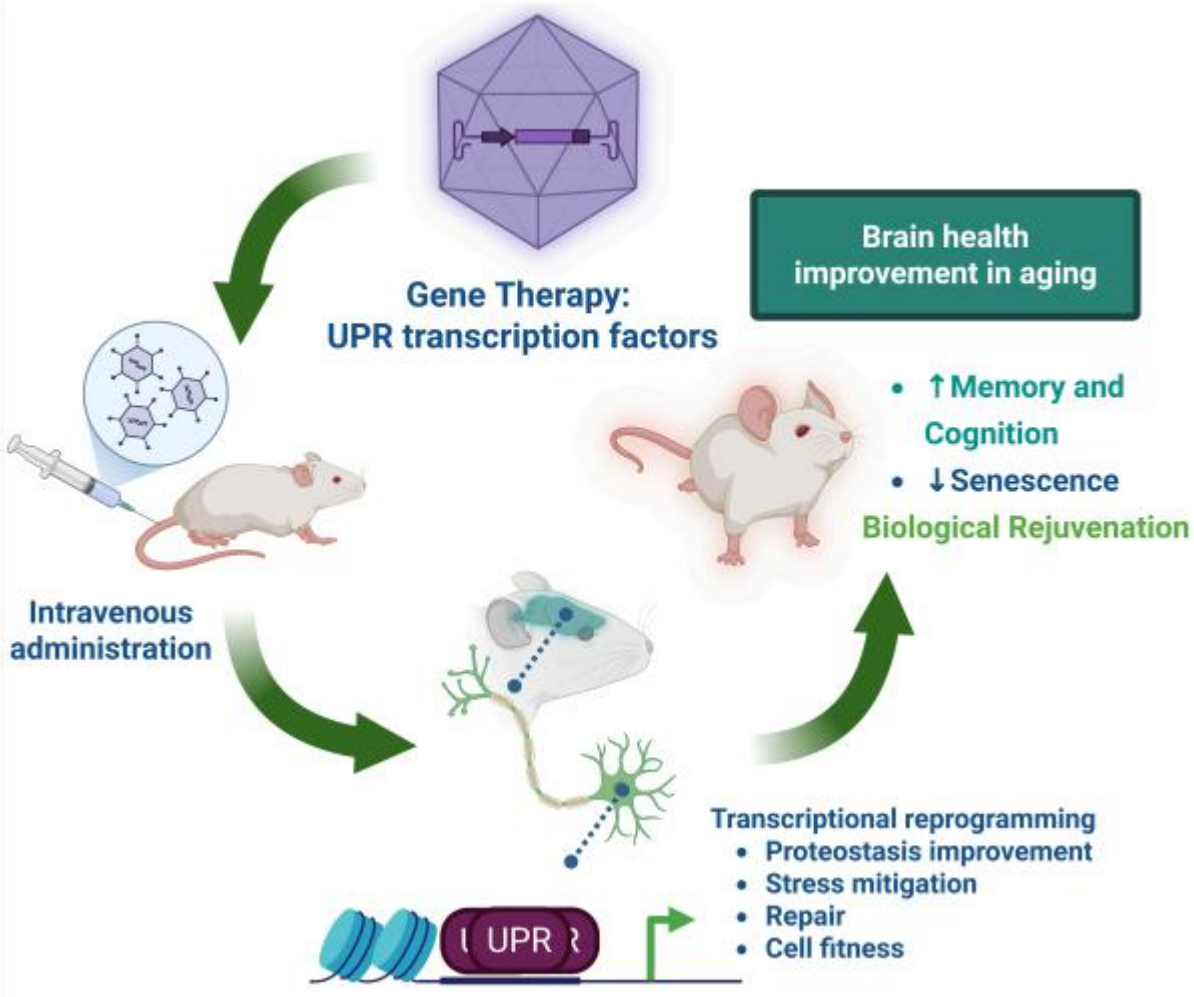

Figure 1. Workflow: neuronal reprograming to extend brain health span. We plan to define and compare the efficacy of administrating a single dose of a gene therapy based on the use of recombinant AAVs ("one and done" intervention). We plan to administrate a new viral serotype (AAVPHP.eB) intravenously to reach the brain with a non-invasive strategy and compare the efficacy in improving brain aging by targeting three different UPR master regulators: the transcription factor XBP1, ATF6 or an artificial heterodimer termed UPRplus. Thus, we plan to determine the consequences of stimulating three distinct UPR-dependent gene expression programs to the course of normal brain aging. We plan to develop a 10-month project (proof-ofconcept) to test strategies to artificially engage the UPR and restore the buffering capacity of the proteostasis network to restore neuronal function. Aged animals of 18 months that already show cognitive impairment will be treated with AAV-ATF6, AAV-XBP1, AAV-UPRPlus or control virus and 3 months later, cognitive assessment will be performed including new object location (NOL) and new object recognition (NOR) and Water maze. As a measure of healthy aging, we will determine possible improvements on "biological age" using gene expression profiling in addition to measure the content of senescent cells in the brain (an independent hallmark of aging).