# 2022 IMPACT CIRCLE

**Project Title**

Predicting Immune Cell Responses to Cosmic Radiation in Humans to Identify Countermeasures for Cellular Senescence and Aging and Enable Deep Space Exploration

**Investigator(s) and collaborations:**

Dr. David Furman (Buck Institute for Research on Aging)

**Unmet Need/Primary Question:**

The DNA damage response (DDR) is a chief orchestrator in the development of senescent cells during aging. However, the molecular determinants of resistance vs susceptibility to DNA damage are largely unknown. Using an unbiased computational immunology approach on human immune cells, we propose to uncover the genes and pathways regulating the DDR to identify biomarkers and compounds aimed to prevent immune cell senescence and mitigate risk associated with spaceflight.

**Novel Hypothesis:**

Baseline immune cell gene expression patterns predict individual variation in the resistance to cosmic radiation.

**Project Proposal:**

Space radiation is one of the main obstacles challenging safe human space exploration. During a typical 6-month mission, astronauts are exposed to the equivalent of over 6,000 chest x-rays, greatly increasing their risk of developing cancer, Alzheimer's, and other diseases of aging, due to increased chronic inflammation. Hence, spaceflight can be deemed as an accelerated model for human aging. The reason spending time in space triggers the onset of age-related diseases is because it induces similar biological effects including DNA damage, mitochondrial dysregulation and a chronic state of inflammation. However, these molecular changes that mimic aging occur much more quickly in space, creating a unique opportunity to study the mechanisms of aging and identify geroprotective interventions.

Using beams of heavy ions at the Brookhaven National Labs (NY), we have simulated the effects of cosmic radiation in samples from 755 subjects and measured their resistance to cellular damage. Baseline immune cells were preserved prior to irradiation to determine the genes and pathways responsible for the quality of the DDR. In this project, we aim to measure the expression of tens of thousands of genes in these samples to find which molecular changes are associated with a higher resistance vs susceptibility to cosmic radiation. We will use this information to find compounds that can induce the same protective molecular changes and thus have the potential not only to be used as mitigators of space radiation but also as **geroprotectors**. Finally, we will experimentally validate these compounds using our *in vitro* simulation of spaceflight environment and the aging models available at the Buck Institute for Research on Aging.

**Description of Potential Impact:**
This project is expected to generate the first platform to measure the susceptibility of astronauts to space radiation before spaceflight, and it will pave the way for future design of personalized countermeasures for astronauts during spaceflight missions. Most importantly, it will enable discovery of genes and pathways predictive of the DNA damage response which dictates cellular senescence during aging and thus, bring to light a list of compounds with the potential to delay age-related pathology.