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Article

Genes in Space 2020 Finalists: Contributing Ideas to Advance Space Biology

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INTRODUCTION

October 30, 2000 was the last day all humans lived alongside one another on the surface of the Earth. The next day, American astronaut William Shepherd and Russian cosmonauts Yuri Gidzenko and Sergei Krikalev were launched to the International Space Station (ISS) where they would live for 136 days. While humans had visited space before, this mission was different. It kicked off the era of a continuous human presence in space, an era that has continued unbroken to this day.

When we celebrate the upcoming anniversary of this milestone, we will be celebrating the ISS as humanity's home away from home for the past twenty years. A hub for scientific research of all kinds, the ISS stands as a monument to what is possible when a massive and diverse group of people work together on a global scale to tackle science and engineering challenges previously considered to be insurmountable.

Thanks to the efforts of this global team, the ISS is available as a one-of-a-kind research platform for scientists interested in the unique opportunities that microgravity offers. But aspiring scientists need not earn their PhDs before they can get involved in research on the ISS. In 2015, the Genes in Space program was established to grant students access to this extraordinary resource. Genes in Space is a competition for middle and high school students who are interested in becoming space biology pioneers. Contestants submit proposals for DNA science experiments that would expand our understanding of how the conditions of space – e.g., microgravity and cosmic radiation – affect biology. Each year, one winning experiment is selected to be flown to the ISS and carried out by astronauts.

In the years since Genes in Space was founded, more than 6400 students have risen to the challenge by submitting a proposal, and a total of six student experiments have flown to the ISS. Their results have informed our nascent understanding of how life is affected by cosmic conditions, and will ultimately aid in the development of safeguards against the risks of spaceflight. Beyond the contest winners, all Genes in Space participants contribute to the advancement of molecular biology in space by sharing their ideas with the scientific community. On the following pages, the 2020 Genes in Space finalists publish their proposals in hopes of inspiring the next generation of explorers and innovators.

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GENES IN SPACE

Assessing the Effects of Space-flight on Blood Clotting

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ABSTRACT

This year, an astronaut on the International Space Station (ISS) was diagnosed with deep vein thrombosis, which resolved only upon returning to earth. In space, cranio-cervical vein capacitance increases and flow patterns change, but whether clotting issues are due to changes at a genetic or physical level remains unknown. Here, we propose a multi-step experiment using zebrafish on the ISS to determine if spaceflight affects clotting gene expression and protein activity. Zebrafish are ideal test organisms as they can survive on the ISS, have 70% gene homology with humans, and are well-characterized for blood clotting on Earth. In both zebrafish and humans, blood clotting involves vessel constriction, platelet plug formation, and clotting cascade activation. Whole exome studies in humans reveal that 55 genes are involved in clotting, with Factors II and V contributing to 75% of all clotting problems. We hypothesize that microgravity in space increases gene expression and protein activity of clotting Factors II and V and decreases expression of anticoagulant Protein C. Testing Protein C abnormalities explores the relationship of gravity and anticoagulation mechanisms. For this experiment, we will use 60 adult male zebrafish (30 on Earth and 30 on the ISS). At each of 5 time points (before launching; 1, 3 and 6 months in the ISS; 1 week after returning to Earth), cohorts of 5-7 fish will undergo (1) serum gel electrophoresis to quantify clotting protein levels in blood samples, (2) pressure-flow analysis using a catheter with a manometer in the vessel, (3) RNA sequencing on liver cells (minION nanopore) to reveal alterations in gene expression of known clotting factors, and (4) morphometric examination of fixed eye blood vessels. This comprehensive examination will provide insights into the effects of spaceflight on RNA expression and protein activity of the blood clotting cascade and could lead to therapeutic targets for the 900,000 people who develop clot-related complications annually on Earth.

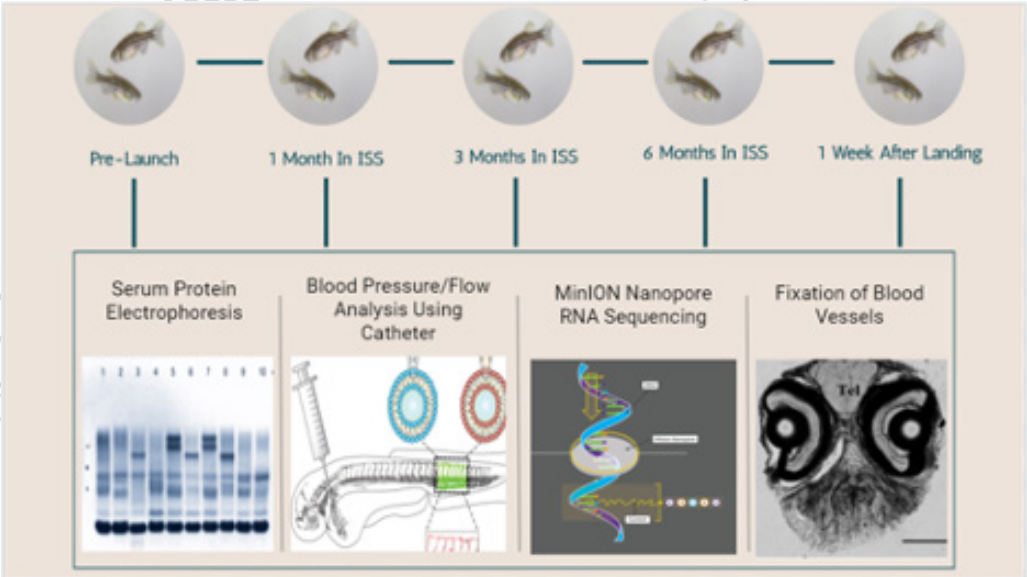

Figure 1: Timeline of the experiment and various factors studied throughout flight and upon return to Earth.

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Neurological Damage in Space: Could a Hormone Our Bodies Already Produce be the Answer?

GENES IN SPACE

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ABSTRACT

This experiment aims to test a hormone, analogous to the third thyroid hormone in humans, as an oral treatment for space-related neuronal damage.

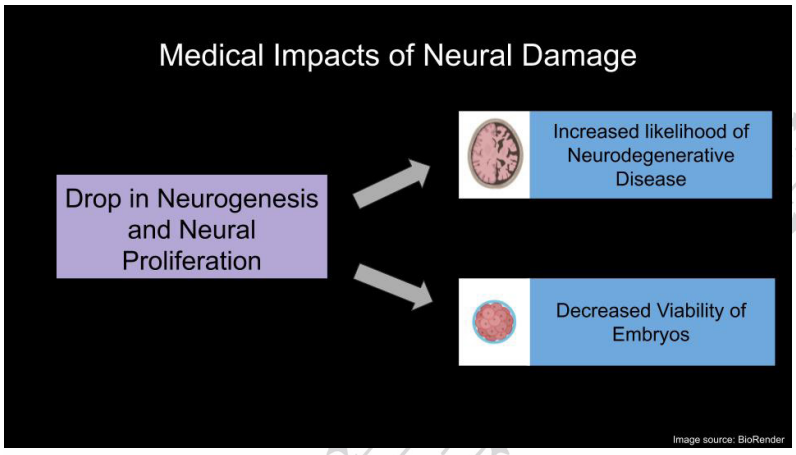
Studies on low energy radiation have shown irregular neuronal regulation and dendritic growth as well as problems with the maturation of neural stem cells, meaning radiation can disrupt hippocampal neurogenesis. These disruptions lead to deficits in memory and cognitive ability, especially spatial memory. These effects could have devastating impacts on the health of the hippocampus of astronauts in space for an extended period of time [1].

Beyond these cognitive effects, these changes in structure of the brain have been shown to contribute to the development of severe neurological disorders. These changes also reduce chances of successful brain development in eventual children born in space [2].

Ecdysone is responsible for the transition of early neurons from their early to late stages in drosophila [3] and is the analog to third human thyroid hormone, T3, which has been shown to increase the proliferation of neurons in mice [4].

It is hypothesized that treating flies with 20-hydroxyecdysone orally will lead to a long-lasting increase in the number and health of neurons within the brain. On the other hand, it is predicted that the untreated group will see significantly decreased neural proliferation as previously seen aboard the ISS.

In order to test this hypothesis, I propose to feed 2.35 mg 20-hydroxyecdysone to drosophila born aboard the ISS orally until pupation occurs. At this point, half of the drosophila will be sacrificed and RNA-sequencing will be performed. The other half will be sacrificed 45 days after birth. A parallel procedure will be carried out in space in untreated fruit flies, as well as on Earth. This will allow for the examination of neural proliferation both with and without ecdysone supplementation.



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Tracking Cytochrome P450 Gene Expression in Space to Understand Altered Drug Metabolism in Astronauts

GENES IN SPACE

2020 GIS Winner!

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ABSTRACT

Astronauts aboard the International Space Station (ISS) take an average of four medications per week to combat fatigue, motion sickness, and even life-threatening blood clots [1]. However, follow-up studies have revealed that their bodies don't respond as they would on Earth: approximately 20% of treatments taken over the course of 79 U.S. shuttle missions were perceived as "not effective" [2]. These inadequacies can reduce mission performance or mean the difference between life and death when the next medical emergency on a long-term mission inevitably arises and requires therapeutic intervention.

This study examines cytochrome P450s (CYPs) in space to understand the basis for this reduced efficacy. CYPs are enzymes primarily found in the liver that metabolize nearly 90% of all drugs [3]. When their expression increases––either because of environmental stress or xenobiotic induction––the half-life and effectiveness of their drug substrates diminish. It is thus hypothesized that space conditions––including microgravity, dietary changes, and altered sleep cycles––are promoting either higher baseline CYP expression or amplifying their induction.

Liver spheroids, or in vitro cellular aggregates that recapitulate CYP expression in the liver, will be cultured on Earth and aboard the ISS. Both cultures will be exposed to a DMSO control, phenytoin, or omeprazole for different amounts of time. These medications were selected because they are potent CYP inducers already present on the ISS [4]. RT-qPCR will be used at timepoints throughout their dosing with the expectation of finding lower cycle threshold values in space compared to Earth, indicating higher CYP expression.

The results from this study represents pharmacology's first departure from the assumption that medicines are processed in the same way on Earth and in space, possibly motivating modifications to drug regimens for astronauts. More broadly, this study also marks a crucial first step towards the development of precision medicines tailored for spaceflight: the gold standard in an environment with no room for error.

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Uncovering the Role of Astrocyte Senescence in Vascular Dysregulation to Prevent Cognitive Decline in Space

GENES IN SPACE

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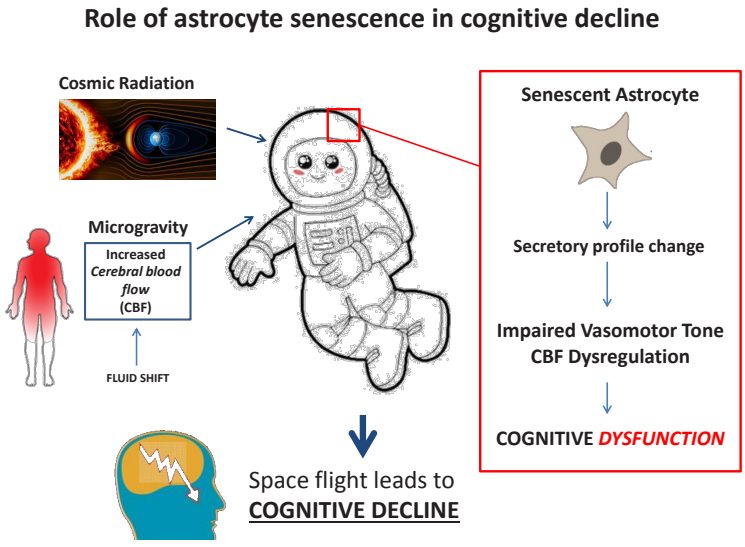
ABSTRACT

Astronauts experience cognitive decline and physical changes to cerebral vasculature after long-duration spaceflight [1, 2]. Data from Earth shows that cerebral blood flow (CBF) dysregulation contributes to cognitive decline [3]. Therefore, examining regulation of CBF in space is critically important as top cognitive function is essential for safe spaceflight. Astrocytes are the key regulators of CBF via communication with vascular endothelial cells and release of vasoactive molecules such as nitric oxide [4, 5]. Nitric oxide participates in several pathways controlling vascular tone [6, 7].

Astronauts are exposed to higher levels of radiation causing DNA damage, a major trigger of cellular senescence [8], characterized by cell cycle arrest and the secretion of proinflammatory factors by the damaged cells. These factors may result in the aberrant production of vasoactive molecules and CBF dysregulation [9, 10]. This proposal would uncover the role of astrocyte senescence in vascular dysregulation which may identify specific pathways leading to cognitive decline in astronauts.

We propose to use an in vitro experiment with primary human astrocytes and cerebral endothelial cells. Two sets of cells will be seeded in 3D culture, both alone and in co-culture. One set will remain on Earth, while the other will be sent to the ISS. Additionally, astrocytes irradiated to induce senescence will be used as an Earth only control. Prior to RNA extraction, co-cultured cells will be sorted by immunopanning to attribute gene expression to a particular cell type. RT-PCR analysis will be performed 1 day and two weeks post arrival to the ISS and assess expression of senescence markers and genes involved in vasoregulation. To gain additional knowledge, RNA sequencing of astrocytes will be performed on Earth and on the ISS.

Identification of dysregulated pathways would ultimately allow for the development of preventative measures to maintain cognitive function during long duration missions.



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Assessing the Relationship Between the Genetics of the Gut Microbiome, Menaquinone Synthesis, and Bone Loss in Astronauts During Spaceflight

GENES IN SPACE

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ABSTRACT

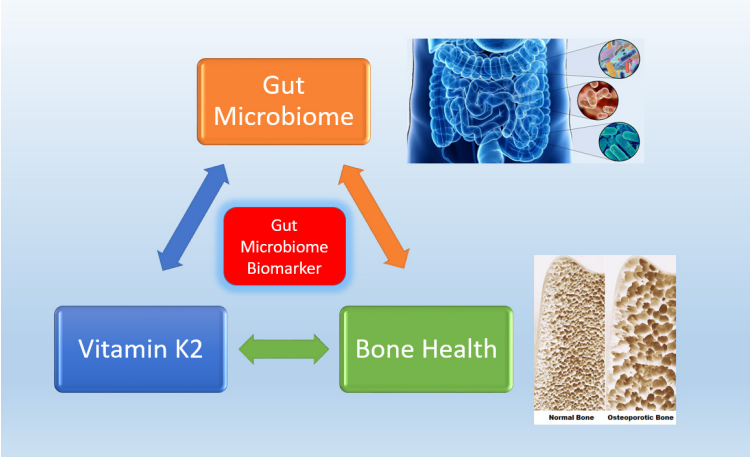
Astronauts lose 1-2% of their bone mass per month in space and are at a high risk of fractures [1, 2]. Although they can recover bone mass after shorter missions, changes in bone structure and strength remain. The mechanisms responsible for the bone deterioration and the significant individual variation in bone loss experienced in space are still unclear; however, the gut microbiome may the missing link that can help explain bone loss during spaceflight.

Vitamin K2, also known as menaquinone, promotes bone health through a variety of mechanisms, including the formation of new bone and the activation of osteocalcin, which binds calcium in the bone [3, 4, 5]. A recent study showed that the disruption of the gut microbiome led to both a decrease in the number of bacterial genes responsible for vitamin K synthesis and a decrease in bone density [6]. Research has further demonstrated that changes in the gut microbiome are associated with spaceflight [7, 8, 9].

I hypothesize that changes in the abundance of bacterial species and the expression of genes synthesizing menaquinone contribute to bone deterioration. Because our microbiomes are only 10% similar and change differently in space, I expect that these gut microbiome changes can also help explain the individual variation in bone loss among astronauts.

I propose an experiment that takes advantage of 16S rRNA amplicon sequencing and RT-qPCR to characterize the gut microbiome of mice in space and measure the expression of menaquinone-related genes.

Osteoporosis affects two-hundred million people, and there is one osteoporotic fracture every three seconds. A better understanding of the connection between the gut microbiome and bone health will make it possible to find ways to manipulate the gut microbiome in order to prevent and treat osteoporosis both on Earth and in space. The discovery of new gut microbiome biomarkers will enable us to select astronauts who would be at a lower risk of experiencing significant bone loss.



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