

## **METABOLOMIC AND GENOMIC MARKERS OF ATHEROSCLEROSIS AS RELATED TO OXIDATIVE STRESS, INFLAMMATION, AND VASCULAR FUNCTION IN TWIN ASTRONAUTS**

Stuart M. C. Lee<sup>1</sup>, Brinda K. Rana<sup>2</sup>, Michael B. Stenger<sup>1</sup>, Dorothy D. Sears<sup>2</sup>, Scott M. Smith<sup>3</sup>, Sara R. Zwart<sup>4</sup>, Brandon R. Macias<sup>1</sup>, Alan R. Hargens<sup>2</sup>, Kumar Sharma<sup>2</sup>, Immaculata De Vivo<sup>5</sup>

<sup>1</sup>KBRwyle, Science, Technology, and Engineering Group, Houston, TX; <sup>2</sup>University of California, San Diego, CA; <sup>3</sup>NASA, JSC Nutritional Biochemistry Laboratory, Houston, TX; <sup>4</sup>University of Texas-Medical Branch, Galveston, TX; <sup>5</sup>Department of Medicine, Harvard Medical School, Channing Division of Network Medicine, Brigham and Women's Hospital, Boston, MA; Department of Epidemiology, Program in Genetic Epidemiology and Statistical Genetics, Harvard School of Public Health, Boston, MA

### **BACKGROUND**

Future human space travel will consist primarily of long-duration missions onboard the International Space Station (ISS) or exploration-class missions to Mars, its moons, or nearby asteroids. Astronauts participating in long-duration missions may be at an increased risk of oxidative stress and inflammatory damage due to radiation, psychological stress, altered physical activity, nutritional insufficiency, and hyperoxia during extravehicular activity. By studying one identical twin during his 1-year ISS mission and his ground-based twin, this work extends a current NASA-funded investigation to determine whether these spaceflight factors contribute to an accelerated progression of atherosclerosis. This study of twins affords a unique opportunity to examine spaceflight-related atherosclerosis risk that is independent of the confounding factors associated with different genotypes.

### **PURPOSE**

The purpose of this investigation was to determine whether biomarkers of oxidative and inflammatory stress are elevated during and after long-duration spaceflight and determine if a relation exists between levels of these biomarkers and structural and functional indices of atherosclerotic risk measured in the carotid and brachial arteries. These physiological and biochemical data will be extended by using an exploratory approach to investigate the relationship between intermediate phenotypes and risk factors for atherosclerosis and the metabolomic signature from plasma and urine samples. Since metabolites are often the indirect products of gene expression, we simultaneously assessed gene expression and DNA methylation in leukocytes.

### **HYPOTHESIS**

We predict that, compared to the ground-based twin, the space-flown twin will experience elevated biomarkers of oxidative stress and inflammatory damage, altered arterial structure and function, accelerated telomere shortening, dysregulation of genes associated with oxidative stress and inflammation, and a metabolic profile shift that is associated with elevated atherosclerosis risk factors.

### **METHODS**

In the space-flown twin, a panel of biomarkers of oxidative and inflammatory stress were measured in venous blood samples and in 24-h (in-flight) and 48-h (pre- and post-flight) urine pools collected twice before flight, six times during the mission (~FD15, 75, 180, 240, 300, 335), and early in the post-flight recovery phase (3-5 days after landing). We also measured metabolomic (targeted and untargeted approaches) and genomic markers (DNA methylation, mRNA gene expression, telomere length) in these samples. Arterial structure, assessed from measures of intima-media thickness, also were measured using standard clinical ultrasound at the same time points. Arterial function was assessed using brachial flow-mediated dilation, a well-validated measure used to assess endothelium-dependent vasodilation and a sensitive predictor of atherosclerotic risk, only before and after spaceflight. All of the same measures were obtained in the ground-based twin, but less frequently.

### **DISCUSSION**

All data collection has been completed for both the space-flown twin and the ground-based twin. Vascular structure and function measures have been analyzed, blood and urine samples have been batch-processed. Results from these individuals will be compared to each other, to data from other Twin Study investigations, and to the larger complement of subjects participating in the companion study currently ongoing in ISS astronauts.

This work supported by NASA Grant/Cooperative Agreement NNX14AN75G.