| | | | |
|---|---|---|---|
| **Fiscal Year:** | FY 2021 | **Task Last Updated:** | FY 12/13/2021 |
| **PI Name:** | Zanello, Susana Ph.D. | | |
| **Project Title:** | A Gene Expression and Histologic Approach to the Study of Cerebrospinal Fluid Production and Outflow in Hindlimb Suspended Rats | | |
| **Division Name:** | Human Research | | |
| **Program/Discipline:** | | | |
| **Program/Discipline--Element/Subdiscipline:** | HUMAN RESEARCH--Biomedical countermeasures | | |
| **Joint Agency Name:** | | **TechPort:** | No |
| **Human Research Program Elements:** | (1) **HHC**:Human Health Countermeasures | | |
| **Human Research Program Risks:** | (1) **SANS**:Risk of Spaceflight Associated Neuro-ocular Syndrome (SANS) | | |
| **Space Biology Element:** | None | | |
| **Space Biology Cross-Element Discipline:** | None | | |
| **Space Biology Special Category:** | None | | |
| **PI Email:** | susana.b.zanello@nasa.gov | **Fax:** | FY |
| **PI Organization Type:** | NASA CENTER | **Phone:** | 832-576-6059 |
| **Organization Name:** | KBR/NASA Johnson Space Center | | |
| **PI Address 1:** | Human Research Program Chief Scientist Office | | |
| **PI Address 2:** | | | |
| **PI Web Page:** | | | |
| **City:** | Houston | **State:** | TX |
| **Zip Code:** | 77058 | **Congressional District:** | 36 |
| **Comments:** | NOTE (January 2021): PI now at KBR/NASA JSC as of December 2020. Previously at imec USA from June 2019-November 2020; NASA JSC (KBRwyle) from August 2017 until spring 2019. Prior to August 2017, PI was with Universities Space Research Association. | | |
| **Project Type:** | Ground | **Solicitation / Funding Source:** | 2013 HERO NNJ13ZSA002N-Crew Health (FLAGSHIP & NSBRI) |
| **Start Date:** | 10/01/2015 | **End Date:** | 07/05/2021 |
| **No. of Post Docs:** | 0 | **No. of PhD Degrees:** | 0 |
| **No. of PhD Candidates:** | 0 | **No. of Master' Degrees:** | 0 |
| **No. of Master's Candidates:** | 0 | **No. of Bachelor's Degrees:** | 0 |
| **No. of Bachelor's Candidates:** | 0 | **Monitoring Center:** | NASA JSC |
| **Contact Monitor:** | Brocato, Becky | **Contact Phone:** | |
| **Contact Email:** | becky.brocato@nasa.gov | | |
| **Flight Program:** | | | |
| **Flight Assignment:** | NOTE: End date changed to 7/5/2021 per PI and R. Schulte/HRP (jp).<br>NOTE: End date changed to 1/1/2021; note also with PI move to imec USA-Florida the PI's 3 projects were combined into one grant, 80NSSC19K1666 ; however, reporting will be required individually, per HRP (Ed., 11/4/19)<br>NOTE: End date changed to 9/30/2019 per HRP (Ed., 11/19/18) | | |
| **Key Personnel Changes/Previous PI:** | | | |
| **COI Name (Institution):** | Rivera, Adreana M.D. ( Houston Methodist Hospital )<br>Theriot, Corey Ph.D. ( University of Texas Galveston )<br>Chevez-Barrios, Patricia M.D. ( The Methodist Hospital Research Institute ) | | |
| **Grant/Contract No.:** | 80NSSC19K1666 ; Internal Project ; NNX15AW48G | | |
| **Performance Goal No.:** | | | |

| | |
|---|---|
| **Performance Goal Text:** | |
| **Task Description:** | The etiology of the Spaceflight-Associated Neuro-Ocular Syndrome (SANS) (formerly called Visual Impairment Intracranial Pressure) is unknown. It is hypothesized that weightlessness-induced cephalad fluid shift, possibly associated with elevated intracranial pressure (ICP), may play a critical role. Cerebrospinal fluid (CSF) dynamics changes may be involved in the ICP increase. Leveraging on an existing hindlimb suspension (HS) analog in rats, we propose to study the molecular aspects of CSF production and outflow modulation as a result of HS in the tissues involved in these two processes of CSF dynamics, namely choroid plexus (CP) and arachnoid granulations (AG), respectively. On available tissue shared from the parent animal experiment (cohorts 3 and 4), we will perform differential gene expression profiling in the CP and AG of rats subjected to HS and their normal posture controls. In addition, we will compare the ultrastructure of the CP and AG and the histologic localization and distribution of putative targets implicated in CSF dynamics (aquaporins and cellular junction proteins) of the CP and the endothelial cell layer of the venous sinuses, in normal posture and in HR rats within each cohort. The research groups involved in this proposal have the necessary resources and techniques in place at their laboratories in order to maximize the likelihood of success in this project. An anticipated product of this study is the reduction of the uncertainty in the likelihood or consequence of the visual impairment risk by gaining a study tool (validated animal model) and knowledge on the molecular basis of the biological processes involved in CSF dynamics changes generated by HS. |
| **Rationale for HRP Directed Research:** | |
| **Research Impact/Earth Benefits:** | By understanding the processes associated with fluid shift and its concomitant increase in intracranial pressure (ICP), we anticipate gaining clues to reduce the impact of increased ICP in disease conditions like idiopathic intracranial hypertension and traumatic brain injury, as well as normal-pressure hydrocephalus. |
| **Task Progress:** | FINAL REPORTING DECEMBER 2021<br>Leveraging on an existing hindlimb suspension (HS) analog in rats, we studied the molecular aspects of CSF production and outflow modulation as a result of HS in the tissues involved in processes of cerebrospinal fluid (CSF) dynamics, namely choroid plexus (CP) and arachnoid villi (AV). On available tissue shared from the parent animal experiment, we performed differential gene expression profiling by RNA sequencing in the CP of rats subjected to HS and their normal posture controls, and in animals exposed to an enriched CO2 air composition versus those exposed to a normal atmosphere. The trasncriptomic profiles of each experimental group were clearly segregated, evidencing an effect of both the HS treatment and the 1% CO2 exposure.<br><br>In addition, we examined the ultrastructure of the CP and AV and the histologic localization and distribution of putative targets implicated in CSF dynamics (aquaporin 4) in normal posture and in HS rats within each cohort. This work has demonstrated that these minute structures in the brain can be accessed for their investigation, gaining a study tool to elucidate the molecular basis of the biological processes involved in CSF dynamics changes generated by HS and CO2 exposure.<br><br>ANNUAL REPORTING JULY 2020<br><br>Currently, it is hypothesized that weightlessness-induced cephalad fluid shift, possibly associated with a chronic elevation of intracranial pressure (ICP), may play a critical role in the pathophysiology of the Spaceflight Associated Neuro-Ocular Syndrome (SANS). Changes in cerebrospinal fluid (CSF) dynamics might also be involved in the ICP increase. It is not known whether CSF production and/or outflow are altered in microgravity, but changes at the molecular and cellular level in the structures that produce and regulate the transcellular and paracellular secretion and reabsorption of CSF may be relevant. These structures are the choroid plexus (CP) and the arachnoid granulations, which in rodents are more rudimentary and called arachnoid villi (AV). Their morphology, ultrastructure, and gene expression profiles might be subject to change by conditions of weightlessness or cephalad fluid shifts. This project examines the responses to extended durations of rodent hindlimb suspension (HS) at various levels: (a) changes within the ultrastructure of the CP and AV, (b) the localization and distribution of key proteins involved in the production and reabsorption of CSF, and (c) the transcriptomic differences in the CP of rats subjected to HS compared to their normal posture controls. Male 9-month-old Long Evans rats were subjected to HS for 14 and 90 days, with a subset of animals completing 90-day HS further studied for recovery periods at normal posture of 14 and 90 days. All HS rats had age-matched cage controls. The rats were sacrificed under anesthesia and the brain carefully removed, cut in 5 mm-thick coronal blocks, and preserved for various analyses. Transmission electron microscopy of glutaraldehyde-fixed sections were used to evaluate the ultrastructure of the CP from the lateral ventricles and AV from the cerebral convexities. Samples stored in Bouin's fixative were used for immunohistochemical analysis of specific targets involved in CSF regulation, such as aquaporins. In addition, similar coronal blocks were frozen without fixation for processing by laser capture microdissection to isolate RNA specifically from the CP for gene expression profiling by RNA sequencing analysis. |
| **Bibliography Type:** | Description: (Last Updated: 09/04/2023) |
| **Abstracts for Journals and Proceedings** | Zanello SB, Theriot CA, Chevez-Barrios P, Rivera A. "A gene expression and histologic approach to study production and outflow of cerebrospinal fluid in hindlimb suspended rats." 2022 NASA Human Research Program Investigators' Workshop, Virtual, February 7-10, 2022.<br>Abstracts. 2022 NASA Human Research Program Investigators' Workshop, Virtual, February 7-10, 2022. , Feb-2022 |