Fiscal Year:	FY 2020	**Task Last Updated:**	FY 08/03/2020
PI Name:	Ford, Andrew Ph.D.		
Project Title:	Investigating the Combinatorial Effects of Intraocular Pressure and Hypobaric Hypoxia on Corneal Function		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:	TRISH--TRISH		
Joint Agency Name:		**TechPort:**	No
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Space Biology Special Category:	None		
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Zip Code:	02155	**Congressional District:**	5
Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	2019 TRISH RFA-1901-PD Translational Research Institute for Space Health (TRISH) Postdoctoral Fellowships
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No. of PhD Candidates:	0	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	0
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Contact Monitor:		**Contact Phone:**	
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Flight Assignment:	NOTE: End date changed to 03/31/2021 per E. Urquieta/TRISH (Ed., 6/2/21)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Kaplan, David Ph.D. (Mentor: Tufts University)		
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Task Description:	POSTDOCTORAL FELLOWSHIP Spaceflight Associated Neuro-ocular Syndrome (SANS) is thought to be caused by cephalad shifts in fluid during microgravity exposure resulting in increased intracranial pressure (ICP) and symptoms such as optic disc edema, globe flattening, choroidal folds, cotton wool spot, or hyperopic shifts. In addition to increased ICP, as much as a 100% increase in intraocular pressure (IOP) can also occur, potentially affecting neuro-ocular functions. Due to its prevalence and potential mission impact, SANS is considered one of the top human system risks in the International Space Station (ISS) Program. Currently, the underlying mechanisms and symptoms associated with SANS are poorly understood with the potential for long-lasting harm to the ocular and central nervous system. Furthermore, SANS occurs as a result of microgravity exposure; however, it is thought that the mildly hypoxic environment of the ISS may exacerbate neurological symptoms. Thus, there is a need to investigate the individual and combined effects of IOP and hypoxia on ocular function. The long-term objective of this project is to develop a tissue system to enable the study of the simultaneous effects of increased IOP and hypoxia on corneal tissue/cell function. This increased understanding will lead to the development of methods to alleviate symptoms associated with spaceflight and maintain ocular health and vision stability of astronauts. We propose to utilize our established, unique, 3D corneal tissue models, containing a neuronal component, in combination with a custom built bioreactor and hypoxia chamber to investigate tissue response to both short (days) and long-term (weeks, months) exposure to high IOP and a hypoxic environment in vitro. We hypothesize introduction of elevated IOP and hypoxia will result in increased neuronal sensitization, as well as morphological and organizational changes to the individual cell components and extracellular matrix components within our cornea tissue models.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	High intraocular pressure (IOP) is an important risk factor to glaucoma progression, leading to the development of many experimental animal models of elevated IOP in multiple species including monkeys, rats, and mice. While these studies provide valuable insight into the pathology associated with increased IOP, direct human relevance of the outcomes remains of concern. A number of studies have investigated the effects of hypoxia on the function of corneal cells both in vivo and in vitro. In vivo studies on corneal hypoxia using animal models yield the same concerns as studies on IOP, whereas in vitro studies have traditionally lacked a sensory nerve supply, which will be key to understanding the neurological impact of hypoxia. The 3D cornea model developed in the sponsor's laboratory utilizes human derived cells, including neurons, and can be cultured for extended time periods under controlled pressure and atmospheric conditions making it an excellent option for studying symptoms associated with SANS. Furthermore, the individual cell components of this model can be easily separated following treatment to determine each cell-type's contribution to corneal function. Our unique, 3D corneal tissue models, containing a neuronal component, in combination with a custom-built bioreactor and hypoxia chamber that can be used to investigate tissue response to both short (days) and long-term (weeks, months) exposure to high IOP and a hypoxic environment in vitro. These aspects allow for an increased understanding of cornea function and will lead to the development of methods to alleviate symptoms associated with spaceflight and maintain ocular health and vision stability of astronauts.
Task Progress:	Spaceflight Associated Neuro-ocular Syndrome (SANS) is thought to be caused by cephalad shifts in fluid during microgravity exposure resulting in increased intracranial pressure (ICP) and symptoms such as optic disc edema, globe flattening, choroidal folds, cotton wool spot, or hyperopic shifts. In addition to increased ICP, as much as a 100% increase in intraocular pressure (IOP) can also occur, potentially affecting neuro ocular functions. Due to its prevalence and potential mission impact, SANS is considered one of the top human system risks in the International Space Station (ISS) Program. Currently, the underlying mechanisms and symptoms associated with SANS are poorly understood with the potential for long-lasting harm to the ocular and central nervous system. Furthermore, SANS occurs as a result of microgravity exposure; however, it is thought that the mildly hypoxic environment of the ISS may exacerbate neurological symptoms. Thus, there is a need to investigate the individual and combined effects of intraocular (IOP), and hypoxia on ocular function. The long-term objective of this project is to develop a tissue system to enable the study of the simultaneous effects of increased IOP and hypoxia on corneal tissue/cell function. This increased understanding will lead to the development of methods to alleviate symptoms associated with space flight and maintain ocular health and vision stability of astronauts. We propose to utilize our established, unique, 3D corneal tissue models, containing a neuronal component, in combination with a custom built bioreactor and hypoxia chamber to investigate tissue response to both short (days) and long-term (weeks, months) exposure to high IOP and a hypoxic environment in vitro. We hypothesize introduction of elevated IOP and hypoxia will result in increased neuronal sensitization, as well as morphological and organizational changes to the individual cell components and extracellular matrix components within our cornea tissue models. Specific Aim 1: Define the effects of intraocular pressure on function and physiology of a 3D cornea tissue model in vitro. The objective is to determine how high IOP, associated with microgravity, may effect cell function in an in vitro 3D corneal model. We hypothesize that when exposed to high (30 mmHg) IOP, similar to that found in astronauts during spaceflight, our corneal tissue model will exhibit changes in neuronal signaling and organization, as well as increased extracellular matrix (ECM) production and remodeling. Specific Aim 2: Define the effects of hypobaric hypoxia on function and physiology of a 3D cornea model in vitro. We hypothesize that the introduction of a hypoxic environment to the corneal tissue constructs will result in increased neuronal sensitization, changes in cellular metabolism, and increased reactive oxygen species production. Corneal constructs will be cultured in a custom hypoxia chamber for acute (days) and chronic (months) exposure studies. Specific Aim 3: Define the combined effects of intraocular pressure and hypobaric hypoxia on function and physiology of a 3D cornea model in vitro. We hypothesize that when combined, high IOP and a hypoxic environment will exacerbate the changes in physiology of our cornea tissue models found in Aim 1 and Aim 2. The bioreactor and hypoxia chamber systems will be interfaced to more accurately simulate the environmental conditions associated with spaceflight. Our initial work has focused on improving our 3D in vitro cornea tissue model to more accurately mimic in vivo cornea structure. Changes to our model assembly protocol have allowed for neuronal axon extension from the tissue periphery (limbus) into the tissue and upwards towards the epithelial surface, stromal cell alignment mimicking lamellae, epithelial cell barrier function, and overall lowered assembly times.

Bibliography Type:	Description: (Last Updated:)