NCATS

COLLABORATE. INNOVATE. ACCELERATE.

NASEM Space Science Week 2023

COMMITTEE ON BIOLOGICAL AND PHYSICAL SCIENCES IN SPACE
March 28-30, 2023

Danilo A. Tagle, Ph.D.

Director, Office of Special Initiatives

National Center for Advancing Translational Sciences, NIH, DHHS

Danilo.Tagle@nih.gov

National Center for Advancing Translational Sciences

Opportunities for Biomedical Research in LEO and Space

- **Understanding Human Biology and Disease Modeling**
  - Capture salient features of diseases and human conditions that may be difficult or will take a long time and lots of resources to model on earth
- **Radiation Health Effects and Other Space Hazards**
  - Better understanding of cosmic radiation effects, isolation, and microgravity on the human body, and developing meaningful countermeasures
- **Biomanufacturing**
  - Formation of larger and more homogeneous protein crystals, improved stem cell proliferation, differentiation and maturation, scaffold-free formation of spheroids/organoids, 3D-volumetric and freeform bioprinting of organs and tissues for regenerative medicine; additive manufacturing capabilities
- **Advanced Medical Capabilities**
  - Telemetry, robotics, autonomous, portable medical capabilities for remote locations and field medical care, including AI/ML for advanced medical decision support software, medical imaging analyses algorithms, data analytics, and reasoning systems to enhance medical care in remote locations
- **Long Shelf-Life Pharmaceuticals and Real-time Manufacturing**
  - Long-term stable storage of critical medications/storage conditions, capabilities for on-demand and automated synthesis of pharmaceuticals, improved flow chemistry, different fluid dynamics and superconductivity
- **Omics, Microbiome and Precision Medicine**
  - Next generation genomics, transcriptomics, proteomics, and metabolomics solutions to improve health and performance through personalized medicine, and understand health effects of the microbiome
- **Sustainable Food Sources and Healthy Habitat**
  - Renewable and eco-friendly alternatives to food sources, including vertical farming and 3D-bioprinted food; Improved tools and technologies to create pods/habitats that incorporates lighting countermeasures that can help anyone working night rotation, extended wake schedules, or traveling across multiple time zones; countermeasures that lessen the effects of isolation and confinement

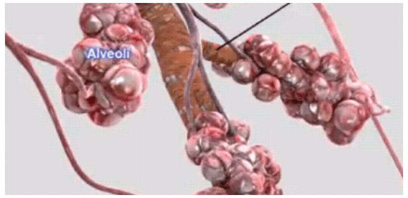
Translates to improved life conditions and health on Earth

Known Health Hazards of Human Spaceflight

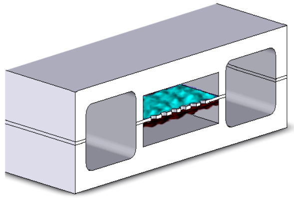
- **Microgravity** – alterations in the genome, epigenome and cellular architecture resulting in profound physiological changes such as accelerated aging effects
- **Space radiation** – increases cancer risk, damage to the central nervous system, and can alter cognitive function, reduce motor function, and prompt behavioral changes
- **Restrictive and closed environments** – emotional health can be affected by habitability factors that include amount of physical/personal space, temperature, lighting, noise, and available recreation
- **Isolation and confinement** – sleep loss, circadian desynchronization, and work overload can lead to subpar performance, adverse health outcomes, behavioral and psychiatric changes
- **Healthcare delivery in remote and resource-limited environments** – limited availability of medical countermeasures for emergencies which can be exacerbated by communication delays and equipment failures

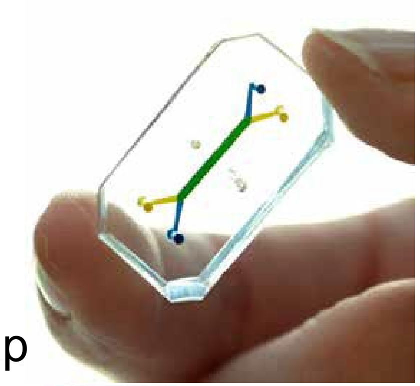
NCATS Tissue Chips for Drug Screening Program

- Program Goal:
  - Develop an *in vitro 3-D* culture system (**tissue chips/microphysiological systems**) that **emulates organ physiology and function using human cells and tissues** through advances in stem cell biology, microfluidics and bioengineering for risk assessment to accurately evaluate the **efficacy, safety and toxicity** of promising therapies



- **Represents 10 Major Organ Systems**
  - **Circulatory**
  - **Endocrine**
  - **Gastrointestinal**
  - **Immune**
  - **Skin**
  - **Musculoskeletal**
  - **Nervous**
  - **Reproductive**
  - **Respiratory**
  - **Urinary**

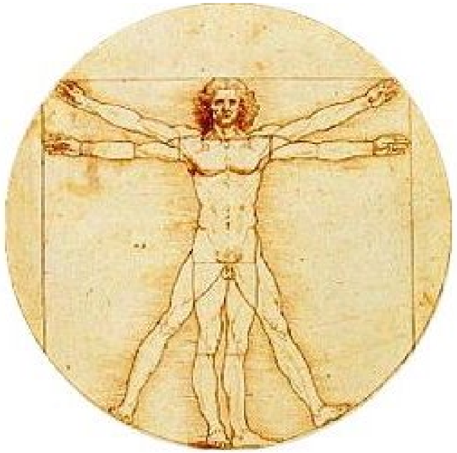




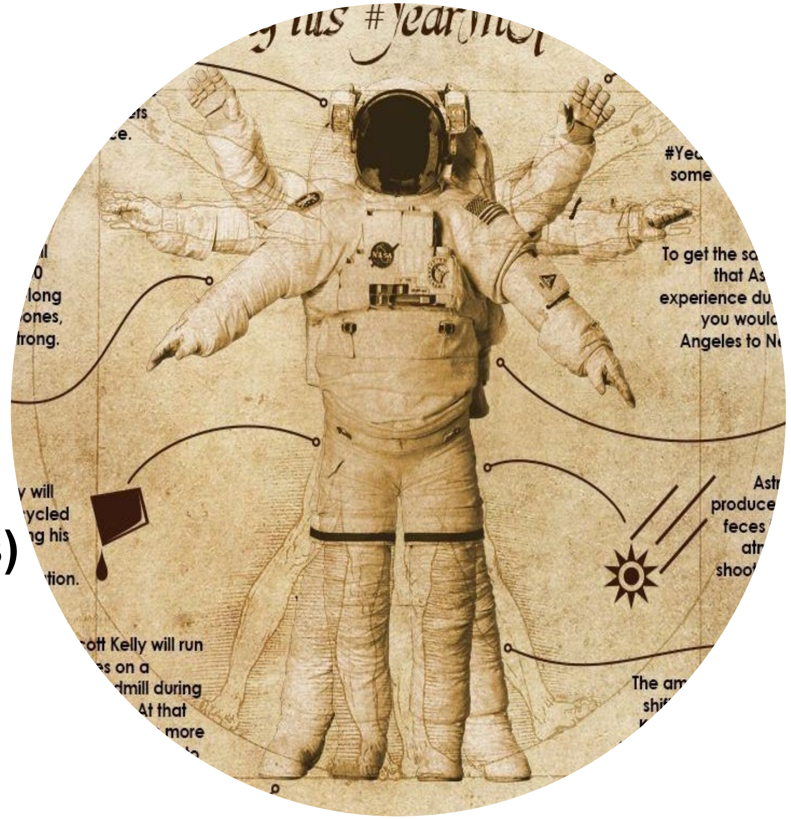
Emulate
Single organ chip

Hesperos 5-organ chip

Physiological Changes under Prolonged Microgravity



- **Early response (<3 weeks)**
  - **Upper body fluid shift**
  - **Neurovestibular disturbances**
  - **Sleep disturbances**
  - **Bone demineralization**
- **Intermediate (3 weeks to 6 months)**
  - **Bone resorption (1.5% loss each month)**
  - **Muscle atrophy**
  - **Cardiovascular deconditioning**
  - **GI disturbances**
  - **Hematological changes**
- **Long Duration (greater than 6 months)**
  - **Muscle atrophy**
  - **Cardiovascular deconditioning**
  - **GI disturbances**
  - **Hematological changes**
  - **Declining immunity**
  - **Renal stone formation**
- **Reverts to normal on return to Earth**



Front Physiol. 2018; 9:1551

Space-related physiological changes resemble those observed during aging

NCATS Tissue Chips in Space Program

Goals: Model age-related diseases under microgravity and to translate that understanding to improve human health on Earth; develop countermeasures

Immunosenescence

UCSF
BioServe Space Technologies

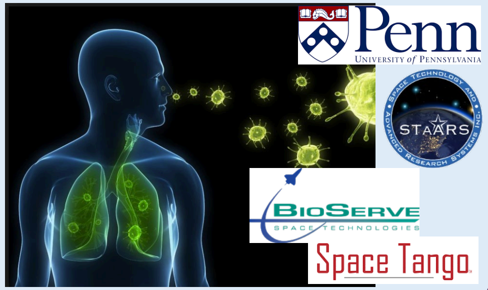
PI: Sonja Schrepfer

Drugs across blood-brain barrier

emulate
Space Tango

PI: Christopher Hinojosa

Lung infection



Penn University of Pennsylvania
STAARS
BioServe Space Technologies
Space Tango

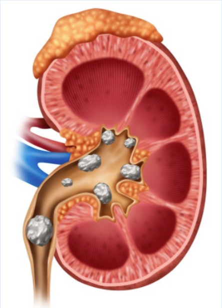
PI: Scott Worthen

Post-traumatic osteoarthritis

MIT
techshot

PI: Al Grodzinsky

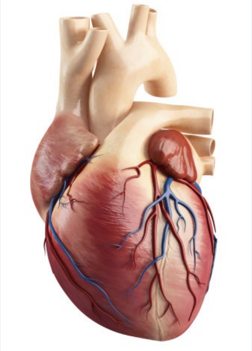
Proteinuria and kidney stones formation



W School of Pharmacy University of Washington
BioServe Space Technologies

PI: Jonathan Himmelfarb

Cardiac dysfunction & engineered heart tissues



Johns Hopkins University
University of Washington
The Ohio State University
BioServe Space Technologies

PI: Deok-Ho Kim

Stanford University
UCSB
BioServe Space Technologies

PI: Joseph Wu

Muscle wasting (sarcopenia)

UF University of Florida
Space Tango
SpacePharma

PI: Siobhan Malany

Gut inflammation & Microbiome

emulate
Space Tango

PI: Christopher Hinojosa

Studies on human biology and disease that otherwise would be difficult or take longer on Earth

- SpaceX 16: December 5, 2018
  - Immunosenescence
- SpaceX 17: May 4, 2019
  - Lung infection/bone marrow; kidney stone formation; osteoarthritis; BBB permeability
- SpaceX 20: March 6, 2020
  - Cardiomyopathy; gut inflammation
- SpaceX 21: Dec 5, 2020
  - Cardiomyopathy; osteoarthritis; muscle wasting
- SpaceX 22: June 3, 2021
  - Kidney stone formation
- SpaceX 24 December 21, 2021
  - Blood-brain barrier
- SpaceX 25 July 15, 2022
  - Immunosenescence; muscle wasting
- SpaceX 26 November 22, 2022
  - Muscle wasting
- SpaceX 27 March 14, 2023
  - Cardiomyopathy

Photo Credit: NASA


Photo Credit: NASA


Photo Credit: Dan Tagle

LONGEVITY EXTENSION OF 3D TISSUES AND MICROPHYSIOLOGICAL SYSTEMS FOR MODELING OF ACUTE AND CHRONIC EXPOSURES TO STRESSORS

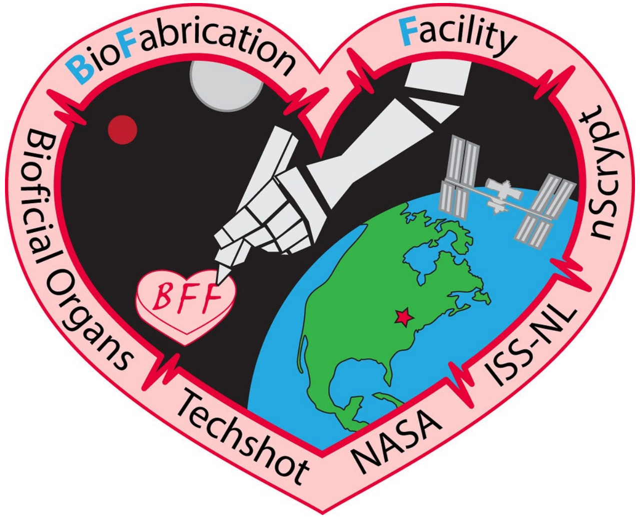
- Partnerships between **NASA, NIH, BARDA and FDA**
- GOALS:
  - To extend the tissue viability and physiological function of tissue chips or microphysiological systems to a **minimum of 6 months**
  - To incorporate automated engineering capabilities for **real-time online readouts** in these complex human in vitro model systems
  - To understand the influence of multiple types of **long-lasting or chronic stressors** on tissue or organ systems and facilitate the translation of results to humans
  - To better understand 1) disease pathomechanisms, 2) drug development, 3) clinical trial design, 4) chemical and environmental exposures and countermeasures, and 5) physiological changes due to the prolonged spaceflight environment

https://science.nasa.gov/science-news/biological-physical/miniature-avatars-take-on-nasas-biggest-challenge

NASA lead – Lisa Carnell

In-space 3-D Bioprinting of Blood Vessels to Model Pre-mature Vascular Aging – Hutchinson-Gilford Progeria

- **Microgravity allows freeform extrusion microfabrication** of complex tissues/organs
- Optimize soft, adhesive ECM bio-inks that allow high-density cells multi-layered functional vascular tissues
- PIs: Shrike Zhang and Marie Gerhard-Herman from Harvard Medical School and Brigham and Women's Hospital
- **Redwire/TechShot BioFabrication Facility at ISS-NL**
- Patient cells from Progeria Research Foundation



npj | Microgravity

www.nature.com/npjmgrav

ARTICLE OPEN

Pembrolizumab microgravity crystallization experimentation

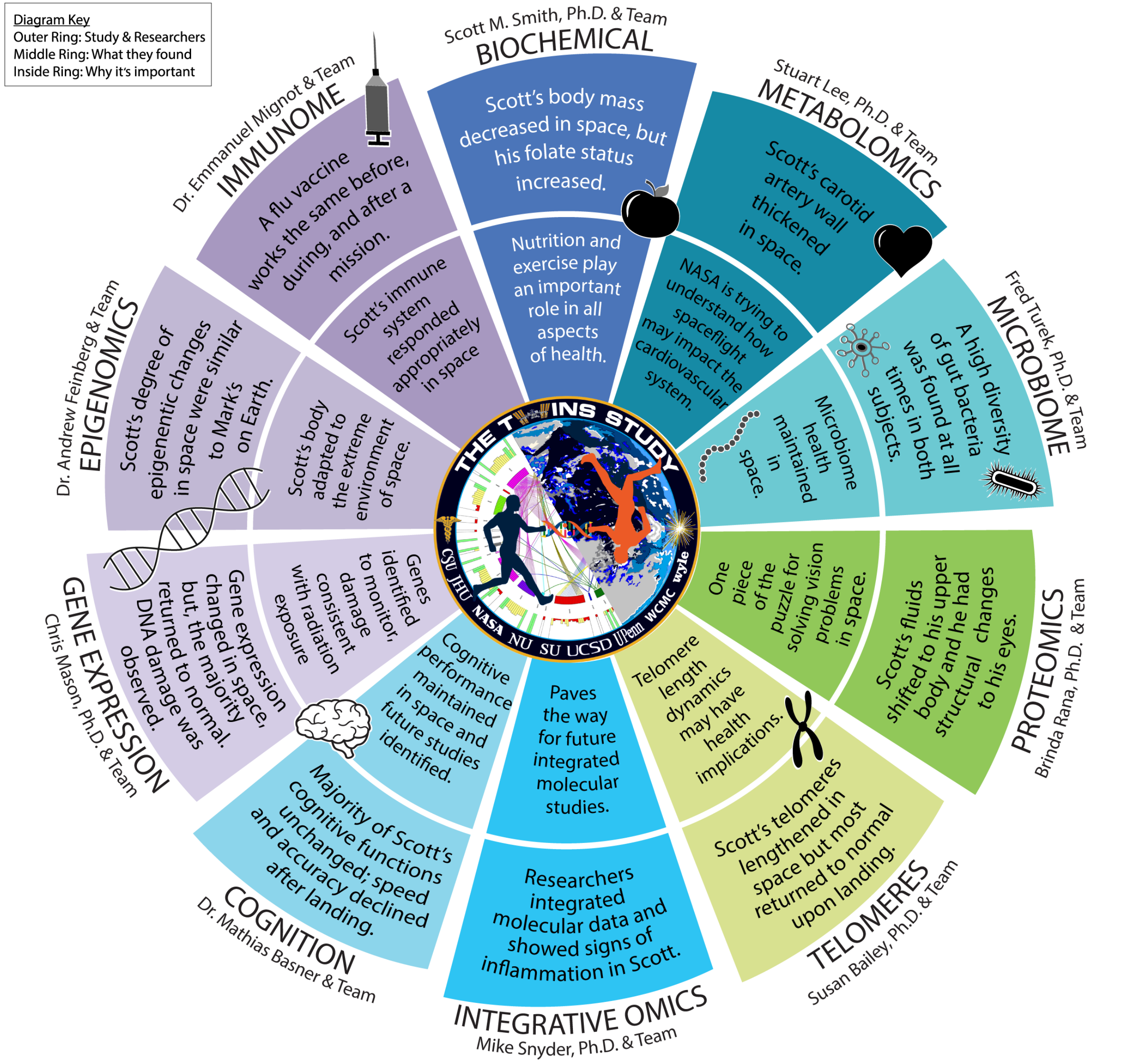
Paul Reichert[1]*, Winifred Prosise[1], Thierry O. Fischmann[1], Giovanna Scapin[1], Chakravarthy Narasimhan[2], April Spinale[3], Ray Polniak[4], Xiaoyu Yang[5], Erika Walsh[2], Daya Patel[5], Wendy Benjamin[2], Johnathan Welch[5], Denarra Simmons[6] and Corey Strickland[1]

Therapeutic mAb Keytruda® (pembrolizumab) is approved by the U.S. Food and Drug Administration (FDA) for the treatment of multiple types of cancer

- Difficult to identify optimal crystallization processes for biologic drugs such as mAbs due to their large size and the flexibility of their structure
- Spaceflight results **informed ground-based production processes**, yielding uniform crystalline suspensions that allowed pembrolizumab to be **administered via a subcutaneous injection** in sharp contrast to the typical intravenous infusion

NASA
Twins Study in Space

Photo and image courtesy of NASA



NASA's Twins Study revealed interesting and assuring data on how a human adapted to space.

SCIENCE 2019 Vol 364, Issue 6436

The **Twins Study team**, which included **several NIH-funded researchers**, detailed many thousands of differences between the Kelley twins at the molecular, cellular, and physiological levels during the **340-day observation period**.

National Center for Advancing Translational Sciences

Digital and Tissue Chip Twins for Precision Medicine

Creation of Digital and Tissue Chip Twins for each Individual to enhance prevention, diagnosis, and treatment of disease in a continuum of care that blends physical and virtual realities in an effective manner

AI Driven In-Silico modelling

- AI utilizes complex algorithms to screen millions of data points to create a **digital twin** and validate pharmacological targets and perform in-silico analysis for safety and efficacy predictions
- AI based target validation and lead discovery is up to **15 times faster than traditional discovery** with lead generations in a few months vs. 4-6 years

Microphysiological Systems (Organs/Tissue Chips)

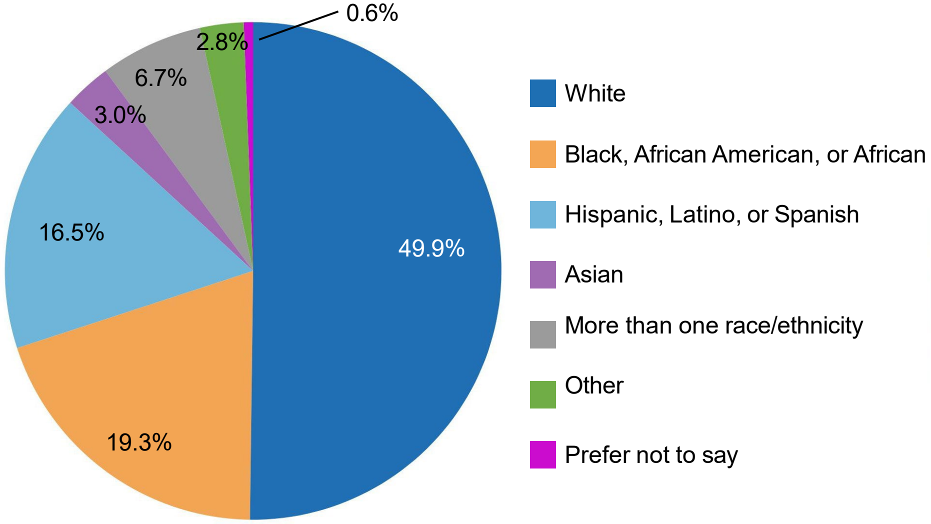
- Organ-on-chip is a microfluidic cell culture chip that simulates activities, mechanics and physiological response of entire organs or systems
- Organ-on-chip models provide a high throughput system with better correlation to human physiology

Digital and Tissue Chip Twins for Precision Medicine

“right medicine to right person at right time” $1.5B over 10 years

- NIH ***All of Us*** program: target >1M individuals across the United States (as of Sep 2022 >**535,000 participants**)

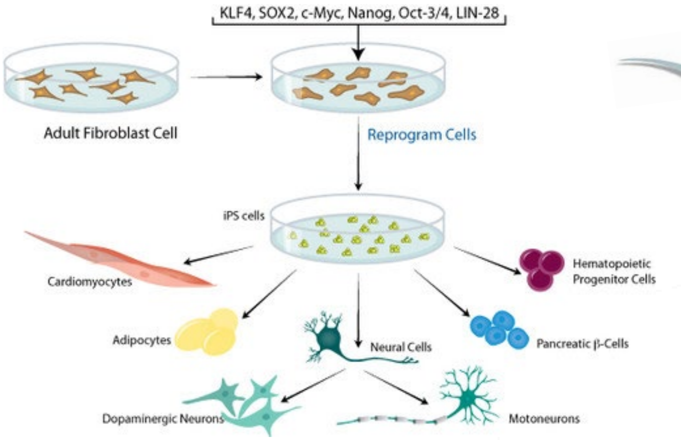
Race and Ethnicity



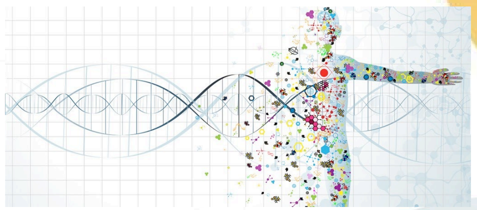
324,000+
Electronic Health Records

394,000+
Biosamples

Digital twin for an individual from **comprehensive longitudinal clinical record** such as medical imaging (e.g. MRI, ultrasound, CT scans); wearable technologies (e.g. smart watches, ECG monitors, glucose monitors); voice recordings; other clinical information; and/or, self-reported data



Tissue chip Twin



Collection of **blood, urine** samples for **omics analysis** (e.g., genomics (whole genome sequencing), transcriptomics, epigenomics, proteomics, metabolomics, microbiomics); **blood to iPSCs**

Potential Discussion: Biomedical Research in LEO

- **Opportunities:**
  - LEO space station(s) as an R&D laboratory for discovery research
  - Make the advantages clear – why do it in LEO, if you can do it on Earth; translation of LEO research that benefits life on Earth; research results that are transformative and catalytic
  - Anticipate medical needs as human presence grows in LEO, and extends to the moon and beyond

- **Challenges:**
  - Biomedical research in LEO is expensive and difficult to access which makes iterative experiments hard
  - Must enable robust, reliable, and reproducible research
  - Legal liabilities and ownership of IP while conducting research in space, especially in a commercial environment

- **Gaps:**
  - Funding is not easy – need PPP, sustainable funding streams
  - Crew time is limited and with little to no laboratory research experience – need STEM and workforce development
  - Lab certifications that might be needed, e.g. GMP facility for biomanufacturing capabilities