Rodent Research on ISS
NASA Update

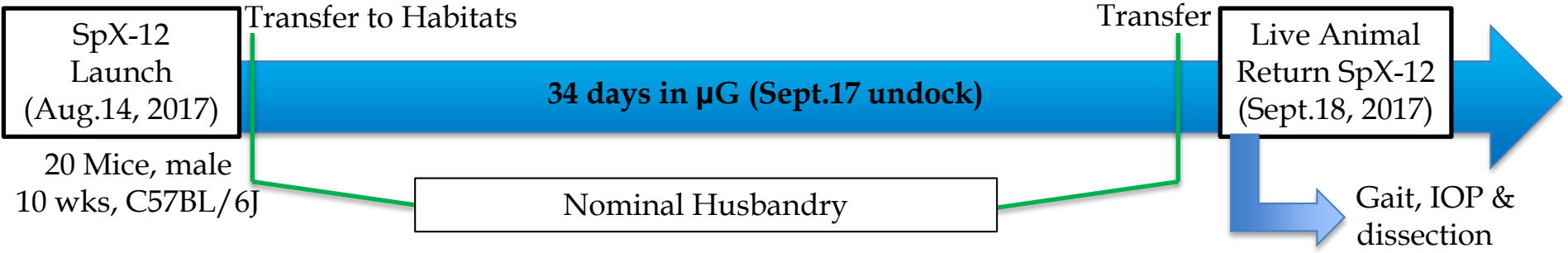
National Aeronautics and
Space Administration

Dennis Leveson-Gower

Joint Working Group

December 2018

Rodent Research-9: update



Upon return to earth:

- All 20 mice return from Long Beach to Loma Linda University and were deemed healthy by a veterinarian. Mice were observed to be actively moving about the Transporter and grooming. No visible signs of stress or dehydration.
- Intraocular pressure (IOP) and gait measurements taken before dissections
- Dissections conducted over ~ 24 hrs in coordination with Ames Biospecimen Sharing (BSP) Team and included measurements on live blood and lymph vessels *ex vivo*.
- Original Ground control animal were lost at KSC due a hurricane and needed to be redone. To compensate for differences between cohorts, animals from original flight cohort that were still available from Jackson Labs were dissected after Flight animals. These would be similar to "vivarium controls" but were aged at the vendor and not KSC.

Specific Research Aims of Investigators:

Delp:

- Aim 1. To determine whether spaceflight alters rodent basilar artery spontaneous tone, myogenic and KCl-evoked vasoconstriction, mechanical stiffness and gross structure.
- Aim 2. To estimate whether spaceflight alters the blood-brain barrier in rodents, as indicated by ultrastructural examination of the junctional complex of the cerebral capillary endothelium.
- Aim 3. To determine whether spaceflight alters rodent basal vein (inside cranium) and jugular vein (outside cranium) spontaneous tone, myogenic and KCl-evoked constriction, distension, and gross structure.
- Aim 4. To determine whether spaceflight alters the ability of the cervical lymphatics to modulate lymph flow, and thus, regulate cerebral fluid homeostasis,

Willey:

- Aim 1: Determine the extent of knee and hip joint degradation in mice after 30 days of spaceflight.
- Aim 2: Use the DigiGait System to assess gait patterns before and after returning from the ISS.

Mao:

- Aim 1. Define relationships between spaceflight condition-induced oxidative stress in reactive oxygen species (ROS) expression and retinal vascular remodeling and BRB function in mice return to Earth alive.
- Aim 2. Determine whether spaceflight condition-induced oxidative damage in the retina is mediated through photoreceptor mitochondrial ROS production.

Rodent Research-7: Background

Investigation Name: Effects Effects of Spaceflight on Gastrointestinal Microbiota in Mice: Mechanisms and Impact on Multi-System Physiology (NNX15AL05G)

PI: Turek, Fred W Ph.D. Northwestern University

Co-Is: Green S PhD (University of Illinois),

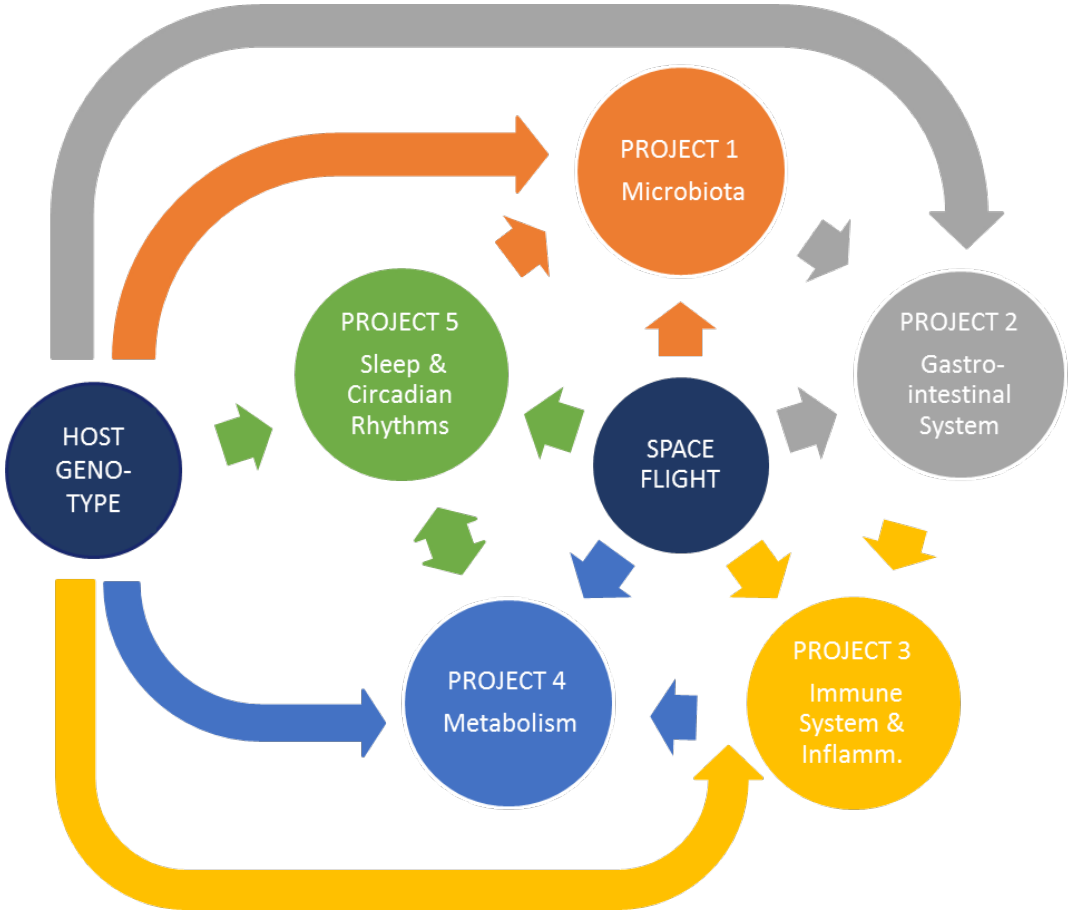
Keshavarzian A MD (Rush University),

Forsyth C PhD (Rush University), and

Vitaterna MH PhD (Northwestern University)

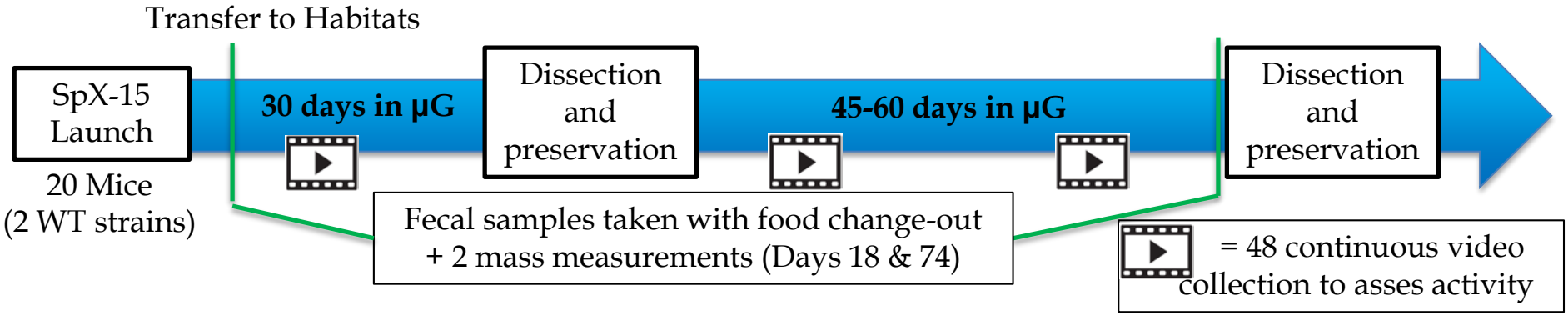
Specific Aims:

1. To define changes in microbiota as a function of time in space.
2. To define gene expression and physiological changes in the colon produced by the space environment, and correlate these markers with assessments of dysbiosis.
3. To define gene expression and changes in the immune system directly impacted by gastrointestinal barrier function.
4. To define gene expression and endocrine changes relevant to metabolism as they relate to other system changes and environmental variables.
5. To determine if spaceflight-associated changes in GI microbiota are exacerbated by the disruptions of sleep and circadian rhythms of spaceflight.



Space Biology Identified relevance/impact: These studies will examine the impact of the space environment on the population structure of the intestinal microbiota of mice, and how multiple physiological systems involving the gastrointestinal (GI), immune, metabolic, circadian, and sleep systems, known to be affected by the microbiota, are impacted by the space environment. The proposed studies will elucidate mechanisms underlying interactions between GI, immune, metabolic, and sleep functions and specifically the role of the microbiota in these interactions. The impact of the proposed studies extends beyond understanding the mechanisms at play in the unique stresses of spaceflight. This knowledge has tremendous potential for guiding development of dysbiosis-targeted interventions for disorders in all of these systems.

Rodent Research-7: Experiment Summary



- Project 1 (University of Illinois at Chicago, PI: SJ Green) will carry out metagenomic sequencing of microbiota from fecal samples and cecal contents.
- Projects 2 and 3 (Rush University Medical Center, PIs: A Keshavarzian and C Forsyth) will use gene expression, physiological and histologic measures of gastrointestinal and immune function respectively.
  - Project 2 will define gene expression and physiological changes in the colon produced by the space environment.
  - Project 3 will define gene expression and changes in the immune system directly impacted by gastrointestinal barrier function.
- Projects 4 and 5 (Northwestern University, PIs: FW Turek and MH Vitaterna) will focus on metabolism, sleep, and circadian behavioral organization.
  - Project 4 will define gene expression and endocrine changes relevant to metabolism as they relate to other system changes and environmental variables.
  - Project 5 will use a set of ground-based controls subjected to sleep/wake and circadian disturbances that mimic the effects of spaceflight on the timing and duration of sleep/wake and feeding behavior

Current Status

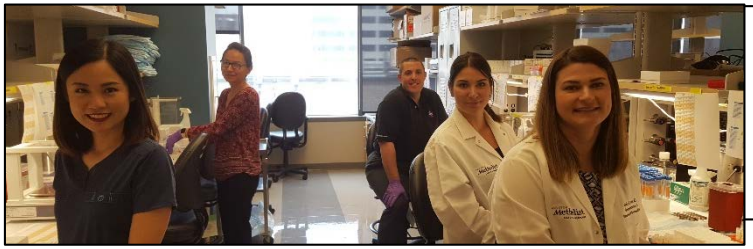
- Total duration in µG was 75-77 days, the longest experiment to date
- Most experiment requirements were met, with minor deviations (e.g. reduced number of mass measurements)
- Frozen tissues and carcass sections being returned to PI lab, coordinated PI / BSP dissections will occur early in 2019.
- PI will published results of pre-flight hind limb unloading studies (for strain selection) in addition to results of flight experiment

Rodent Research BSP Planning

- Rodent Research-7
  - Directed BSP with 5 investigators identified from Northwestern University. 13 tissue types identified for NASA.
  - Possibility for tissue sharing with IMBP.
- Rodent Research-11
  - MOU being drafted to determine which tissues will be used by GeneLab. 21 tissue types identified for NASA.
  - Possibility for tissue sharing with IMBP.
- Rodent Research-12
  - MOU being drafted to determine which tissues will be used by GeneLab. 29 tissue types identified for NASA.
  - Possibility for tissue sharing with IMBP.
- Rodent Research-10
  - CASIS co-sponsored BSP. 17 tissue types identified for NASA.
  - MOU being drafted to determine which tissues will be used by GeneLab.
  - Possibility for tissue sharing with IMBP.

Biospecimen Sharing Program

BSP Accomplishments	Date
MHU-2 JAXA Ground control dissections completed at JAXA- Tsukuba, Japan. This concluded the MHU-2 dissections (Live Animal Return dissections were in September 2017). • 8 Tissue types collected. • 7 tissues stored in ALSDA, 1 tissue sent to BSP collaborator.	March 2018
Rutkove rat dissections (ground study) completed at Harvard Medical School/Beth Israel Deaconess Medical Center, Boston, Massachusetts. • 8 Tissue types collected- all stored in ALSDA.	April 2018
RR-6 Live Animal Return and Ground Control dissections completed at Novartis, San Diego, CA and Houston Methodist Research Center, Houston, TX. This concluded the RR-6 dissections (Baseline dissections were in December 2017). • 19 Tissue types collected. • 14 tissues stored in ALSDA, 5 tissues sent to GeneLab.	January and May 2018
RR-9 Ground control dissections completed at KSC, Florida. This concluded the RR-9 dissections (Live Animal Return dissections were in September 2017). • Over 40 Tissue types collected and stored in ALSDA. • Over 10 tissues sent to GeneLab and awarded to tissue recipients.	June 2018



Pictures: RR-6 PI and NASA teams at Houston Methodist Research Center.

Biospecimen Sharing Program

Upcoming Milestones	Date
RR-7 Flight and Ground Control dissections at Northwestern University, Evanston, Illinois. • 13 Tissue types will be collected.	January 2018
RR-11 Baseline dissections at Kennedy Space Center, FL and Flight/Ground Control dissections at University of California- San Francisco, CA. • 21 Tissue types will be collected.	February and March 2018
MHU-2 JAXA Live Animal Return dissections at Explora BioLabs, San Diego, CA. • TBD Tissue types that will be collected.	March 2018
RR-12 Baseline dissections at Wallops Flight Facility/Eastern Virginia Medical School, VA. • 29 Tissue types will be collected.	April 2018
RR-10 Baseline dissections at Kennedy Space Center, FL. • 17 Tissue types will be collected.	October 2018

Picture: RR-9 PI and NASA Teams at KSC.