National Aeronautics and Space Administration

Mitochondria Dysfunction Central in Driving Health Risks Associated with Spaceflight

Afshin Beheshti, PhD

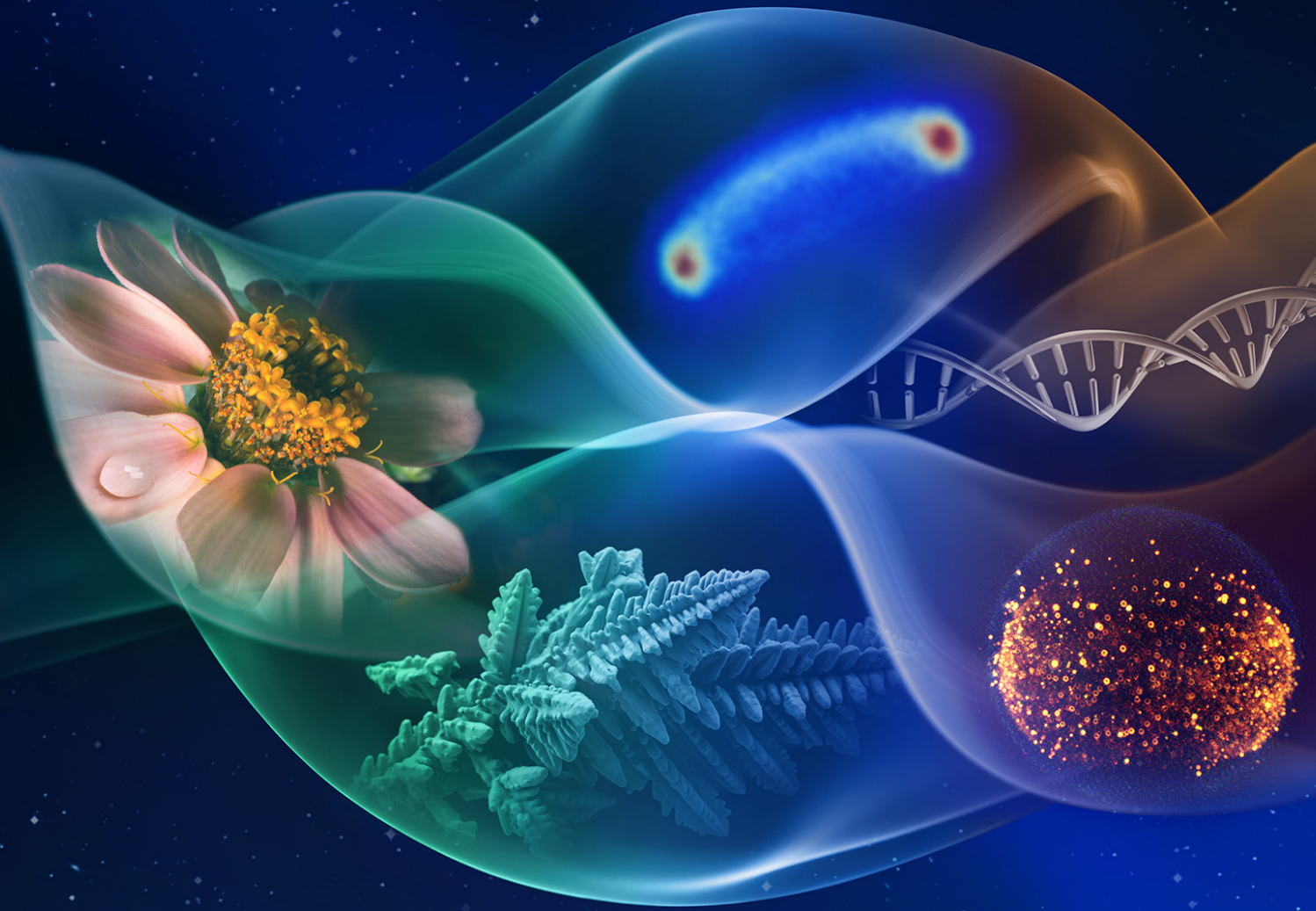
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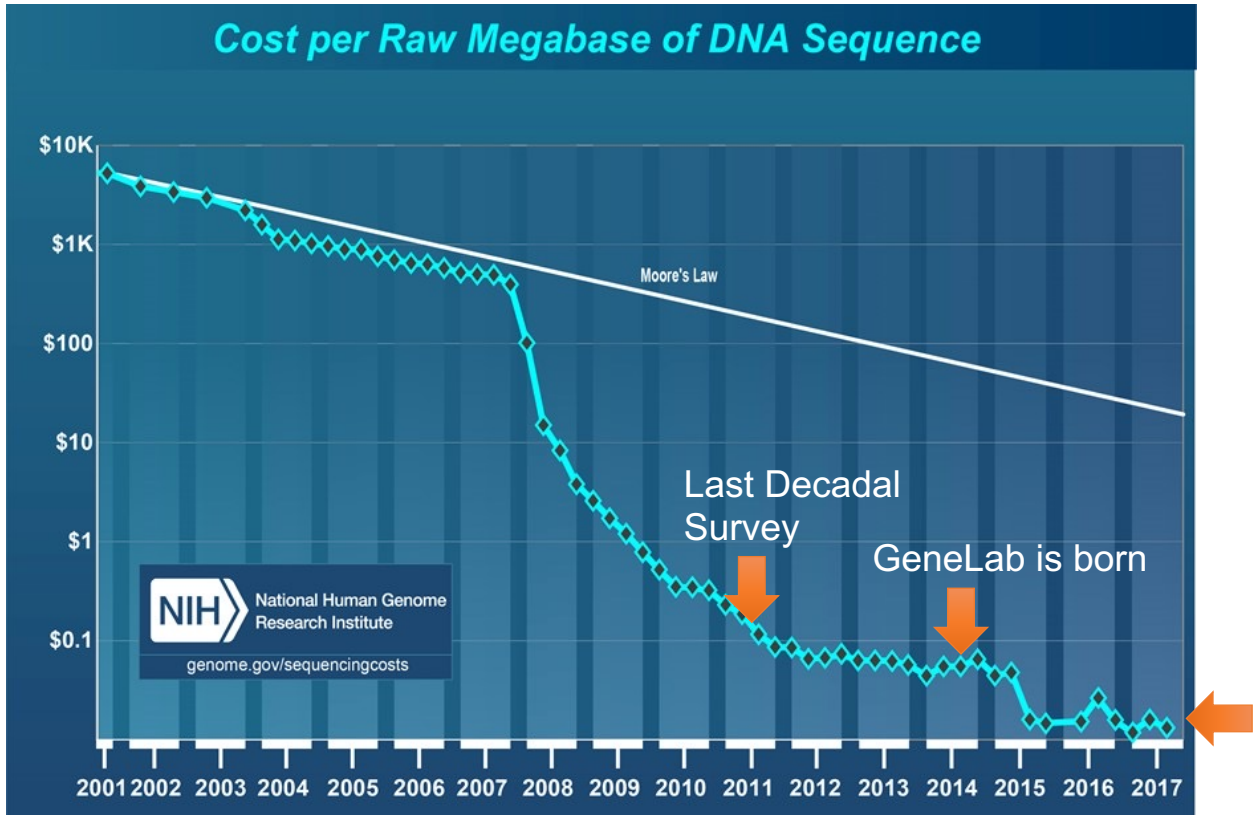
President
COVID-19 International Research Team (COV-IRT)
afshin.beheshti@cov-irt.org
www.cov-irt.org

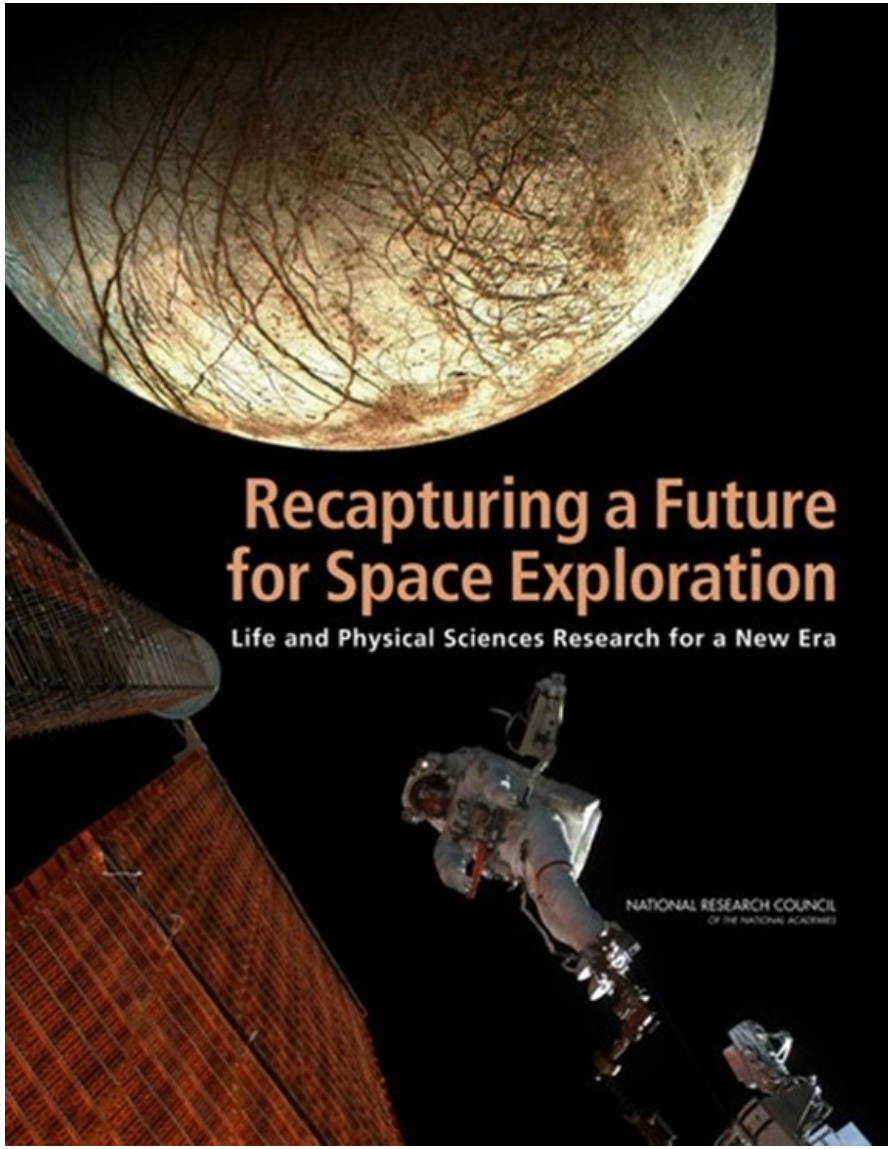


Background on Spaceflight, Experiments, and Resources for the Data That was used for the Mitochondrial project



2011 NRC Decadal Survey and the Sequencing Paradigm Shift

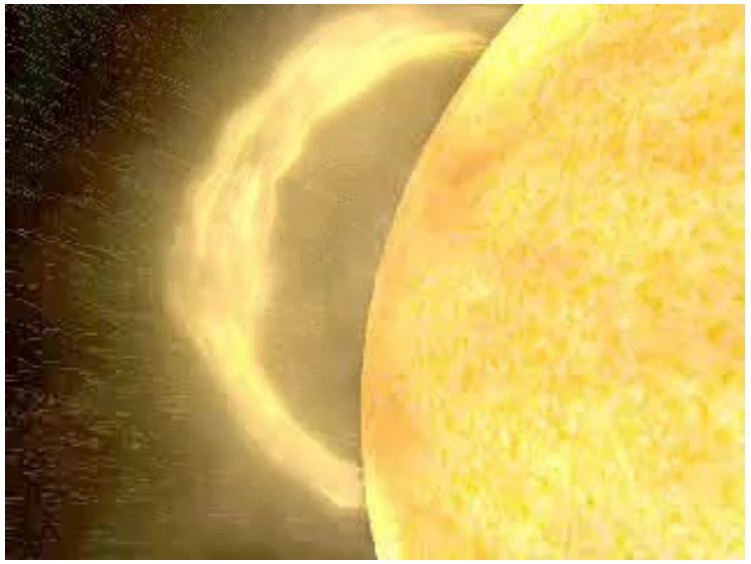




*"…**genomics, transcriptomics, proteomics, and metabolomics** offer an immense opportunity to understand the effects of spaceflight on biological systems…"*

*"…Such techniques generate considerable amounts of **data that can be mined and analyzed** for information by multiple researchers…"*

Space Environment



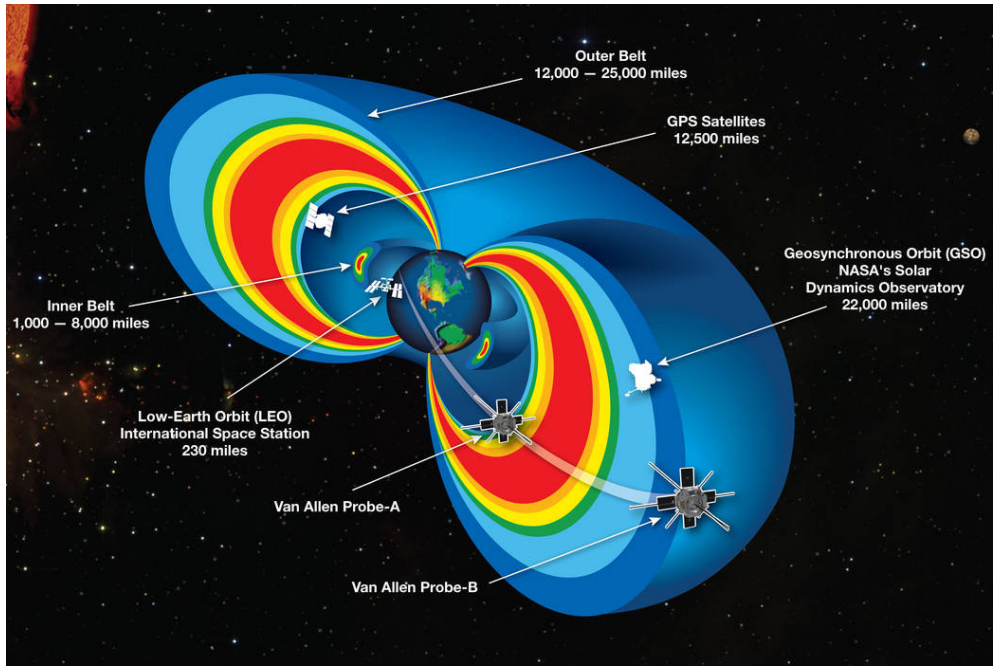


Image obtained from: https://www.nasa.gov/mission_pages/sunearth/news/gallery/20130228-radiationbelts.html

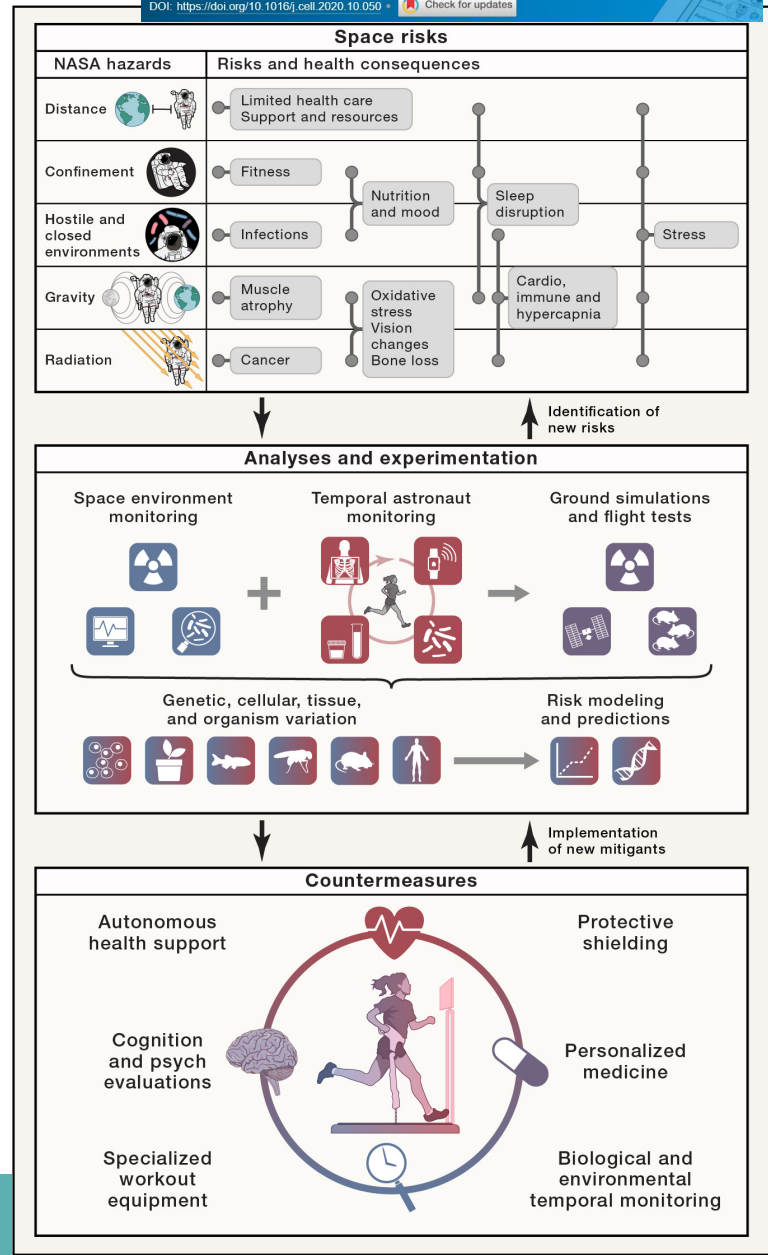


Cell

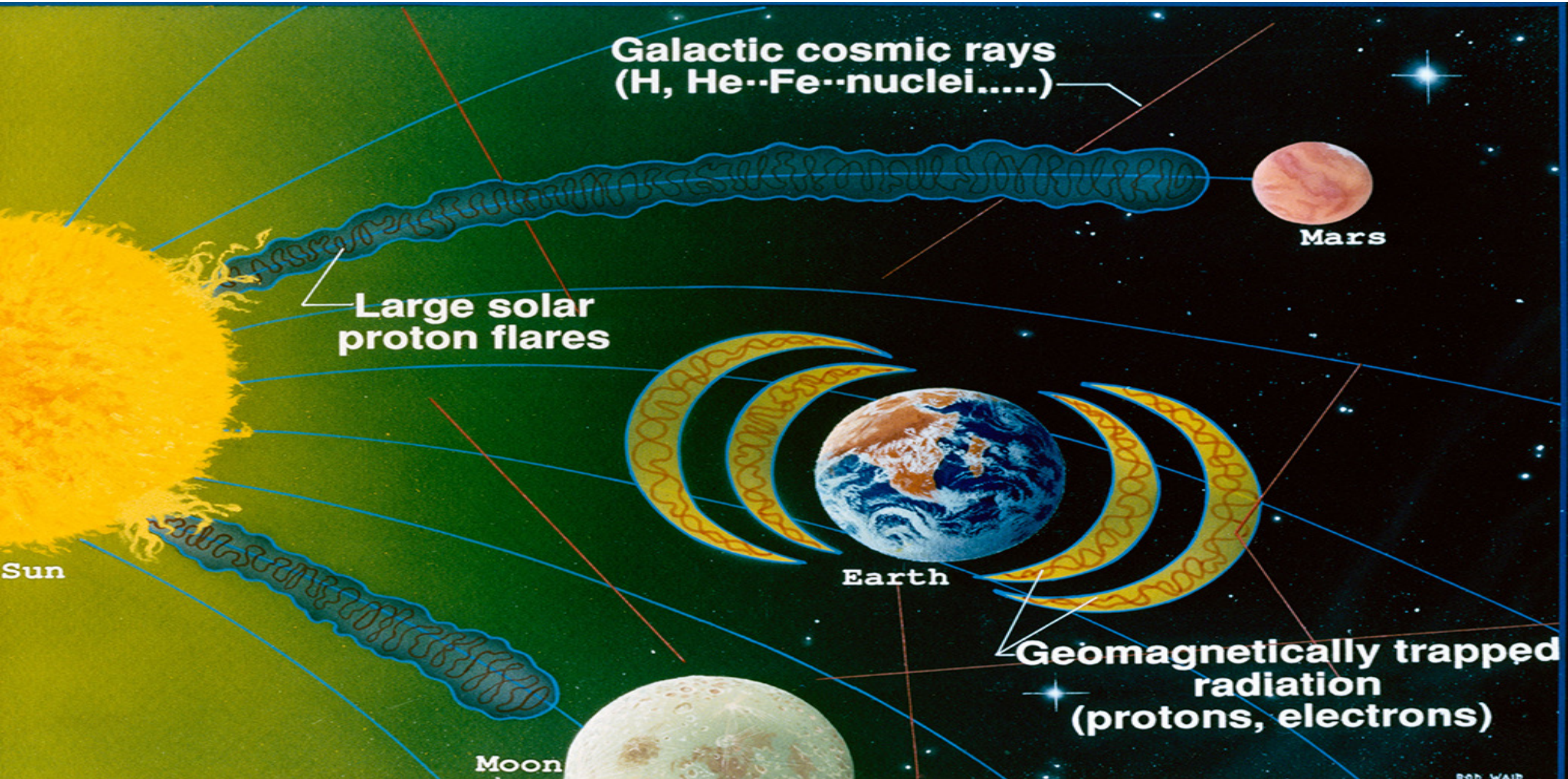
Fundamental Biological Features of Spaceflight: Advancing the Field to Enable Deep-Space Exploration

Ebrahim Afshinnekoo [34] • Ryan T. Scott [34] • Matthew J. MacKay [34] • ... Sylvain V. Costes [35] • Christopher E. Mason [35] • Afshin Beheshti [35] • Show all authors • Show footnotes

DOI: https://doi.org/10.1016/j.cell.2020.10.050 • Check for updates

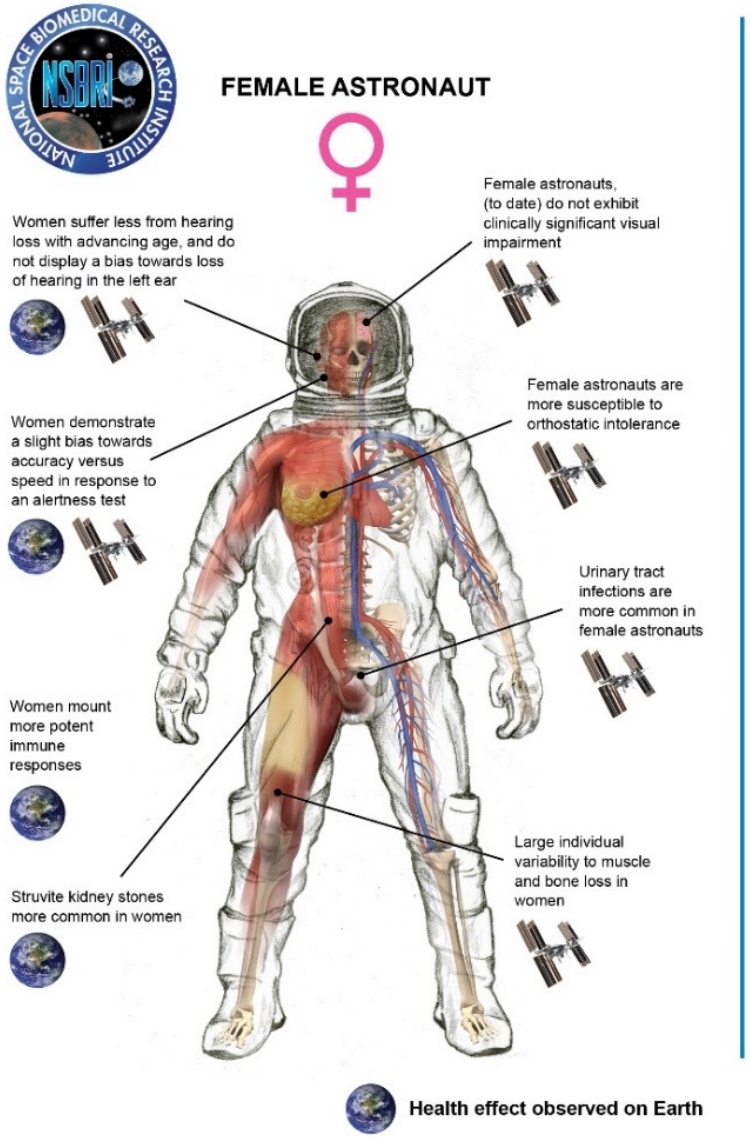


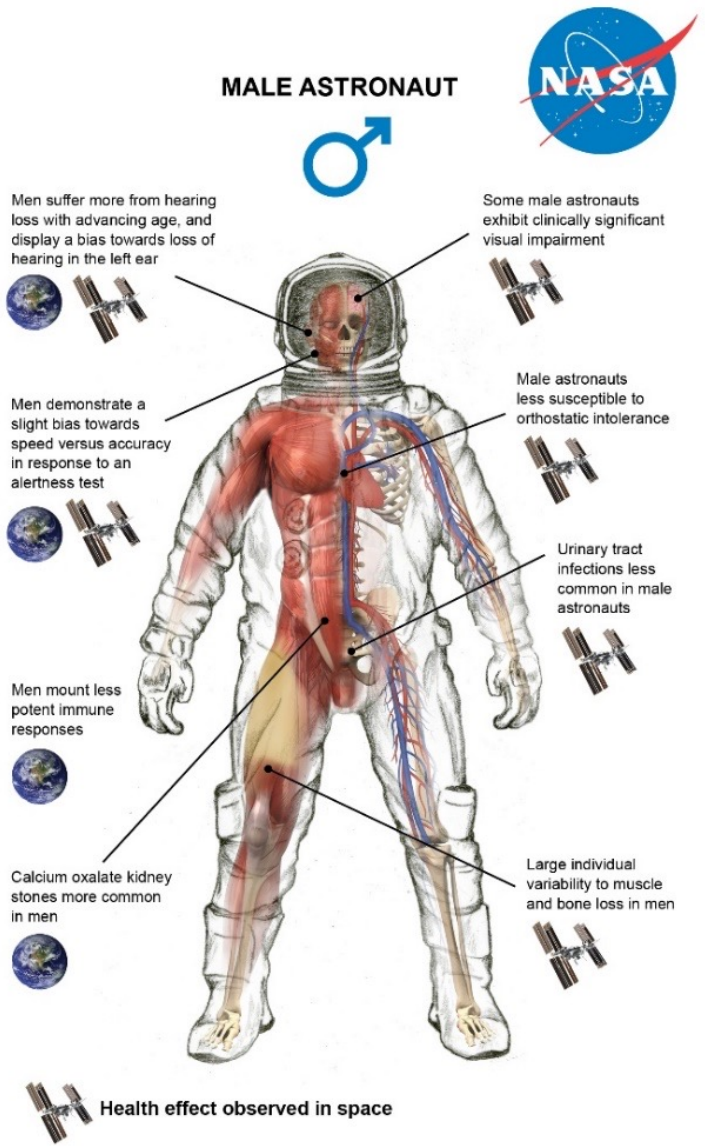
Deep Space Radiation



Space Environment Health Risks On Astronauts

Cell
Fundamental Biological Features of Spaceflight: Advancing the Field to Enable Deep-Space Exploration
Ebrahim Afshinnekoo [34] • Ryan T. Scott [34] • Matthew J. MacKay [34] • ... Sylvain V. Costes [35] • Christopher E. Mason [35] • Afshin Beheshti [35] • Show all authors • Show footnotes
DOI: https://doi.org/10.1016/j.cell.2020.10.050 • Check for updates



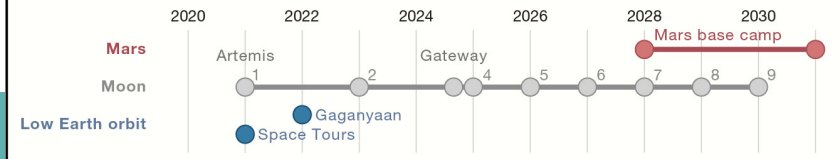


A Mission and long-term health risks

Mission type	Low Earth orbit		Low Earth orbit		Deep space sortie		Lunar visit/ habitat		Deep space journey		Planetary visit/habitat	
Mission duration	6 months		12 months		1 month		12 months		12 months		36 months	
Return duration	<= 1 day		<= 1 day		< 5 days		5 days		Weeks/ months		Months	
Radiation	Van Allen		Van Allen		Deep Space		Lunar		Deep Space		Variable	
Gravity	Micro		Micro		Micro		1/6g		Micro		Variable	
Health risks	Mission	Long-term	Mission	Long-term	Mission	Long-term	Mission	Long-term	Mission	Long-term	Mission	Long-term
Renal	🟡	🟡	🟡	🟡	🟡	🟡	🟡	🟡	🔴	🔴	🔴	🔴
Medical	🟡	🟡	🟡	🟡	🟡	🟢	🟡	🟡	🔴	🔴	🔴	🔴
SANS	🟡	🟡	🟡	🟡	🟢	🟢	🟡	🟡	🔴	🔴	🔴	🔴
Arrhythmia	🟡	🟡	🟡	🟡	🟡	🟡	🟡	🟡	🔴	🟡	🔴	🟡
BMed	🟡	🟡	🟡	🟡	🟡	🟢	🟡	🟡	🟡	🟡	🔴	🔴
Occupant protection	🟡	🟡	🟡	🟡	🟡	🟡	🟡	🟡	🟡	🟡	🟡	🟡
Hypobaric hypoxia	🟡	🟡	🟡	🟡	🟡	🟢	🟡	🟡	🟡	🟡	🟡	🟡
EVA	🟢	🟡	🟢	🟡	🟡	🟡	🟡	🟡	🟡	🟡	🟡	🔴
Degen	🟢	🟡	🟢	🟡	🟢	🟡	🟢	🟡	🟢	🔴	🟢	🔴
CNS	🟢	🟡	🟢	🟡	🟢	🟡	🟢	🟡	🟡	🟡	🟡	🟡
Team	🟡	🟢	🟡	🟢	🟡	🟢	🟡	🟢	🟡	🟢	🔴	🟡
Sleep	🟡	🟢	🟡	🟢	🟡	🟢	🟡	🟢	🟡	🟡	🟡	🟡
Sensorimotor	🟡	🟢	🟡	🟢	🟡	🟢	🟡	🟢	🟡	🟢	🟡	🟡
Cancer	🟢	🟡	🟢	🟡	🟢	🟢	🟢	🟡	🟢	🔴	🟢	🔴
Muscle	🟡	🟢	🟡	🟢	🟡	🟢	🟡	🟢	🟡	🟢	🟡	🟡
Aerobic	🟡	🟢	🟡	🟢	🟡	🟢	🟡	🟢	🟡	🟢	🟡	🟡
Immune	🟡	🟢	🟡	🟢	🟡	🟢	🟡	🟢	🟡	🟢	🟡	🟡
Microhost	🟡	🟢	🟡	🟢	🟡	🟢	🟡	🟢	🟡	🟢	🟡	🟡
DCS	🟢	🟢	🟢	🟢	🟡	🟢	🟡	🟢	🟡	🟢	🟡	🟢
Stability	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🔴	🔴
OI	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟡	🟢
ARS	🟢		🟢		🟢		🟢		🟢		🟢	
Dust							🟡	🟡				

Risk level 🟢 Low 🟡 Medium 🔴 High

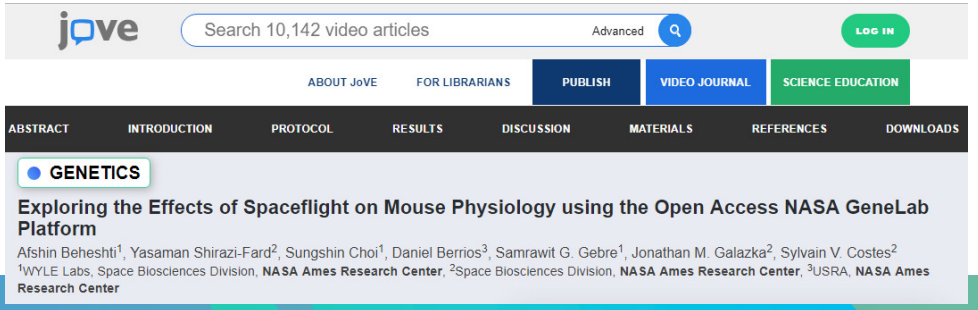
B Planned human missions



Type of Experiments Related to Space Biology

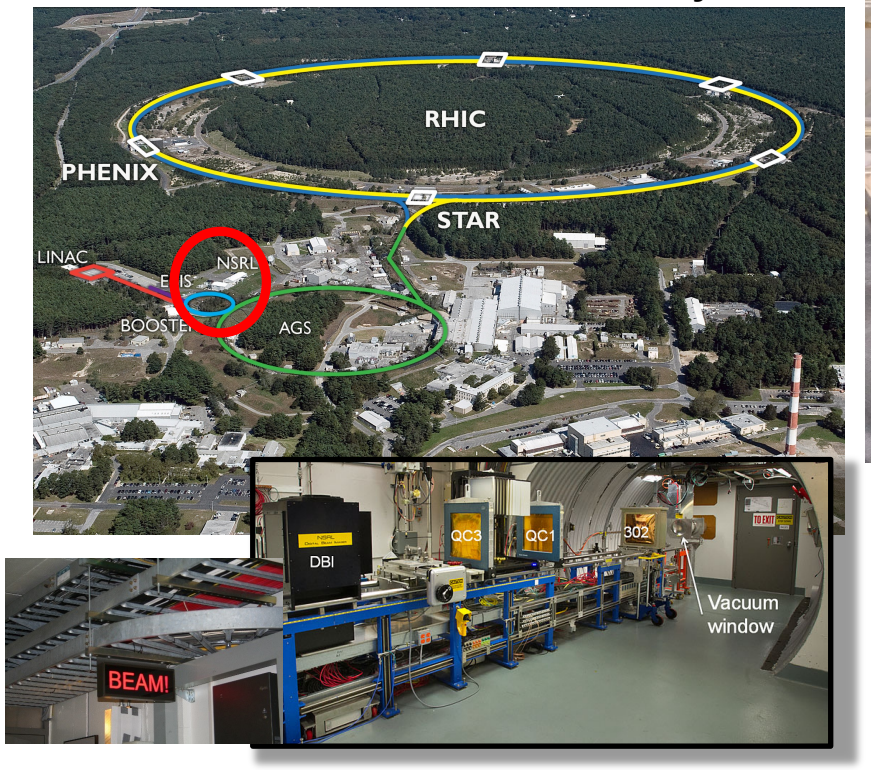
Experiments Done in Space





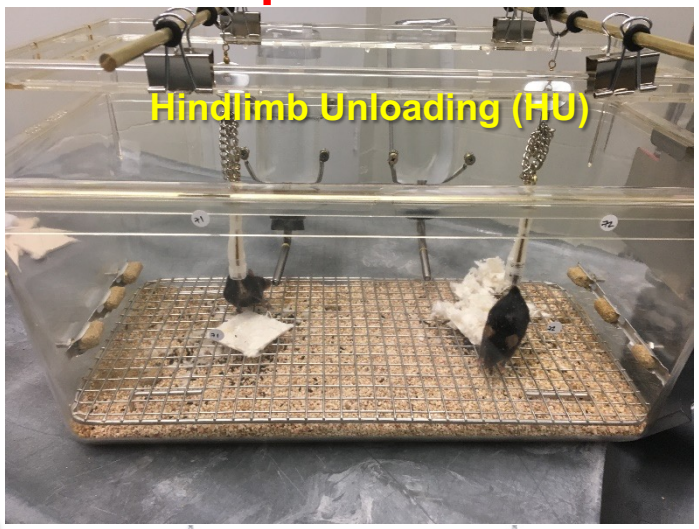
Space Radiation Simulated Experiments

Brookhaven National Laboratory



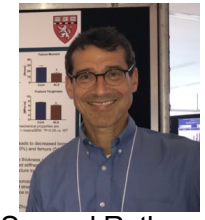


Microgravity Simulated Experiments



Partial Weight Bearing Rat Model





Seward Rutkove



Marie Mortreux

Beth Israel Deaconess Medical Center
A teaching hospital of Harvard Medical School

https://www.rutkovelab.org/nasa/

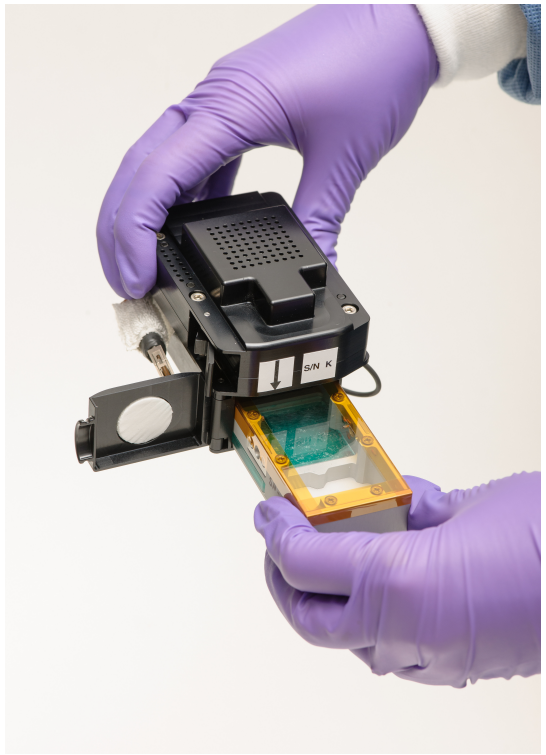
Other Types of Experiments on the ISS







Credits: NASA/Ames Research Center/Dominic Hart



Each fly cassette—a food-containing habitat for fruit flies—fits inside of a camera and lighting unit that records high-definition video and provides a day/night cycle for the flies.

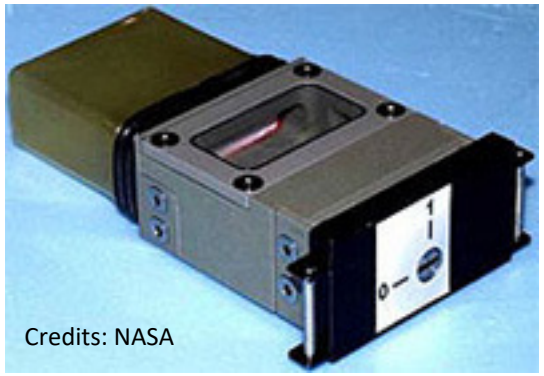


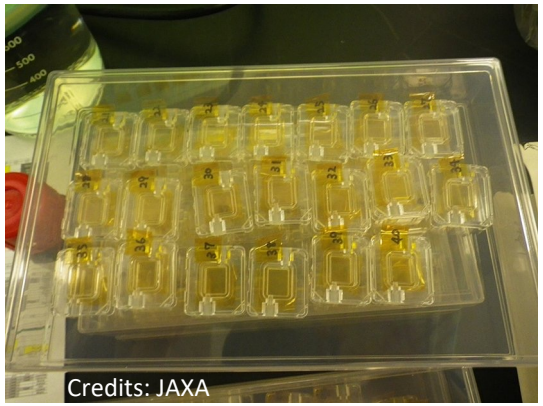
An astronaut placing Vented Fly Boxes into the correct configuration inside an incubator on the International Space Station.

Credits: NASA/Ames Research Center/Christina Cheung

Other Types of Experiments on the ISS

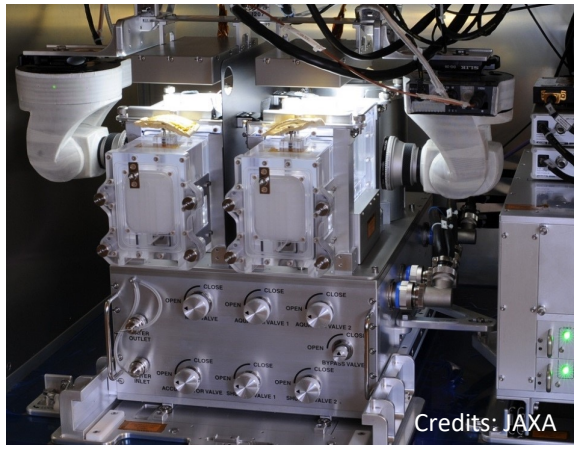


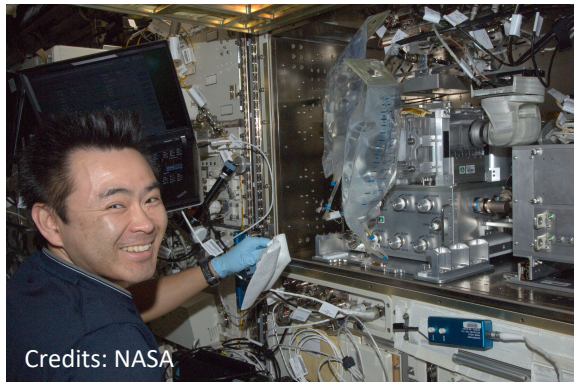




C. elegans culture chambers for the Space Aging experiment aboard the ISS

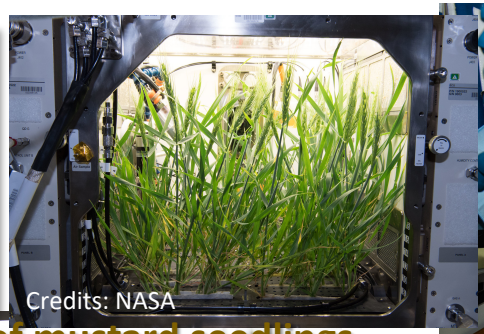






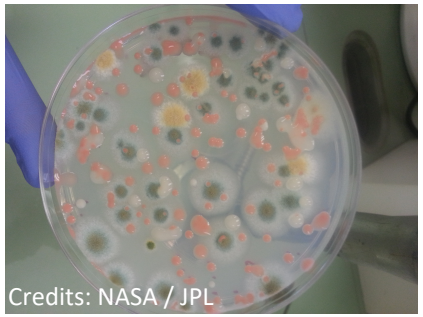
The Zebrafish Muscle investigation employs the ISS Aquatic Habitat, an aquarium in microgravity.

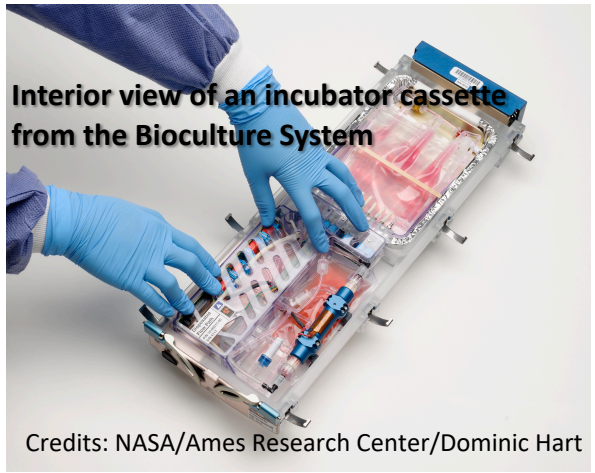






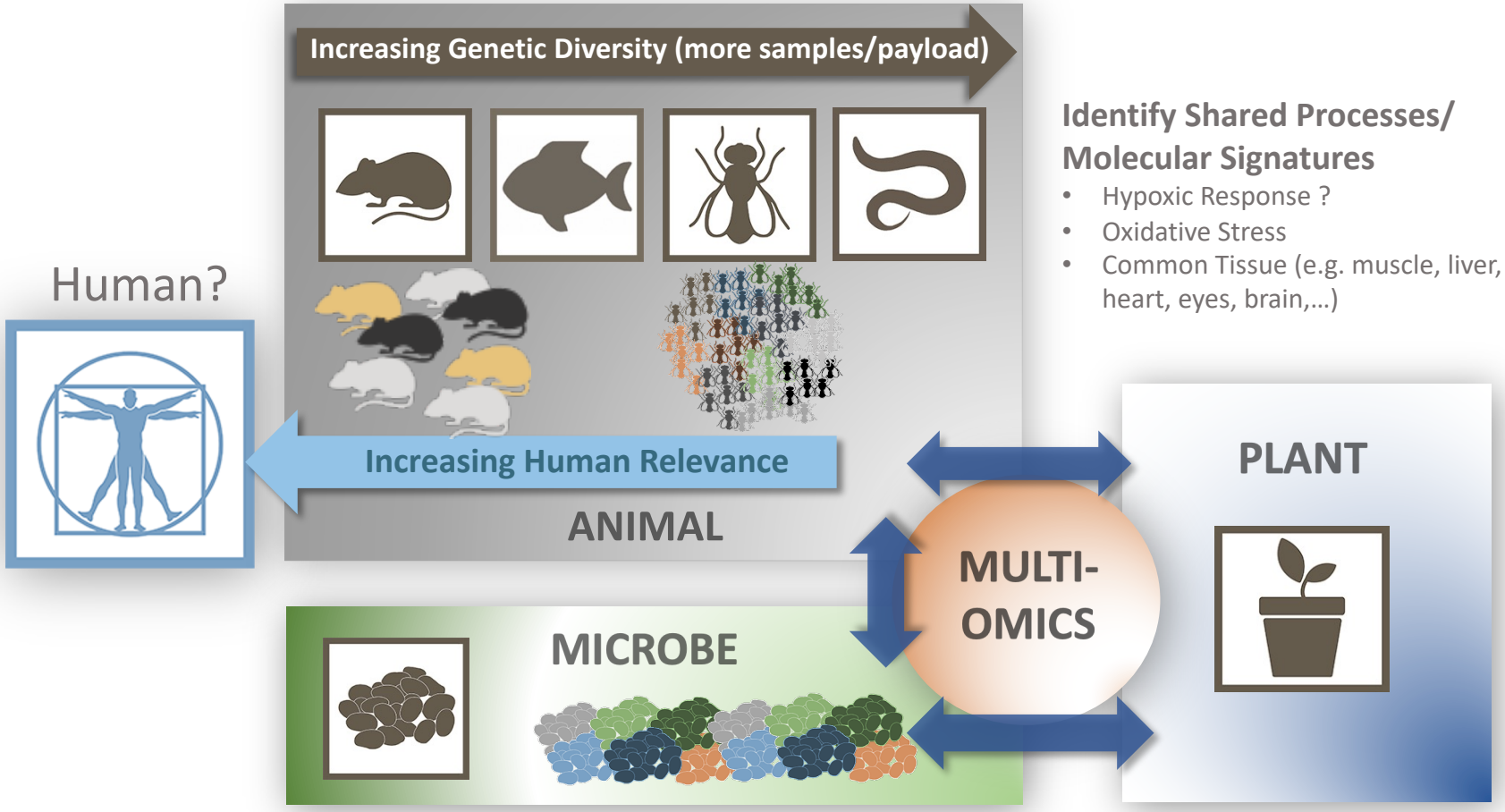






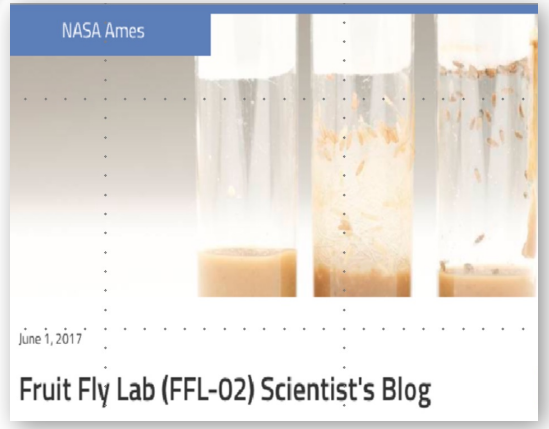


GeneLab ecosystem: maximizing knowledge by bringing experiments together as a system



Identify Shared Processes/ Molecular Signatures

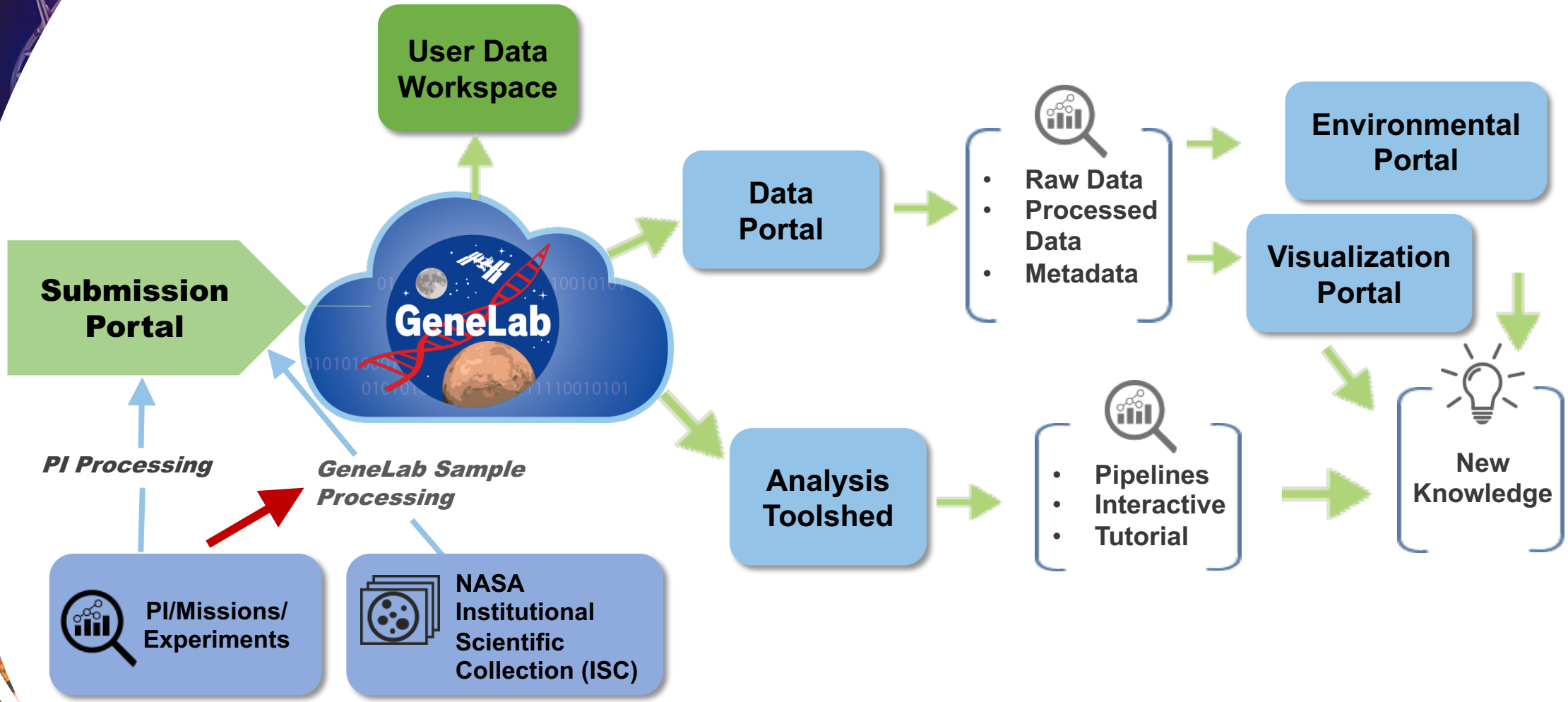
- Hypoxic Response ?
- Oxidative Stress
- Common Tissue (e.g. muscle, liver, heart, eyes, brain,…)



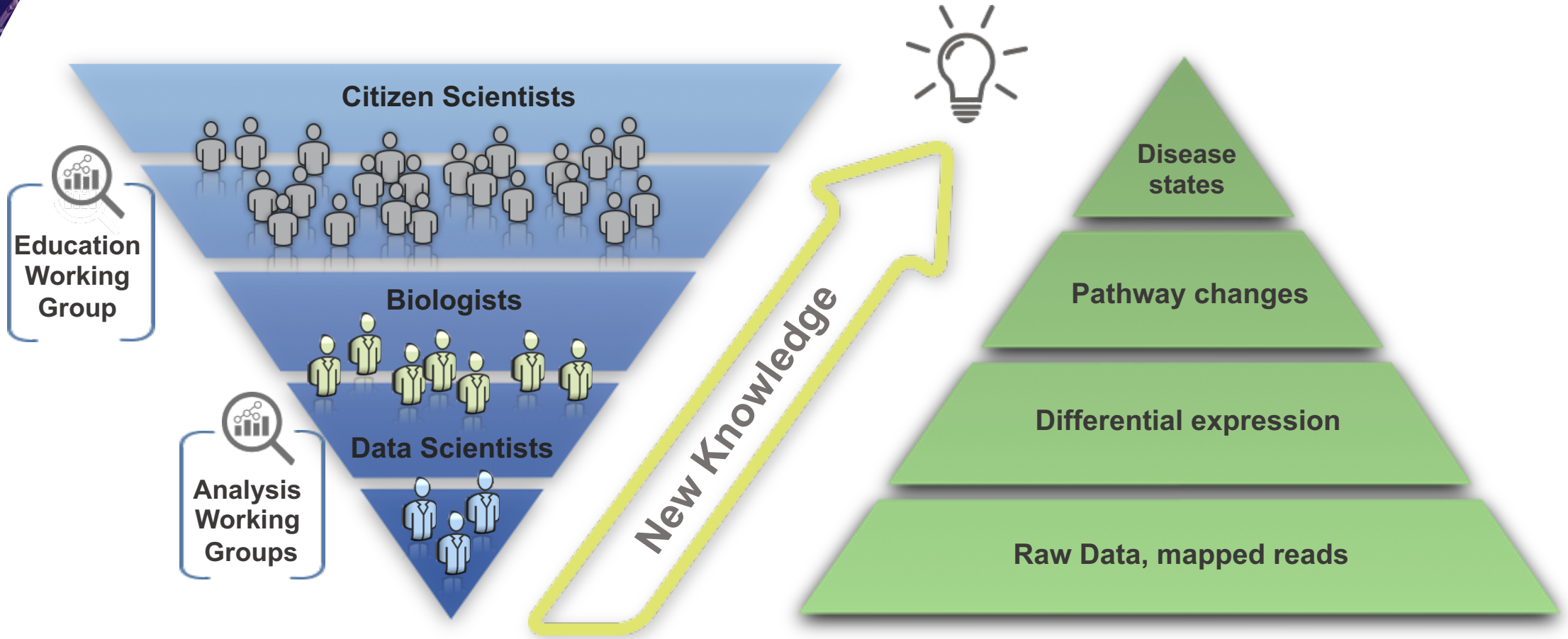
For Spaceflight

- High “n” number – statistically significant data
- Genetically identical animals
- Low resource requirements
- Short life cycle - multiple generations
- Measure response of a whole multicellular animal
- **Flies used as a model for humans for innate immunity, circadian rhythm, oxidative stress, neurobehavior, development, genetics, GWAS, “omics” studies etc**

GeneLab Data Democratization



Data Democratization



GeneLab Power Users

GeneLab Analysis Working Groups (AWGs) *consist of 120+ scientists from multiple space agencies, international institutions, and industry. Scientists meet monthly with each group to analyze data in the GeneLab repository. Majority of members are non-NASA PI's – many have applied for NASA funding following AWG interactions.*

https://genelab.nasa.gov/awg/join

Total AWG Members: ~150

Members are now group leads

AWG Members Per Group:

Animal	30
Multi-Omics/System Biology	65
Plants	15
Microbes	17

**Some members are in multiple groups*

Educational Working Work (EWG) *consists of educators and scientists spanning across high school and college, focusing on developing content to learn about spaceflight OMICS, promoting the use of GeneLab's database via the repository, and the visualization and analytical portals.*

Contact us for more information.



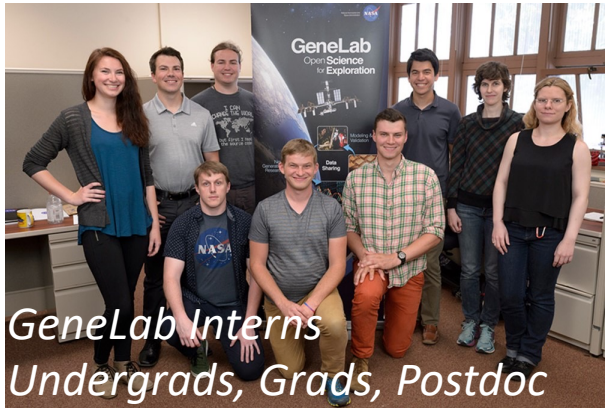
GeneLab for High School (Tutorial + Tools)

SJSU SAN JOSÉ STATE UNIVERSITY

GeneLab included in Bioinformatics curriculum of degree granting university



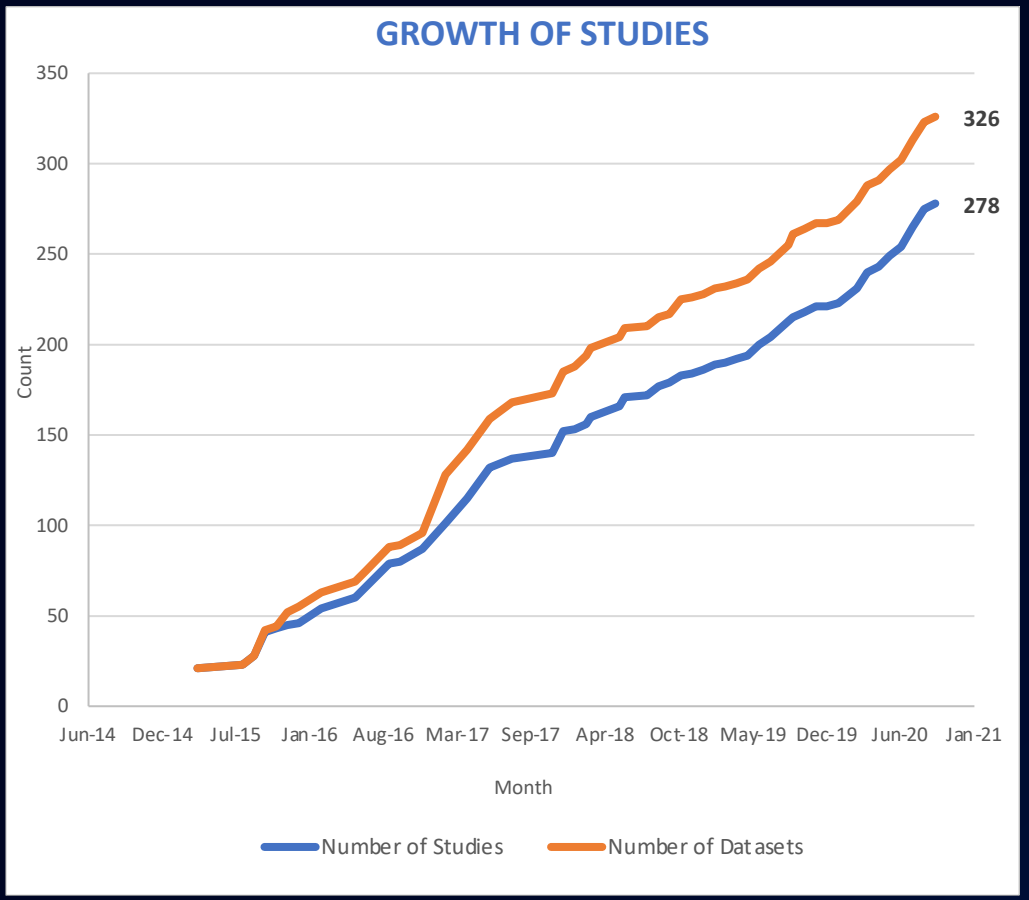
Annual AWG Workshop



GeneLab Interns Undergrads, Grads, Postdoc

AWG Members represent:

- 48 US Universities
- 4 NASA Centers
- 4 Other Government-funded Organizations
- 3 Institutes or Private Industry
- 3 International Universities



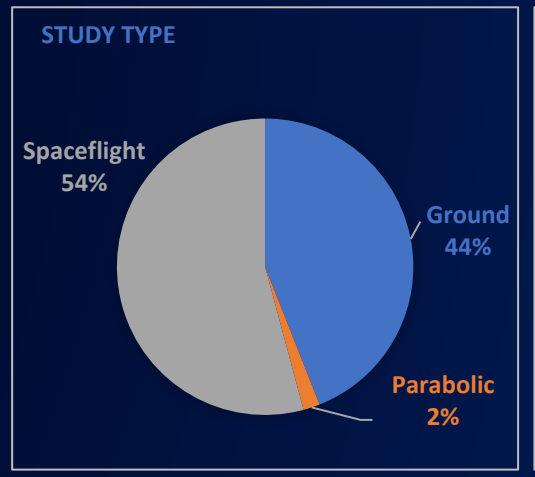
298
Studies

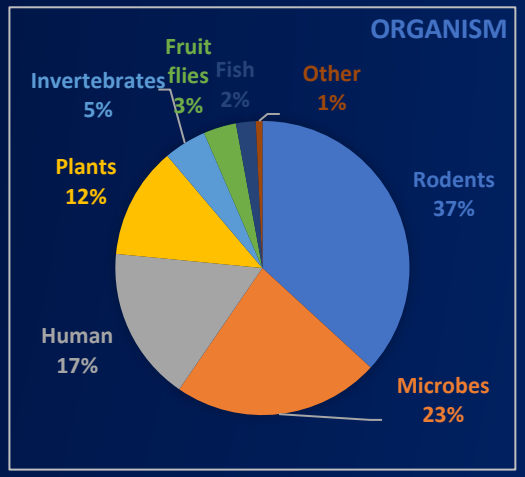
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Datasets

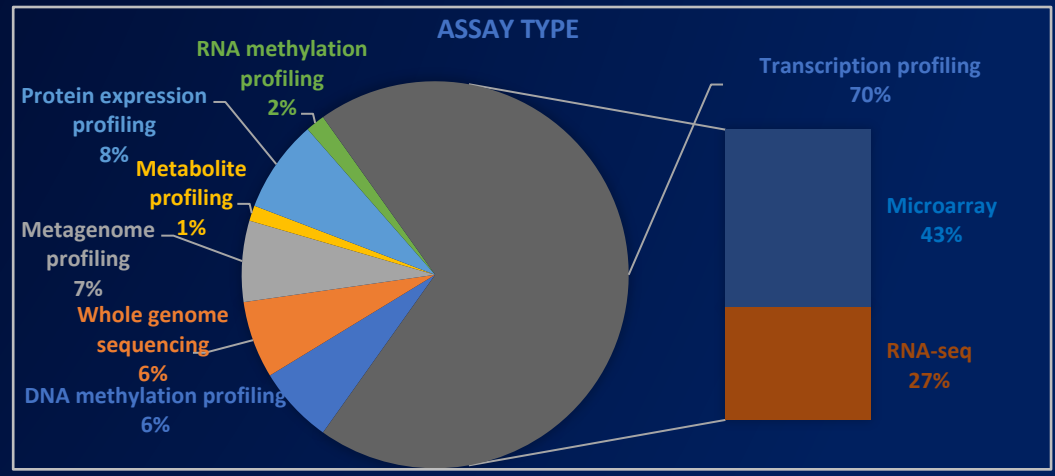
45
Species

>10
Assays

>130TB
Data







GeneLab (genelab.nasa.gov)

GeneLab Open Science for Life in Space

GeneLab Open Science for Life in Space

Home | About | Data & Tools | Research & Resources | Working Groups | Help

Keywords



Welcome to NASA GeneLab - the first comprehensive space-related omics database; users can upload, download, share, store, and analyze spaceflight and spaceflight-relevant data from experiments using model organisms.

Data Repository
Search and upload spaceflight datasets

Analyze Data
Perform large-scale analysis of biological omics data

Environmental Data
Radiation data collected during experiments conducted in space

Collaborative Workspace
Share, organize and store files

Submit Data BETA
Have space-relevant data to submit to GeneLab?

Visualize Data
Interact with GeneLab processed data

Environmental Data

Supporting data for space flown experiments: Summarized STS and ISS Radiation dosimetry, ISS Cabin CO2, Temperature, Humidity



Environmental Data
Radiation data collected during experiments conducted in space

ENVIRONMENTAL DATA

+ Environmental Data for Spaceflight Experiments
  - STS (Space Shuttle) Radiation Dosimetry
  - BION-M1 Radiation Dosimetry
  - Foton-M4 Radiation Dosimetry
  - Shenzhou-8 Radiation Dosimetry
  - ISS Radiation Dosimetry Data
    - Rodent Research Radiation Dosimetry
    - US Lab Radiation Dosimetry
    - International Labs Radiation Dosimetry

Radiation Metadata for GLDS Studies

Table 1 contains information used to calculate the absorbed dose of radiation for STS ("space shuttle") experiments. The absorbed dose from ionizing radiation received by the specimens (animals, plants, cells) was estimated from data recorded by three passive radiation dosimeter (PRD) packages, designated DLOC1, DLOC2, and DLOC3, in the middeck of the space shuttle, where biological payloads were located. Each package contains a number of TLD-100 thermoluminescent detectors. The TLDs are passive detectors: they integrate dose and must be processed--in the case of TLDs, by heating. (As opposed to active detectors which are powered and can be read out continuously, in real-time.) The detectors are returned post-flight and the data analysed by the Space Radiation Analysis Group at NASA-Johnson Space Center. The reported dose for each PRD is the average over all the TLDs +/- the standard deviation, with appropriate background subtraction and error propagation. Correction for dose accumulated on the ground pre- and post-flight is done by subtracting the dose in identical detectors that remain on the ground, and a calibration factor is applied to convert dose in the TLDs to dose in water.

Radiation Metadata Table 1

GLDS Accession Number	GLDS-63	GLDS-21	GLDS-11 GLDS-15 GLDS-20	GLDS-4	GLDS-1 GLDS-3	GLDS-50	GLDS-17 GLDS-44 GLDS-121	GLDS-25 GLDS-54 GLDS-72 GLDS-87 GLDS-108 GLDS-116 GLDS-173 GLDS-222
Mission	STS-70	STS-108	STS-115	STS-118	STS-121	STS-126	STS-131	STS-135
Inclination	28.45	51.60	51.60	51.60	51.60	51.60	51.60	51.60
Launch/mission start	07-13-95	12-05-01	09-09-06	08-08-07	07-04-06	11-14-08	04-05-10	07-08-11

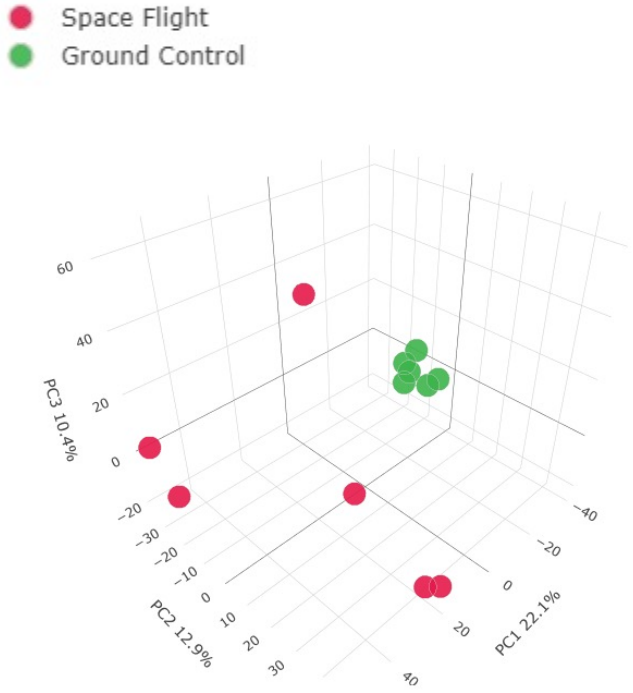
Data Visualization

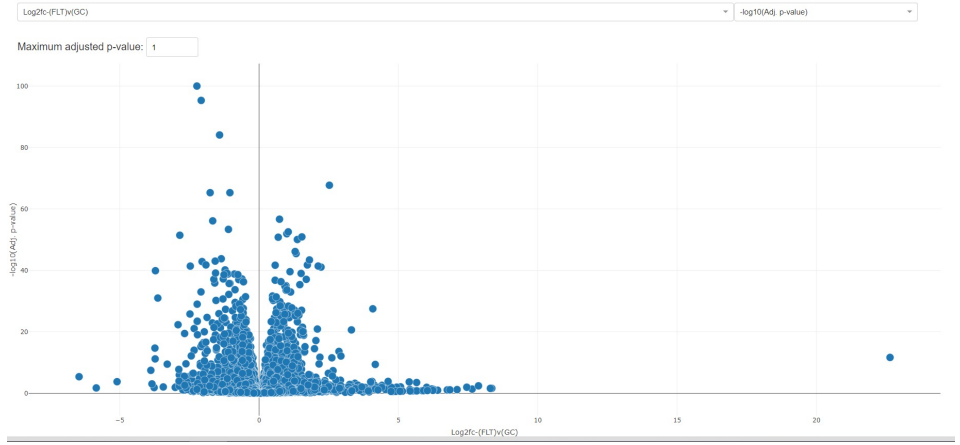
By study, users can visualize processed transcriptomics data in GeneLab

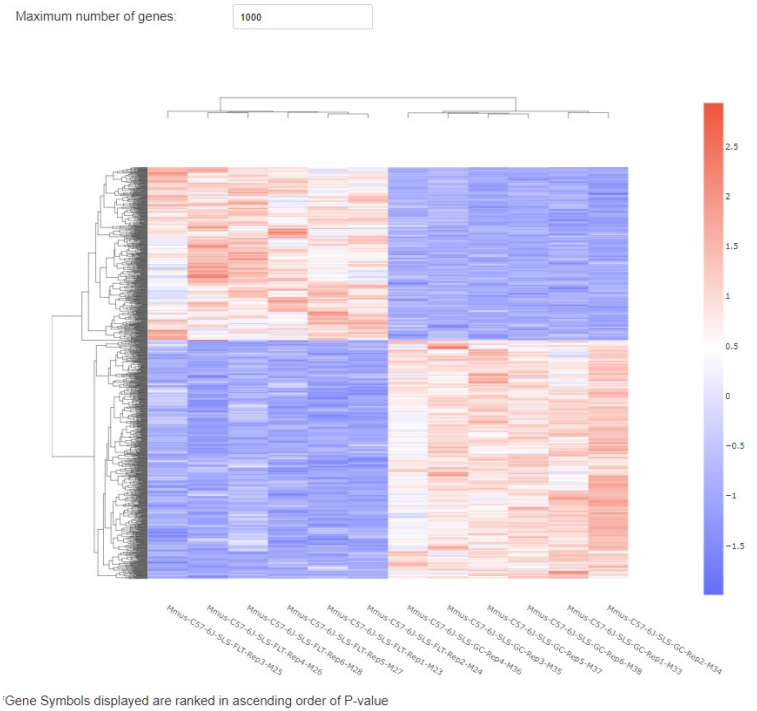
Visualize Data
Interact with GeneLab processed data

GLDS-104: Rodent Research-1 (RR1) NASA Validation Flight: Mouse soleus muscle transcriptomic and epigenomic data

PCA | QUERY DATA | PAIR PLOTS | VOLCANO PLOTS | DENDROGRAM | HEATMAP | SPLOT





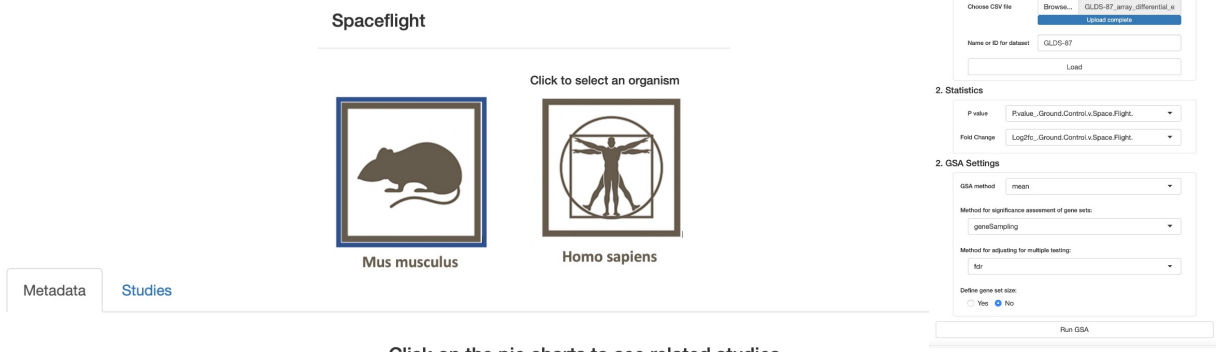


[1]Gene Symbols displayed are ranked in ascending order of P-value

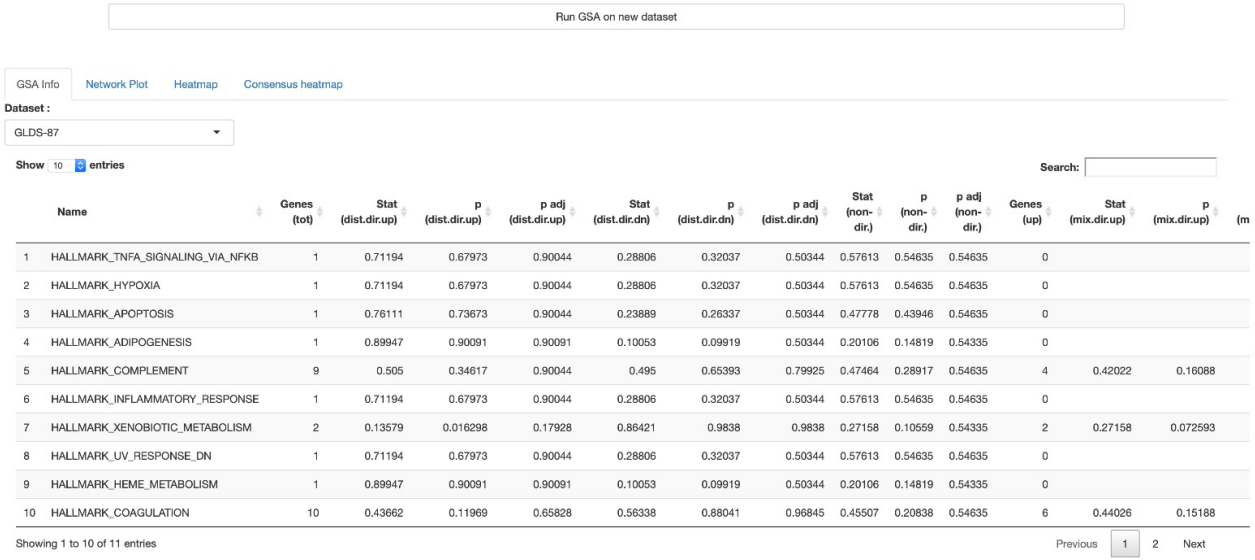
Data Visualization 2.0

Add new types of visualization tools and extend the ability to visualize and compare multiple datasets.

Coming soon!



Pathway analysis by Gene set enrichment

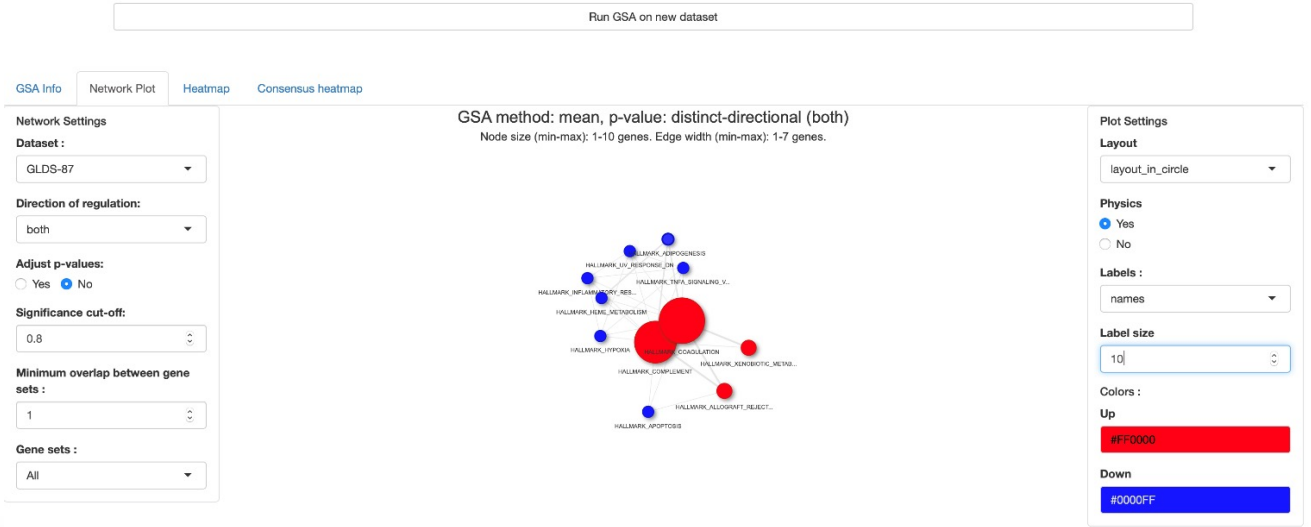


	Name	Genes (tot)	Stat (dist.dir.up)	p (dist.dir.up)	p adj (dist.dir.up)	Stat (dist.dir.dn)	p (dist.dir.dn)	p adj (dist.dir.dn)	Stat (non-dir.)	p (non-dir.)	p adj (non-dir.)	Genes (up)	Stat (mix.dir.up)	p (mix.dir.up)	(m
1	HALLMARK_TNFA_SIGNALING_VIA_NFKB	1	0.71194	0.67973	0.90044	0.28806	0.32037	0.50344	0.57613	0.54635	0.54635	0			
2	HALLMARK_HYPOXIA	1	0.71194	0.67973	0.90044	0.28806	0.32037	0.50344	0.57613	0.54635	0.54635	0			
3	HALLMARK_APOPTOSIS	1	0.76111	0.73673	0.90044	0.23889	0.26337	0.50344	0.47778	0.43946	0.54635	0			
4	HALLMARK_ADIPOGENESIS	1	0.89947	0.90091	0.90091	0.10053	0.09919	0.50344	0.20106	0.14819	0.54335	0			
5	HALLMARK_COMPLEMENT	9	0.505	0.34617	0.90044	0.495	0.65393	0.79925	0.47464	0.28917	0.54635	4	0.42022	0.16088	
6	HALLMARK_INFLAMMATORY_RESPONSE	1	0.71194	0.67973	0.90044	0.28806	0.32037	0.50344	0.57613	0.54635	0.54635	0			
7	HALLMARK_XENOBIOTIC_METABOLISM	2	0.13579	0.016298	0.17928	0.86421	0.9838	0.9838	0.27158	0.10559	0.54335	2	0.27158	0.072593	
8	HALLMARK_UV_RESPONSE_DN	1	0.71194	0.67973	0.90044	0.28806	0.32037	0.50344	0.57613	0.54635	0.54635	0			
9	HALLMARK_HEME_METABOLISM	1	0.89947	0.90091	0.90091	0.10053	0.09919	0.50344	0.20106	0.14819	0.54335	0			
10	HALLMARK_COAGULATION	10	0.43662	0.11969	0.65828	0.56338	0.88041	0.96845	0.45507	0.20838	0.54635	6	0.44026	0.15188	

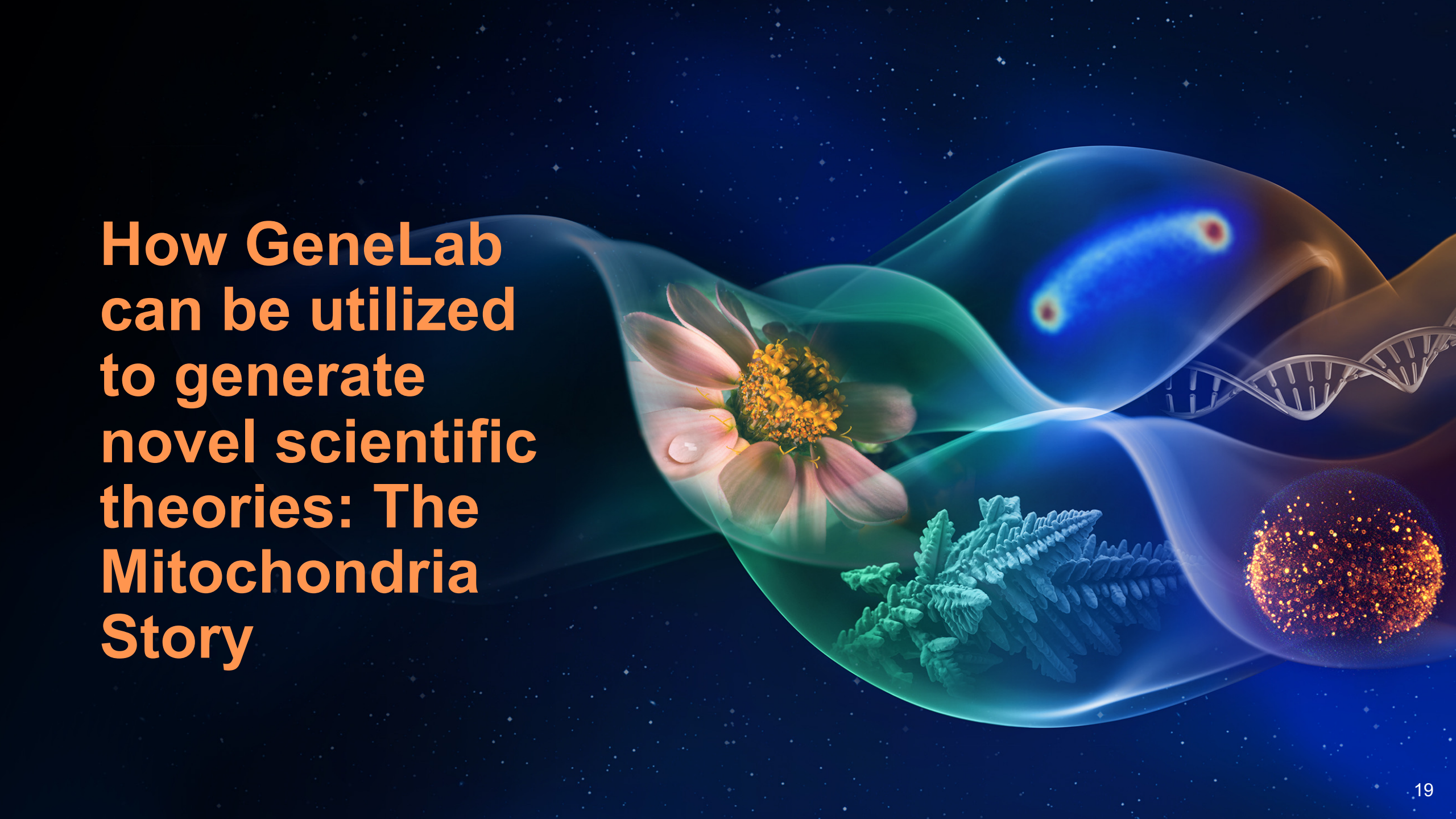
Showing 1 to 10 of 11 entries

Previous 1 2 Next

Interactive Network Plot



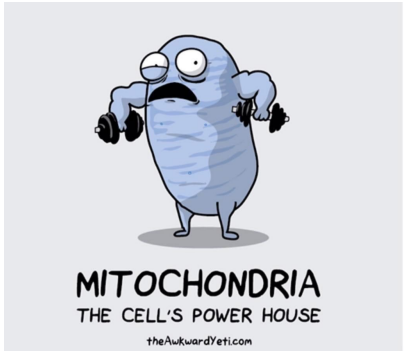
How GeneLab can be utilized to generate novel scientific theories: The Mitochondria Story



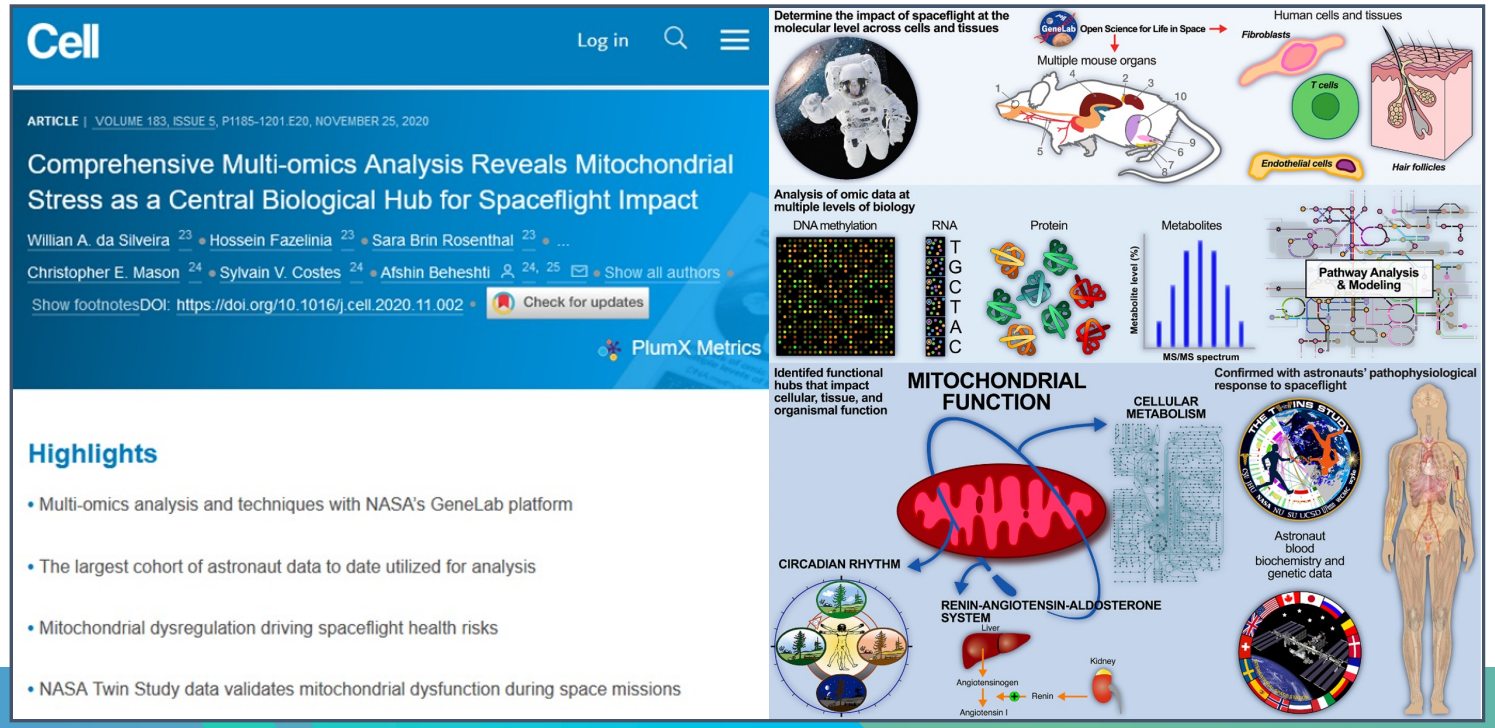
Multi-Omics Analysis Using GeneLab Database Recognizes Mitochondrial Dysfunction as a Mediator of Spaceflight Health Risks

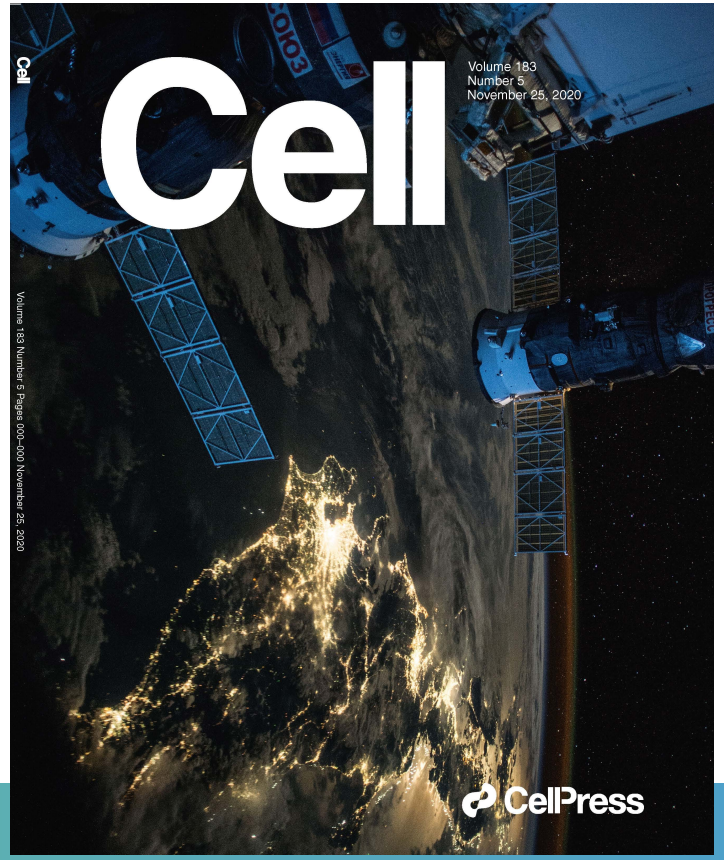
https://www.cell.com/c/the-biology-of-spaceflight





As humankind reaches for the stars to journey to the next frontier in space, research on spaceflight biology is critical for understanding how living systems, including human health, may be affected by spaceflight and space exploration. This special collection on the biology of spaceflight, published in *Cell* and other Cell Press journals, includes research articles, short communications, and a review article that cover studies with model systems and astronaut samples. The work, which was done in collaboration between NASA and other space agencies around the world, uncovers the impact of known hazards of spaceflight, such as radiation and microgravity, and discusses the standards for multi-omics from space and the preparations needed for Mars and other missions in the next two decades.





Analysis Working Group (AWG) Members and Others Involved


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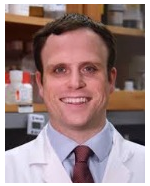

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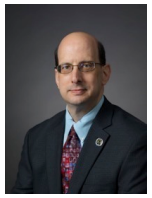
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Jeffrey Willey

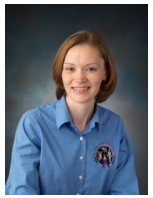
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Scott Smith

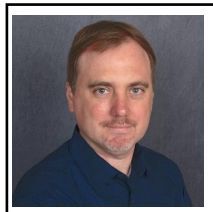

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Susana Zanello

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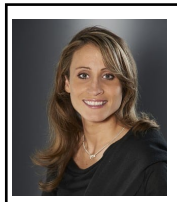
SPACE CENTER HOUSTON Manned Space Flight Education Foundation


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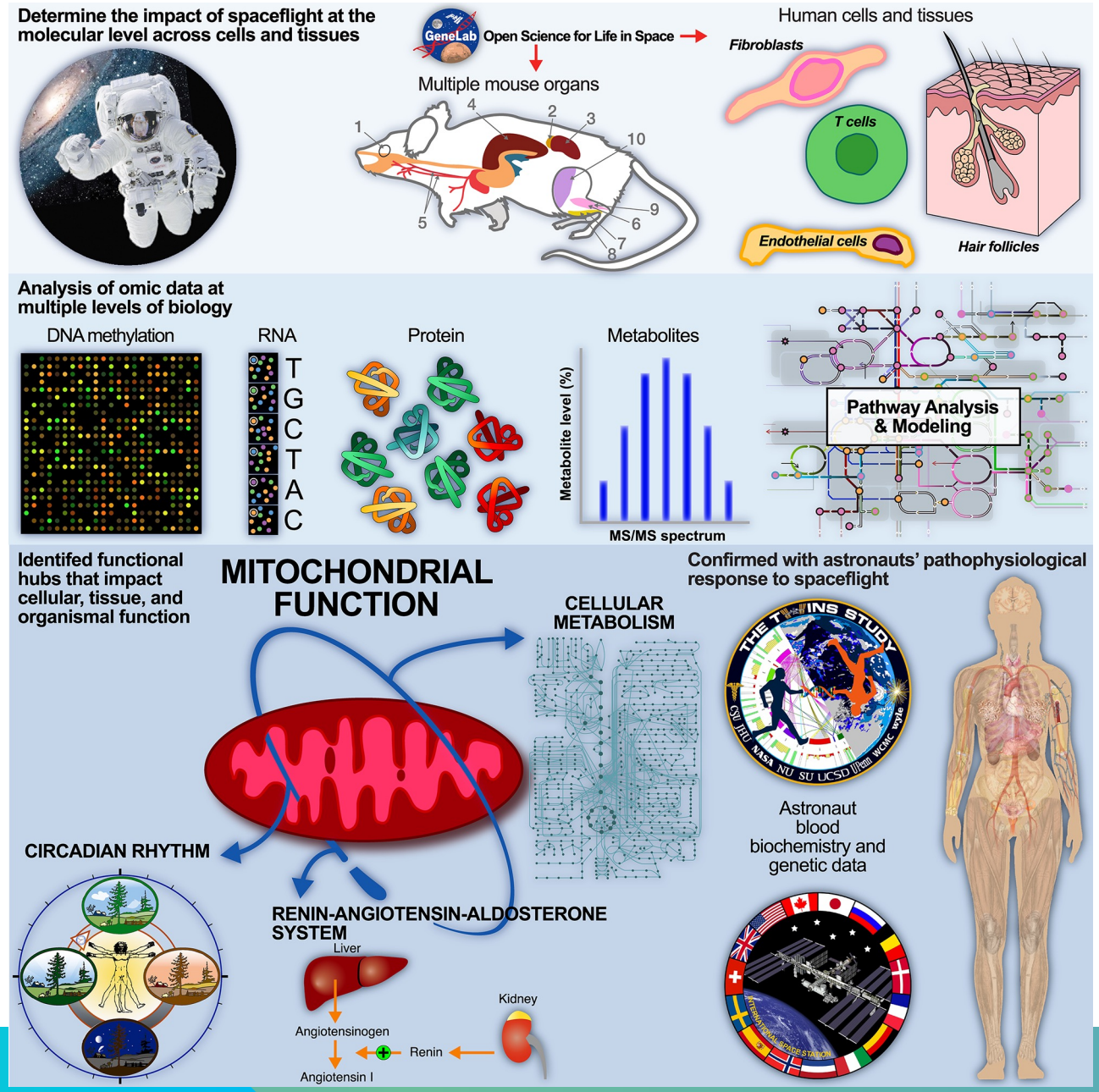
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Afshin Beheshti


Sylvain Costes

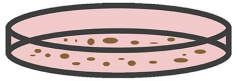
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Overview of Data Utilized for this Work and Project

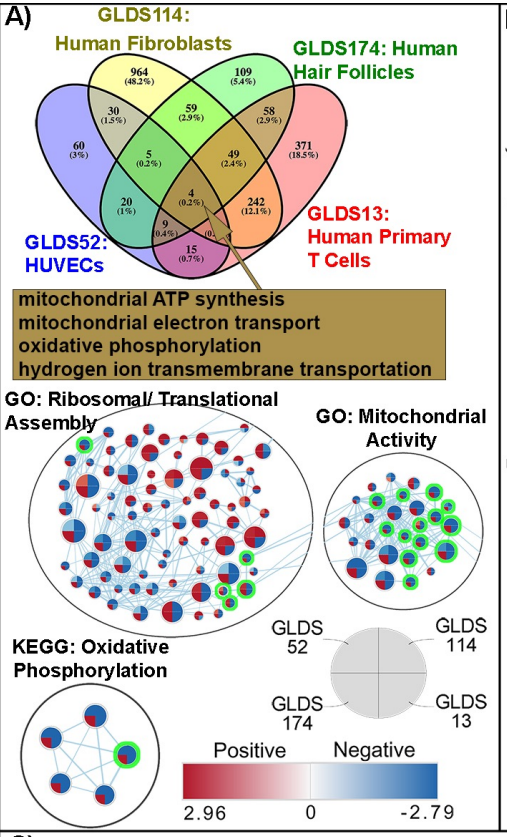


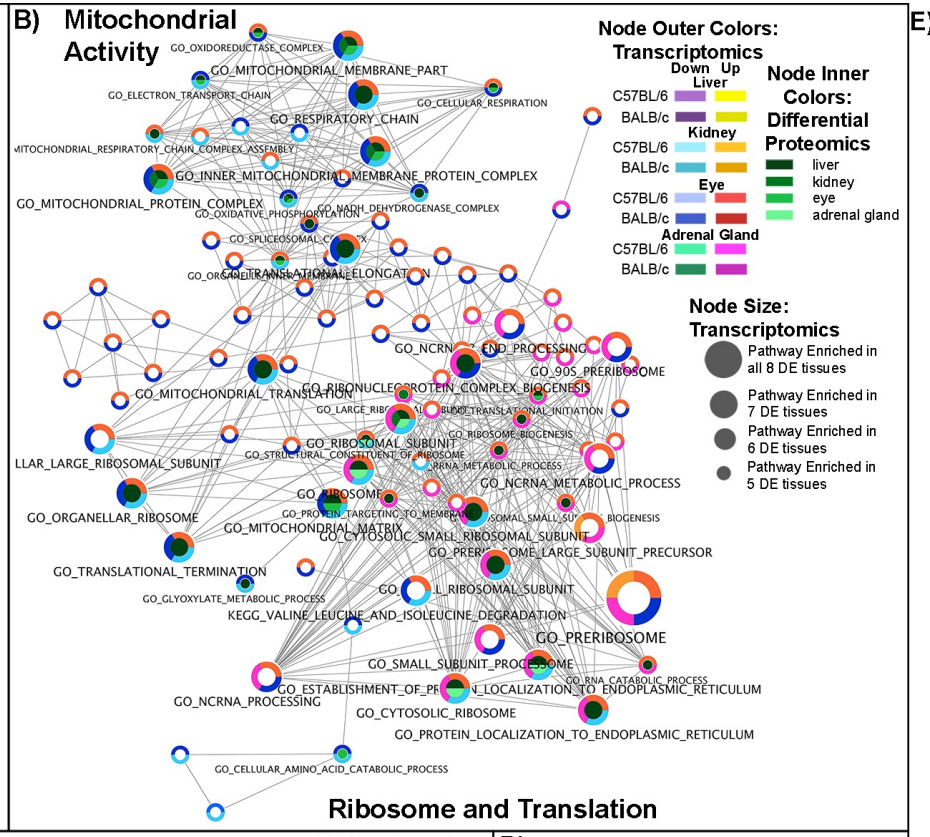
Largest amount of astronaut data in one paper!!

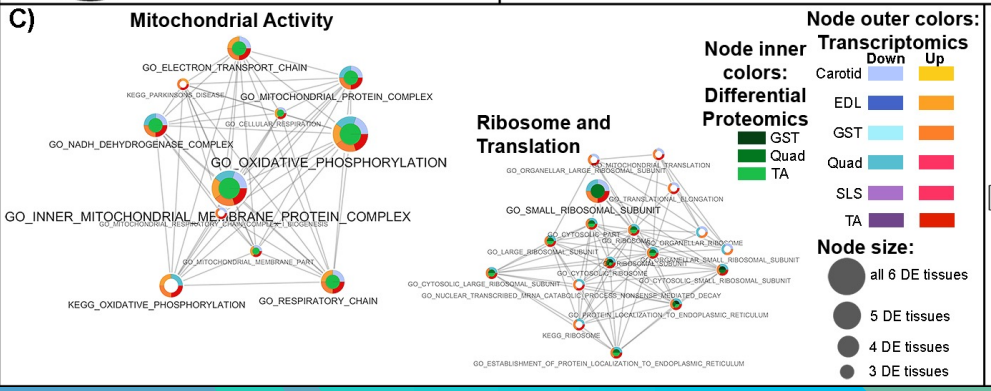
Universal Mitochondrial Changes

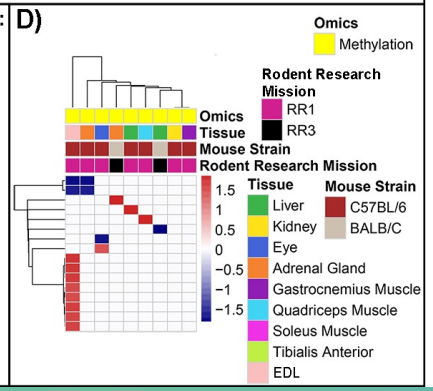


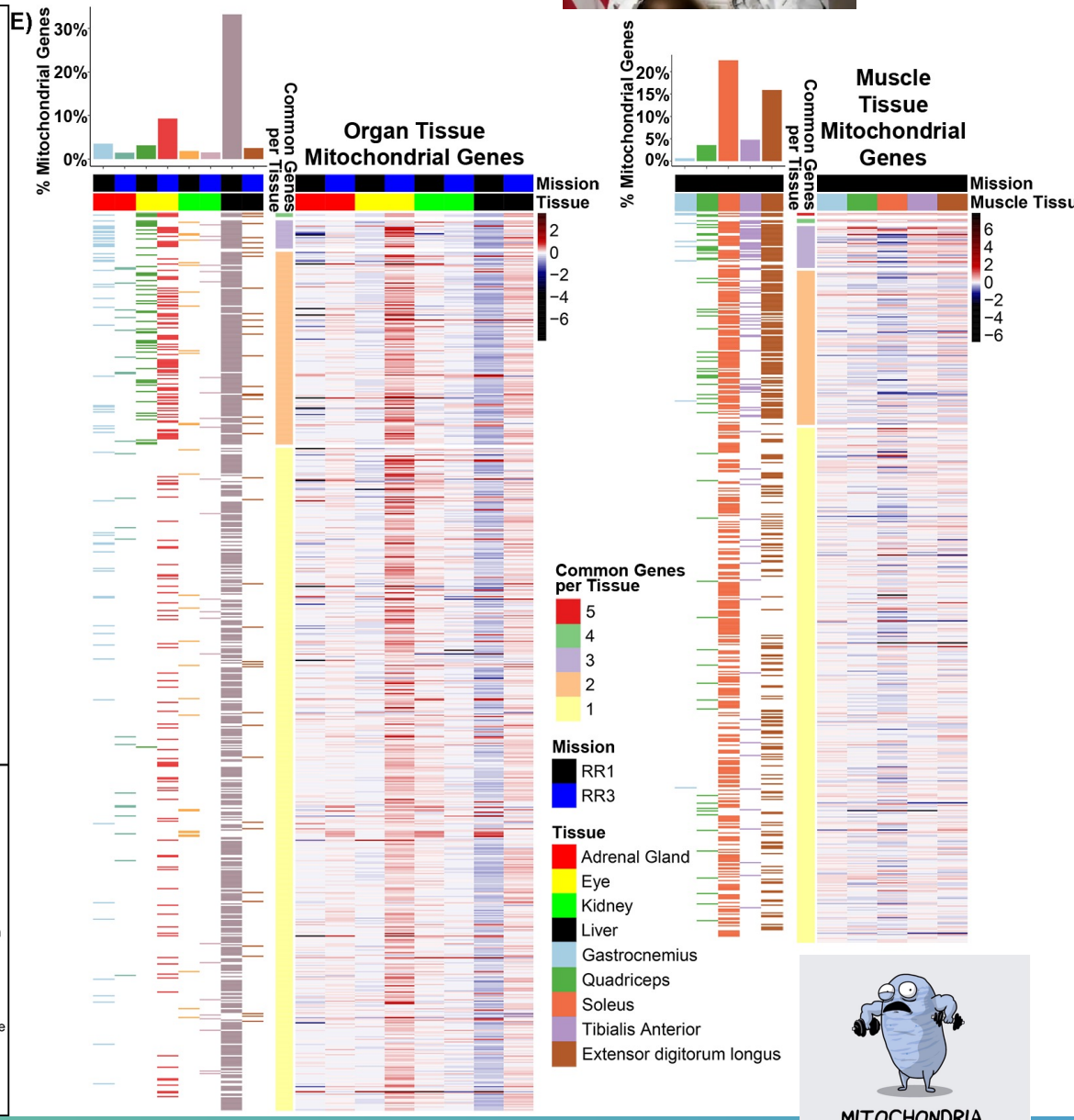


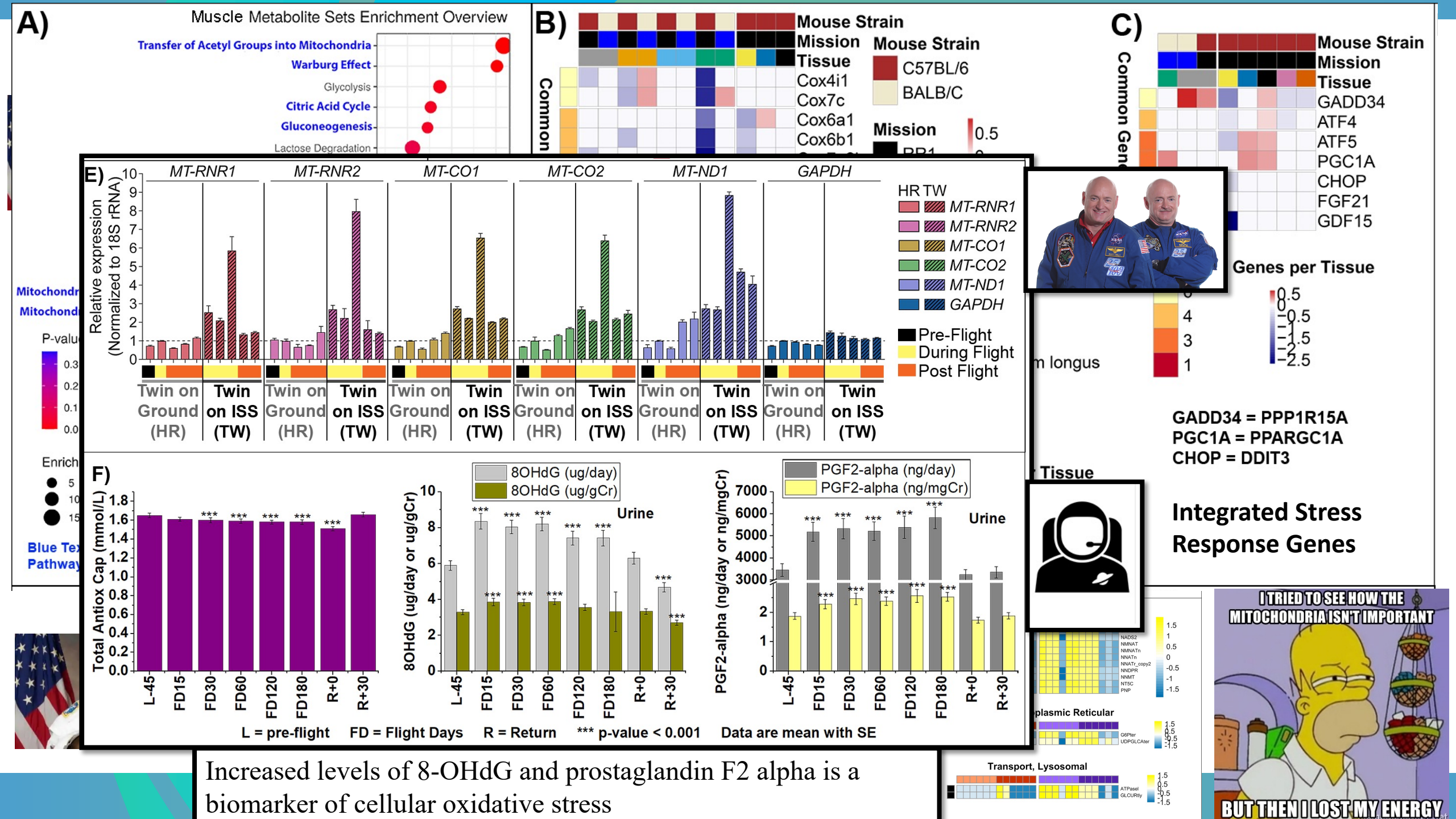










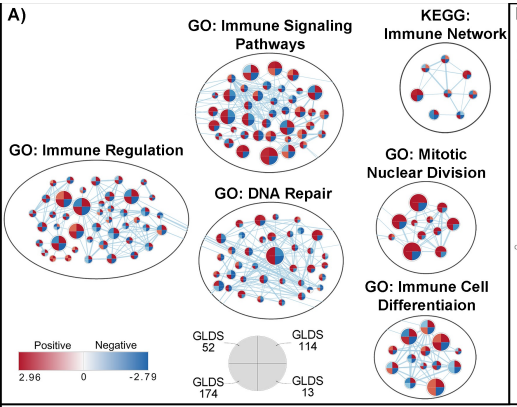


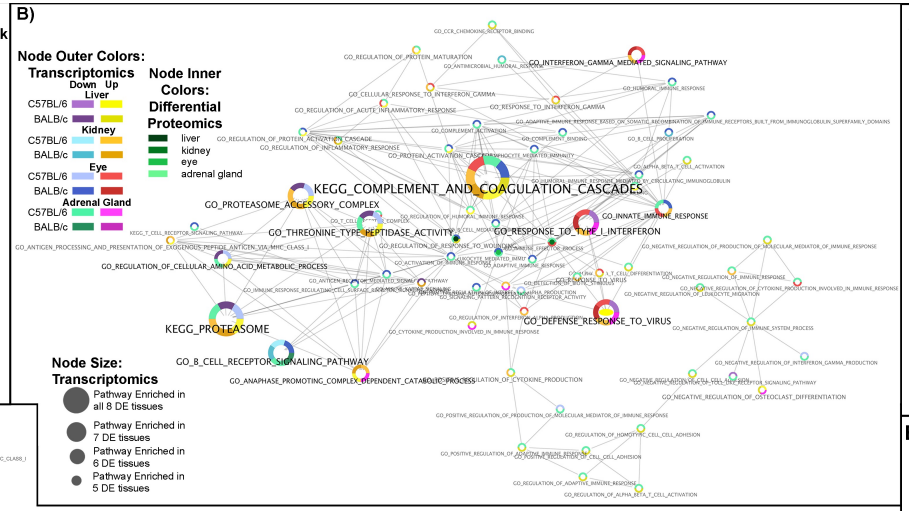
Increased levels of 8-OHdG and prostaglandin F2 alpha is a biomarker of cellular oxidative stress

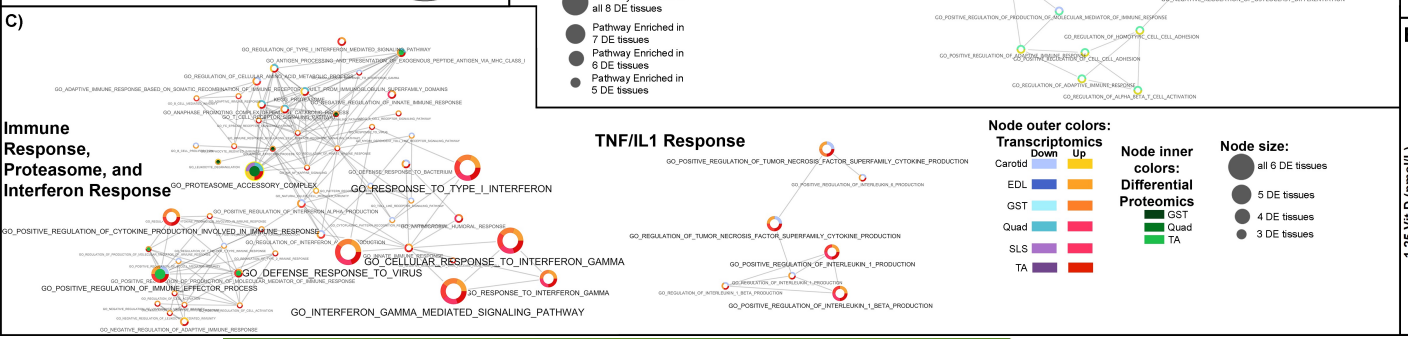
Universal Mitochondrial Changes Leads to Downstream Immune Dysfunction

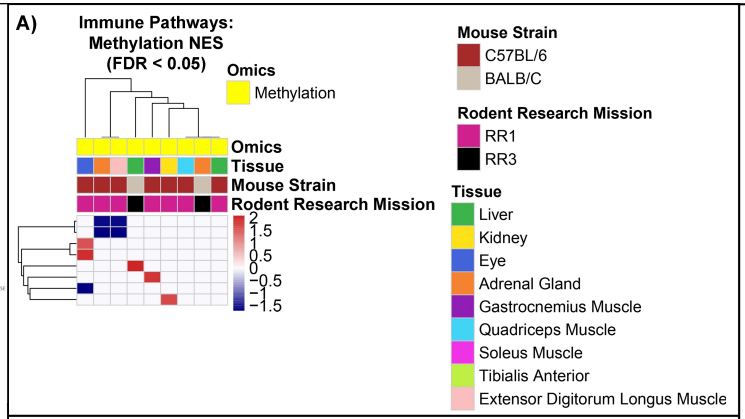


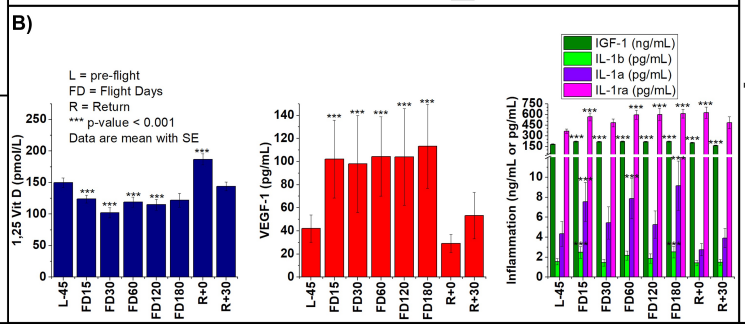


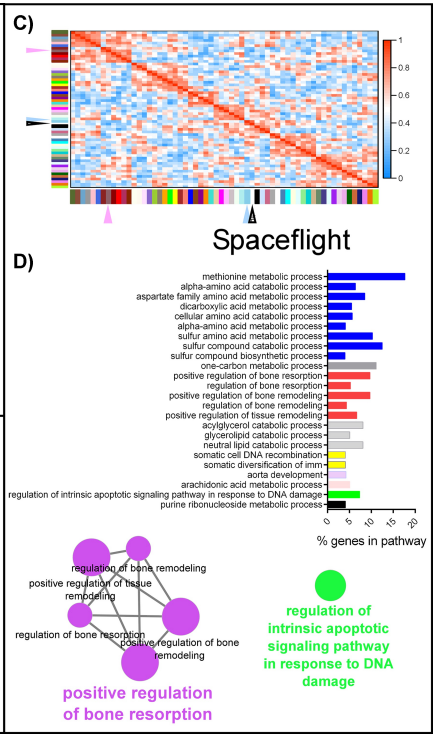


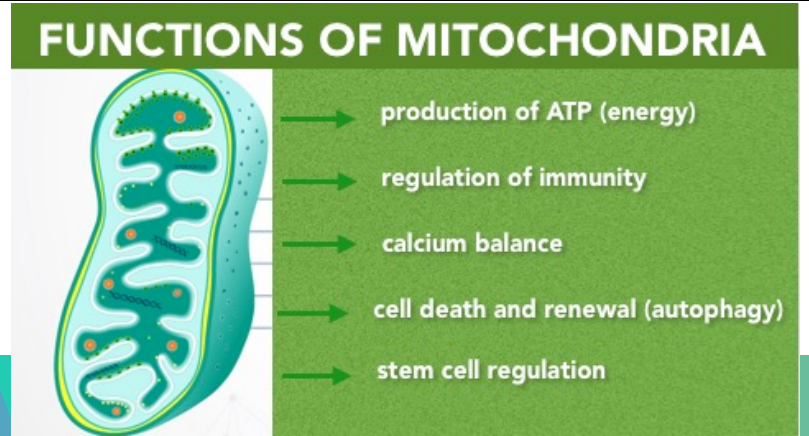






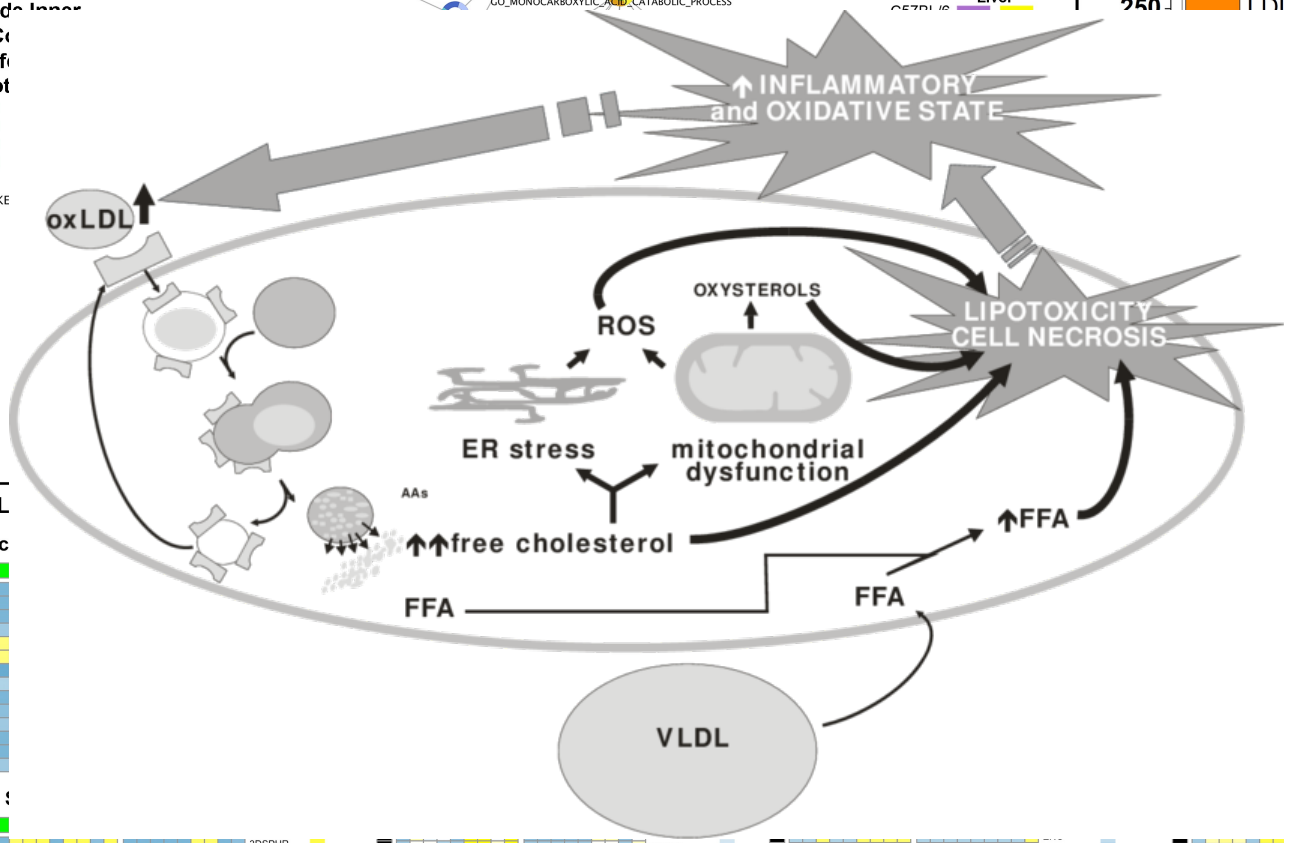






Universal Mitochondrial Changes Leads to Downstream Lipid and Fatty Acid Dysregulation







Current Drug Metabolism

Mitochondrial Dysfunction and Lipid Homeostasis

Author(s): Joseph Vamecq, Anne-Frederique Dessein, Monique Fontaine, Gilbert Briand, Nicole Porchet, Norbert Latruffe, Pierre Andreolotti, Mustapha Cherkaoui-Malki

Journal Name: Current Drug Metabolism

Volume 13 , Issue 10 , 2012

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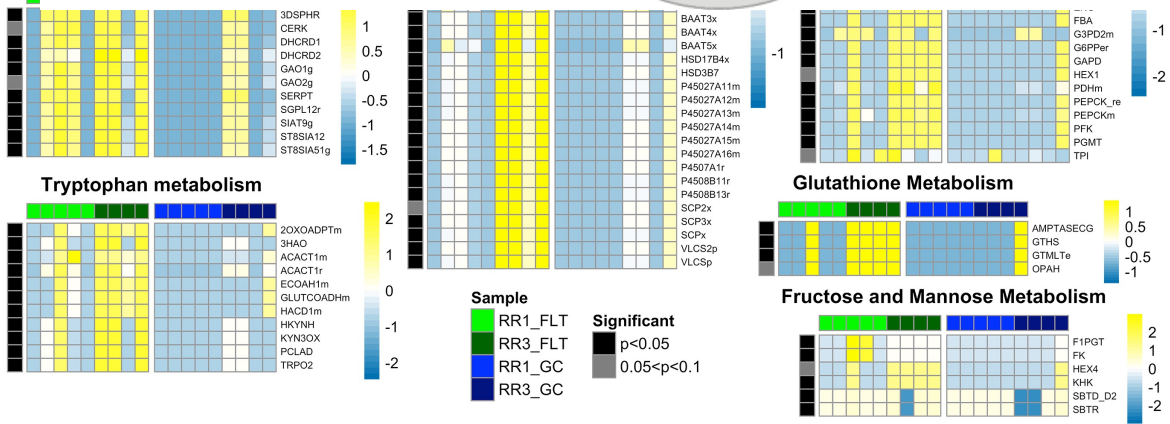
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Abstract:

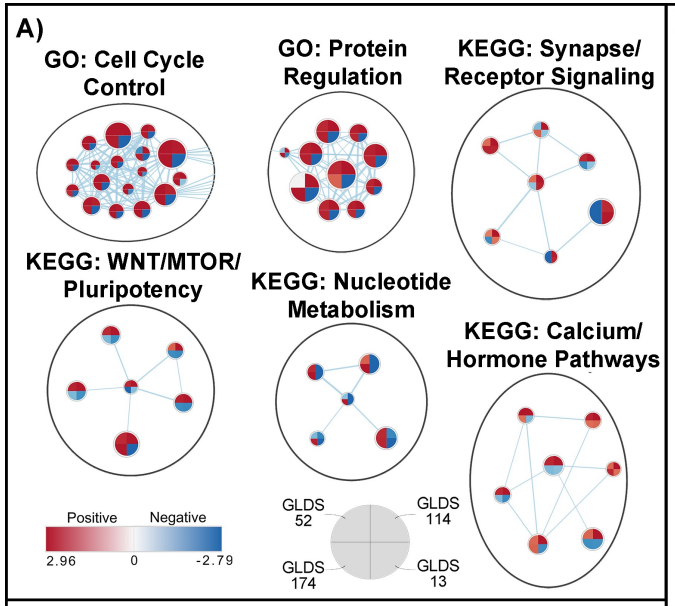
This review is aimed at illustrating that mitochondrial dysfunction and altered lipid homeostasis may concur in a variety of pathogenesis states, being either contributive or consecutive to primary disease events. Underlying mechanisms for this concurrence are far from being the exhaustive elements taking place in disease development. They may however complicate, contribute or cause the disease. In the first part of the review, physiological roles of mitochondria in coordinating lipid metabolism and in controlling reactive oxygen species (ROS), ATP and calcium levels are briefly presented. In a second part, clues for how mitochondria-driven alterations in lipid metabolism may induce toxicity are discussed. In the third part, it is illustrated how mitochondrial dysfunction and lipid homeostasis disruption may be associated (i) to complicate type 1 diabetes (pancreatic β-cell mitochondrial dysfunction in ATP yield induces reduced insulin secretion and hence disruption of glucose and lipid metabolism), (ii) to contribute to type 2 diabetes and other insulin resistant states (mitochondrial impairment may induce adipocyte dysfunction with subsequent increase in circulating free fatty acids and their abnormal deposit in non adipose tissues (pancreatic β-cells, skeletal muscle and liver) which results in lipotoxicity and mitochondrial dysfunction), (iii) to offer new clues in our understanding of how the brain controls feeding supply and energy expenditure, (iv) to promote cancer development notably via fatty acid oxidation/synthesis imbalance (in favor of synthesis) further strengthened in some cancers by a lipogenetic benefit induced by a HER2/fatty acid synthase cross-talk, and (v) to favor cardiovascular disorders by impacting heart function and arterial wall integrity.

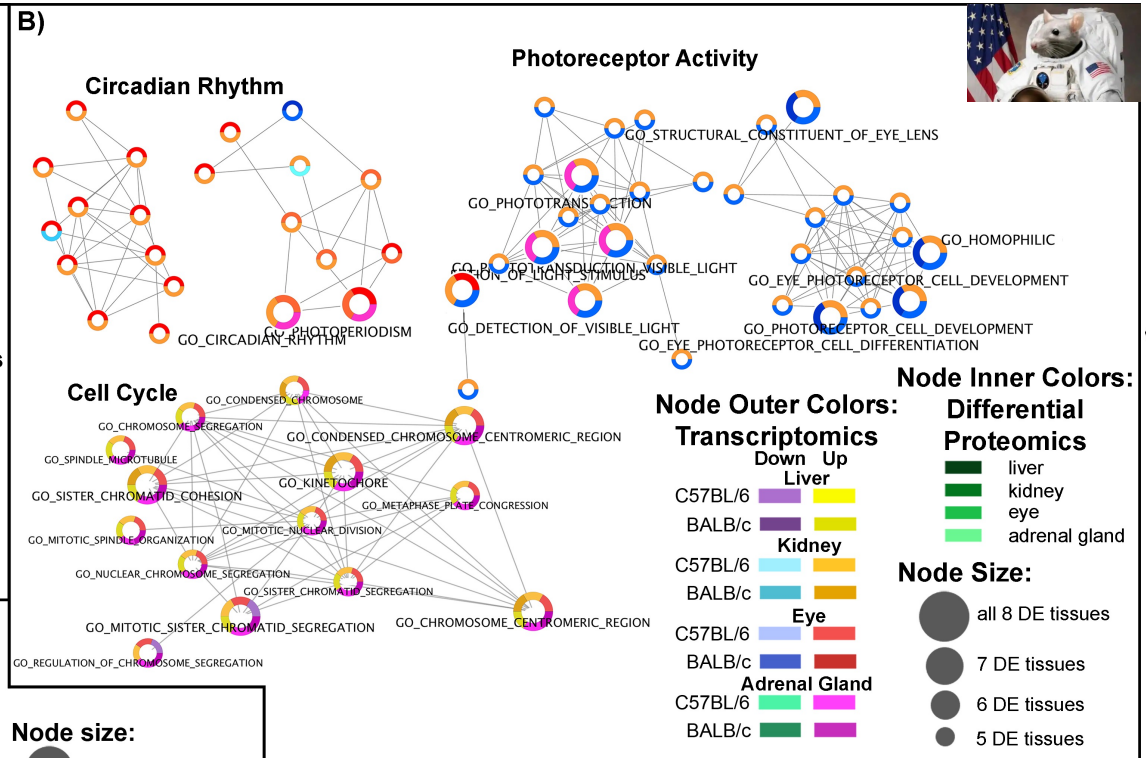
Keywords: ATP, calcium, ceramides, fatty acids, lipotoxicity, metabolic syndrome, mitochondria, reactive oxygen species

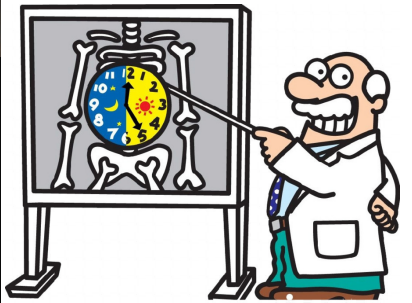


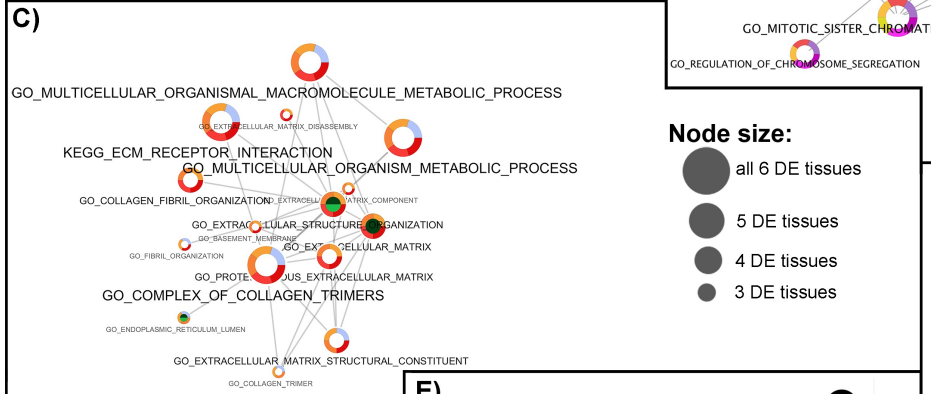
Universal Mitochondrial Changes Leads to Downstream Cell Cycle and Circadian Rhythm Issues

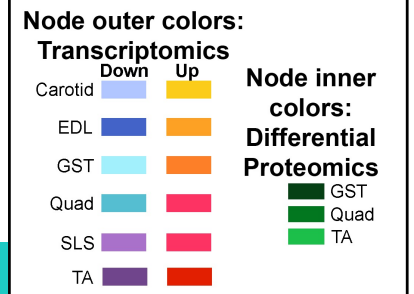


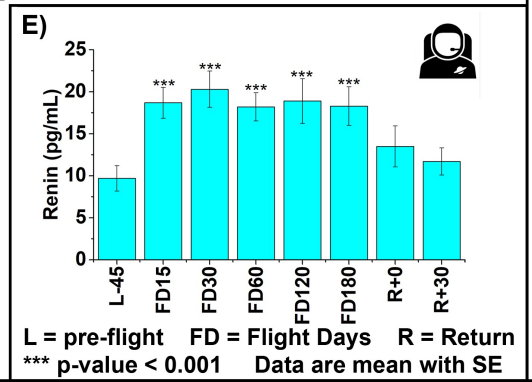


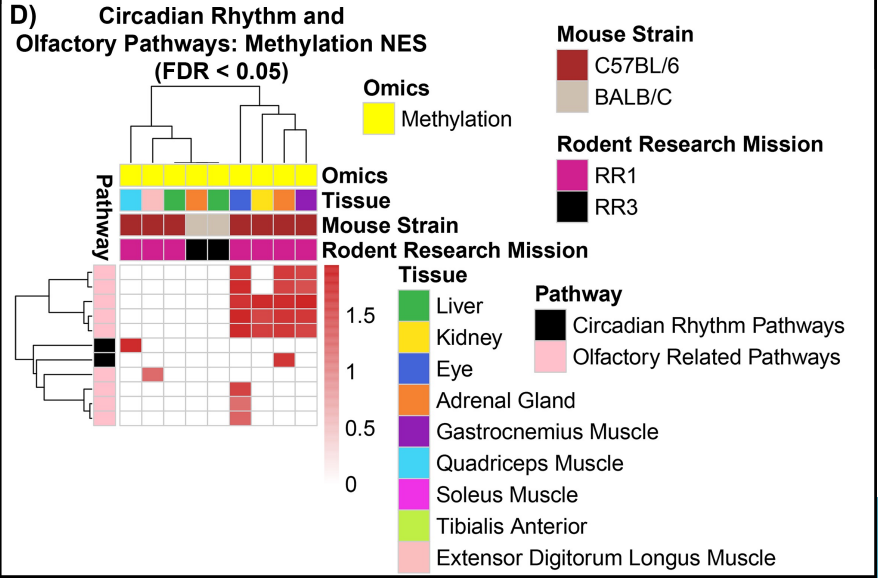


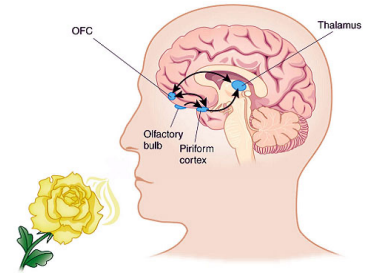






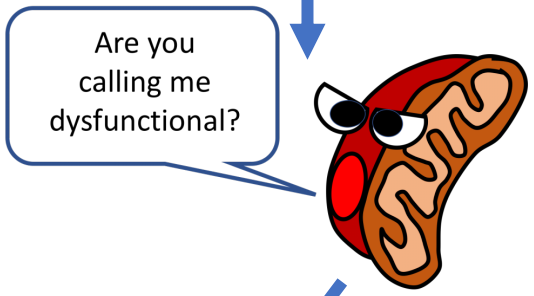


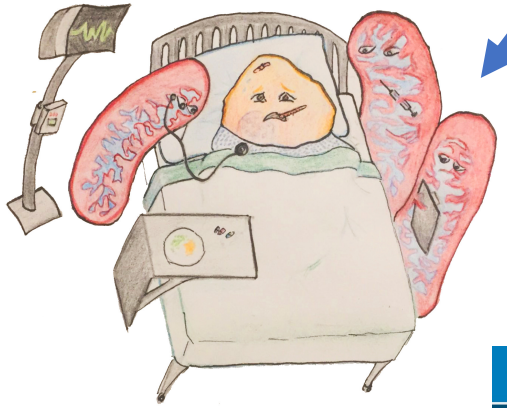


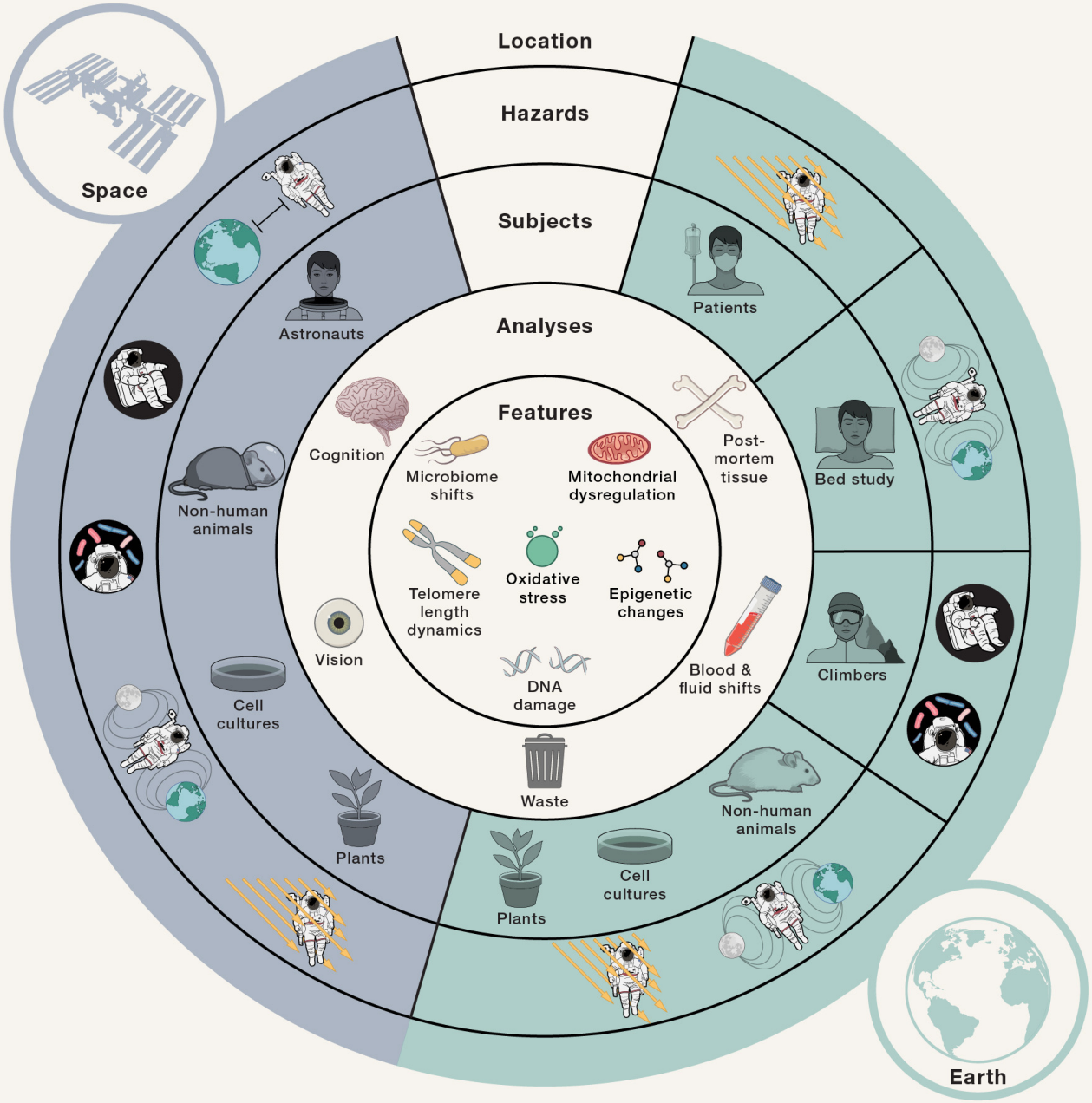


Summary of the Work









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Fundamental Biological Features of Spaceflight: Advancing the Field to Enable Deep-Space Exploration

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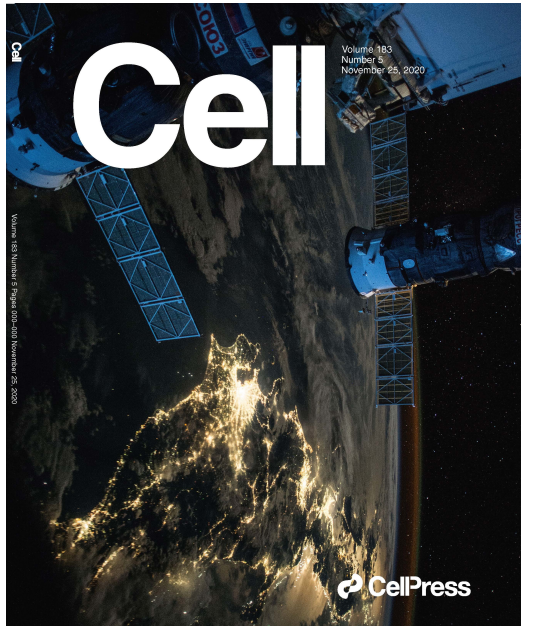
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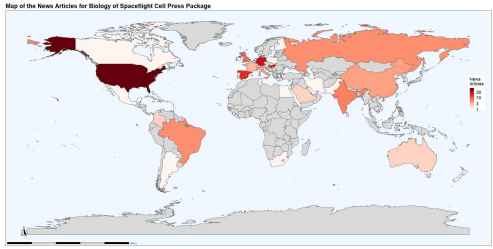
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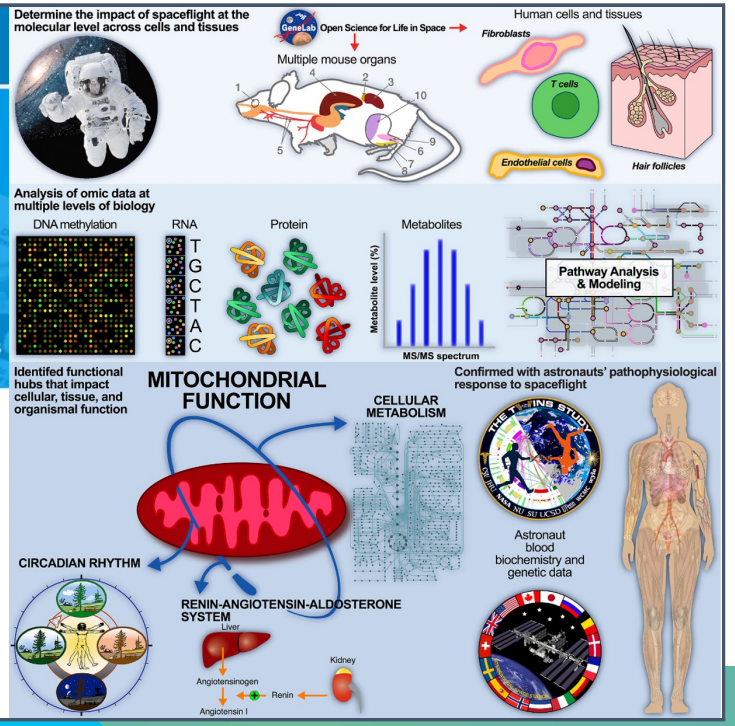
Comprehensive Multi-omics Analysis Reveals Mitochondrial Stress as a Central Biological Hub for Spaceflight Impact

Willian A. da Silveira [23] • Hossein Fazelinia [23] • Sara Brin Rosenthal [23] • ...
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PlumX Metrics

Highlights

- Multi-omics analysis and techniques with NASA's GeneLab platform
- The largest cohort of astronaut data to date utilized for analysis
- Mitochondrial dysregulation driving spaceflight health risks
- NASA Twin Study data validates mitochondrial dysfunction during space missions







Thank you!

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2017-2018



2018-2021



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