

Systemic alterations with spaceflight associated health risks originating from both circulating miRNAs and mitochondrial biology

National Aeronautics and
Space Administration



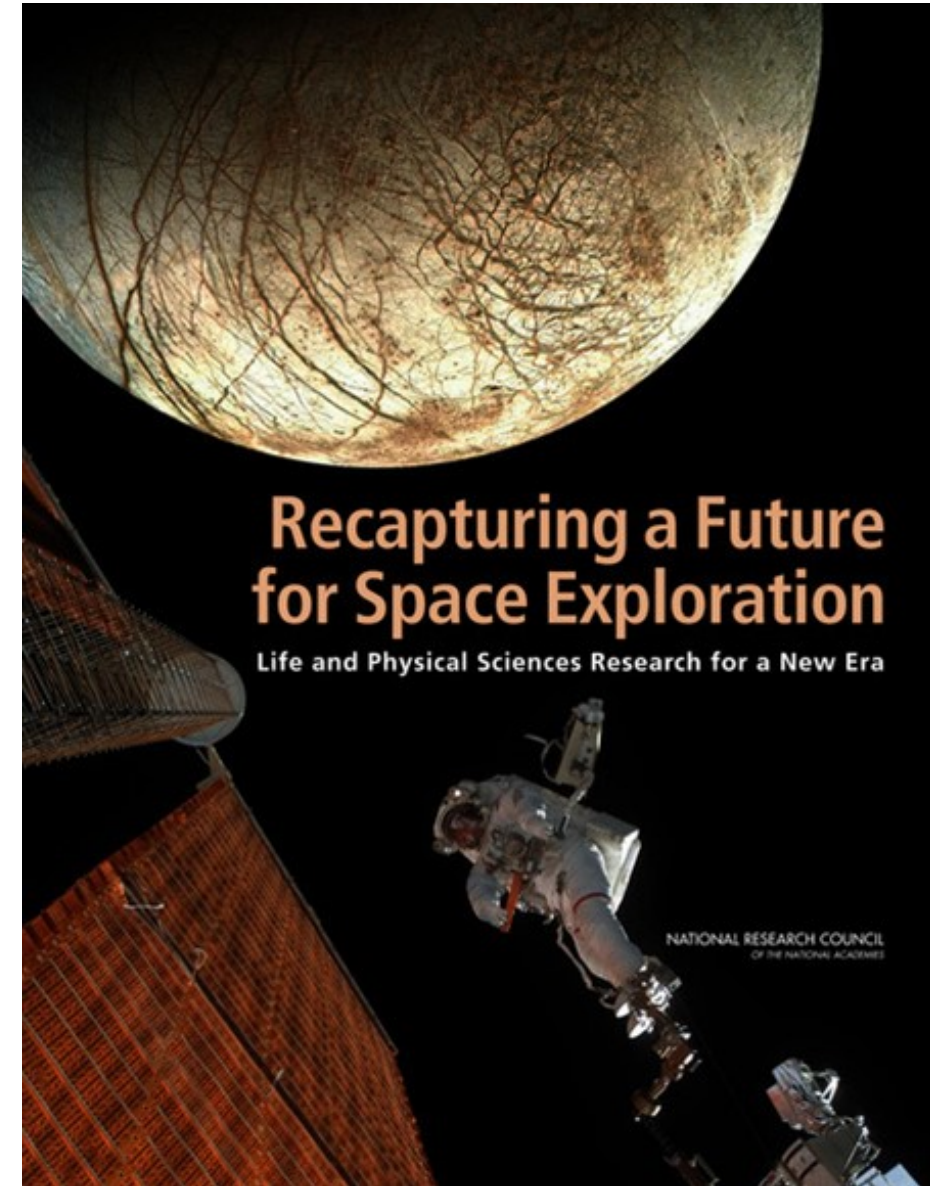
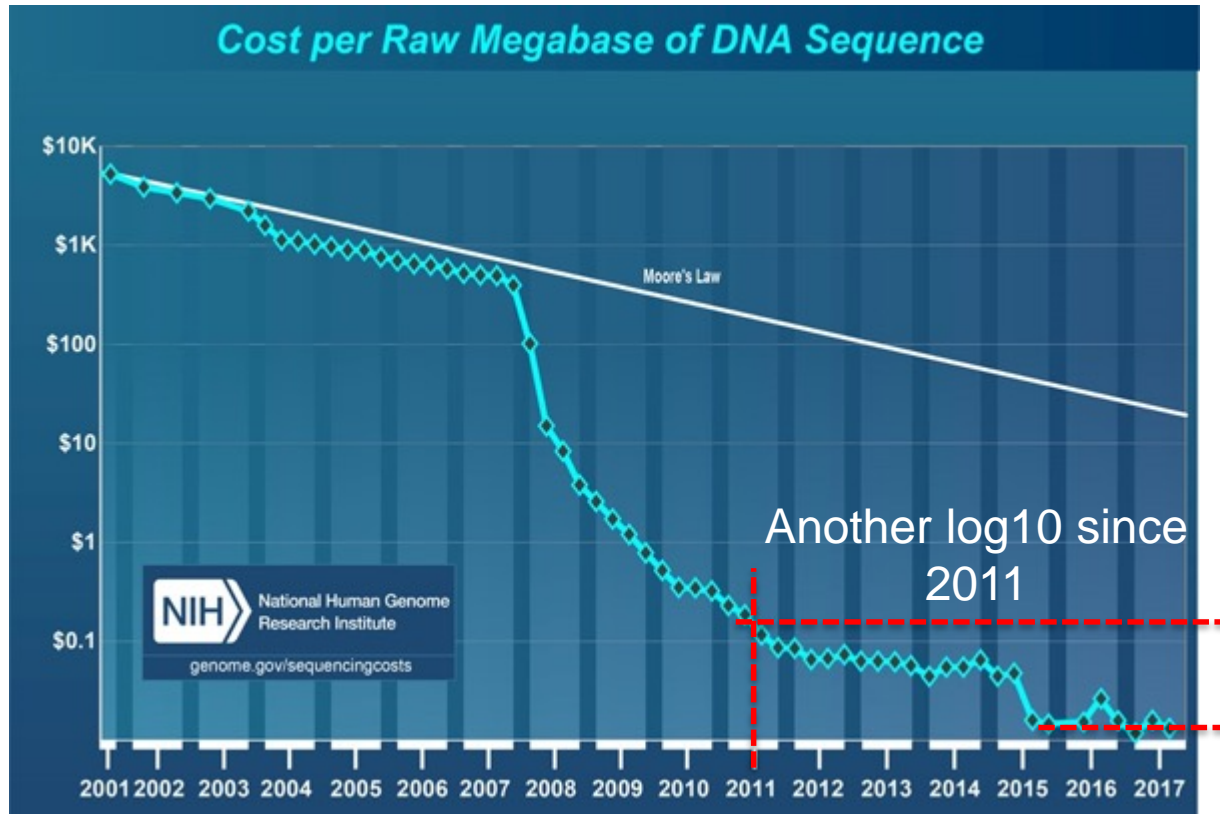
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Space Biosciences Division, KBRWyle
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Adjunct Assistant Professor at Department of Medicine
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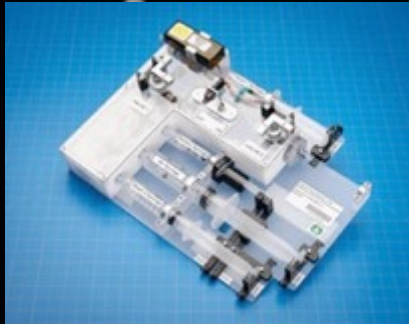
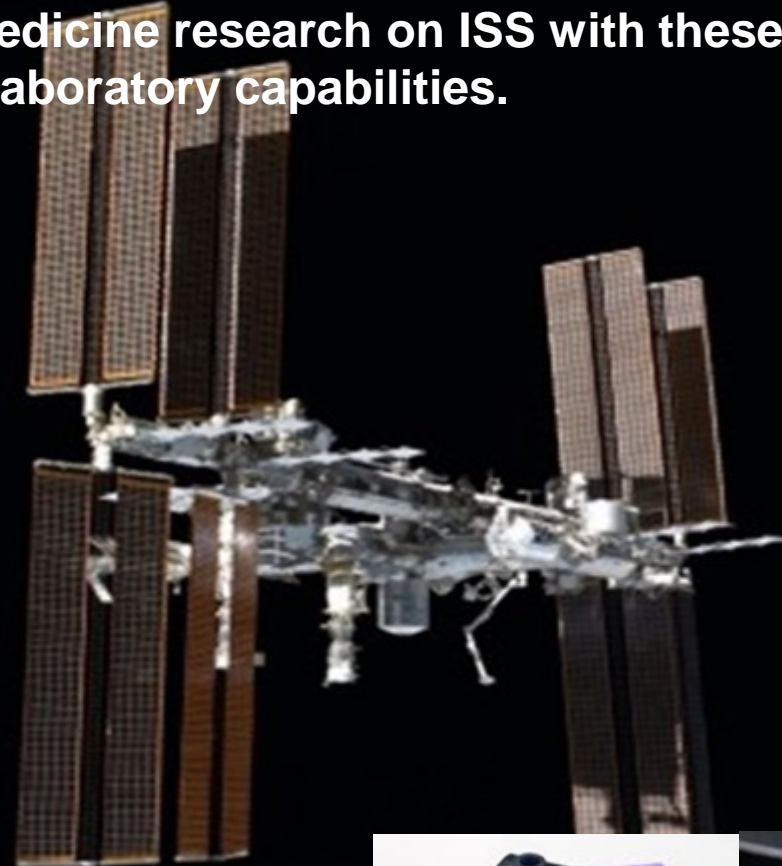


“...genomics, transcriptomics, proteomics, and metabolomics offer an immense opportunity to understand the effects of spaceflight on biological systems...”

*“...Such techniques generate considerable amounts of **data that can be mined and analyzed** for information by multiple researchers...”*

Omics Acquisition in Space is Now a Reality

This is truly an exciting time for cellular and molecular biology, omics and biomedicine research on ISS with these amazing additions to the suite of ISS Laboratory capabilities.

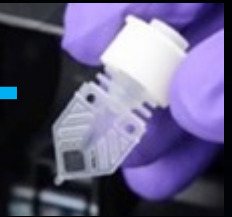


Sample Preparation Module

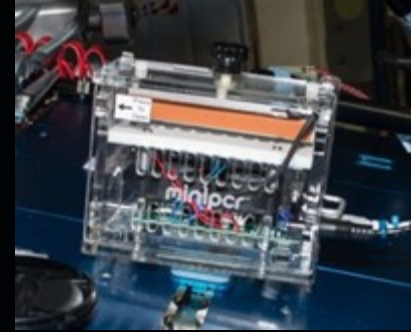


Oxford Nanopore MinION Gene Sequencer

Cepheid Smart Cycler qRT-PCR



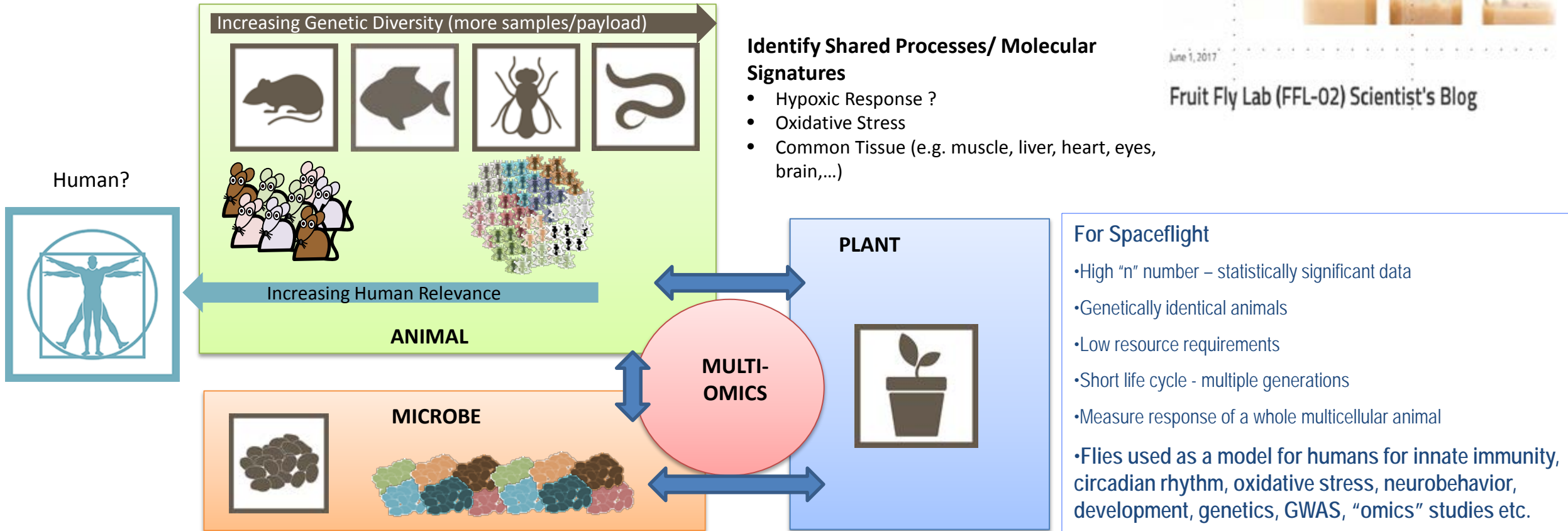
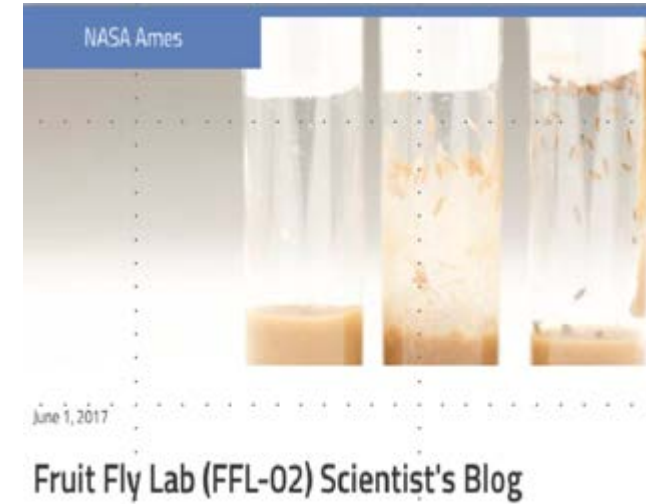
Reaction tube containing lyophilized chemical assay bead (proprietary)



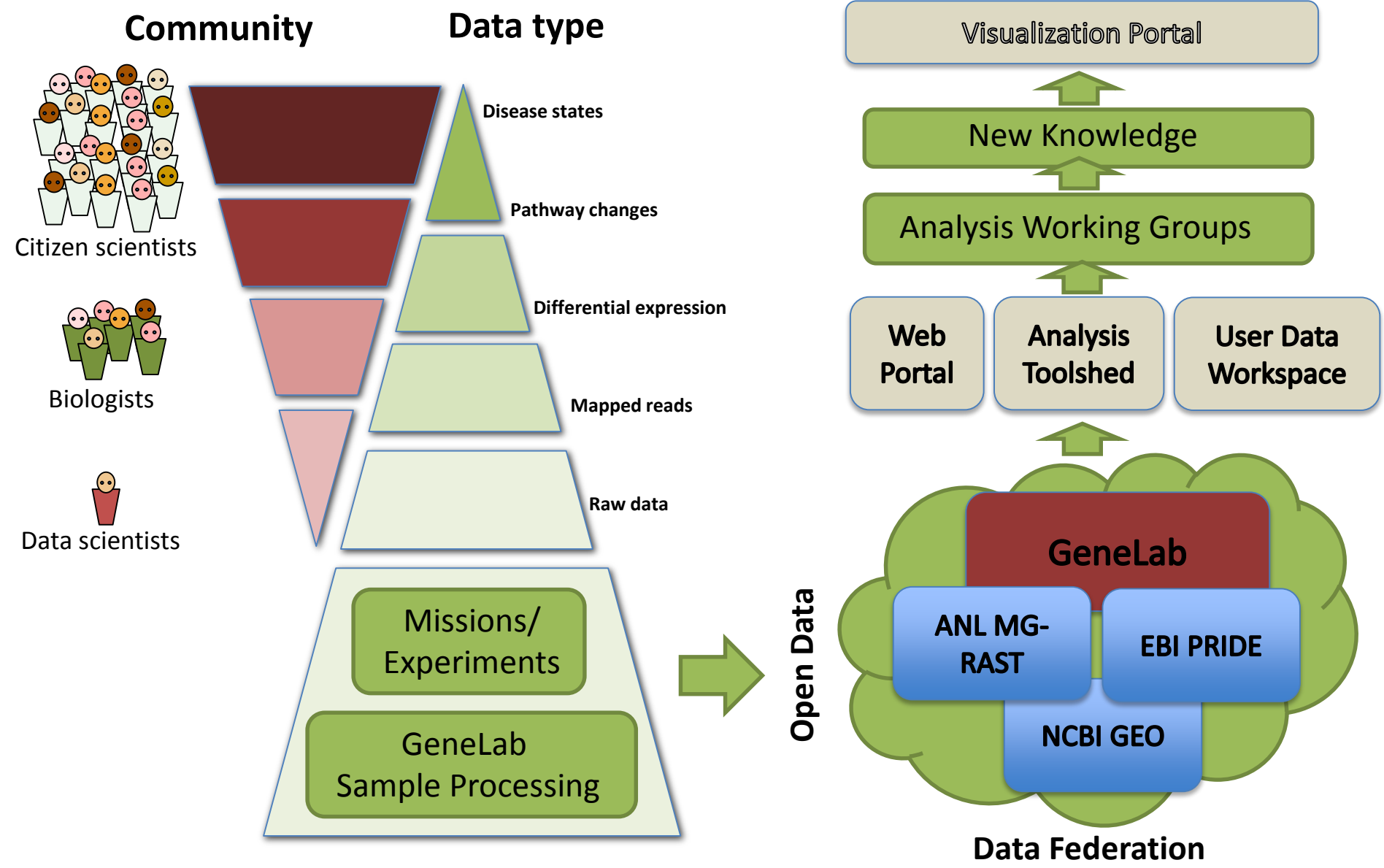
Mini-PCR

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

- Sequencing on ISS is still limited in the amount of data generated
 - Most of the work needs to happen on earth
- Measurements on human cannot be too invasive and limited in numbers
 - Usage of animals



GeneLab Data Democratization





GeneLab Webpage: genelab.nasa.gov



Tools

search tools

Get Data
Send Data
Epigenomics
RNA-Seq
Other Tools
Picard Tool Suite
SAMTools Suite
Microarray
Sequencing General
Microarray Tools
Metagenomics Tools

Workflows
All workflows

History

search datasets

Afshin's History
5 shown, 4 deleted

1.16 MB

9: GeneLab GenomeSpace Exporter on data 5
5: GenomeSpace importer on GLDS-1 metadata A-AFFY-35.adf.txt
3: GSM458594.CEL
2: GSM458595.CEL
1: GSM458594.CEL

Using 23%

Hello, NASA GeneLab Analysis Platform is running!

Take an interactive tour: [Galaxy UI](#) [History](#)

NASA GeneLab's Analysis Platform is an open platform for performing large-scale analysis of space-relevant omics data using a customized suite of data analysis tools, powered by [Galaxy](#).

To access **GeneLab RNAseq processed data** go to 'Shared Data' → 'Data Libraries' → 'GeneLab Data Repository' → click on the GLDS dataset you are interested in.

To report any issues with this platform, contact the NASA GeneLab project at: arc-dl-gene-lab-it@mail.nasa.gov

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Search Data

All GeneLab NIH GEO EBI PRIDE ANL MG-RAST

Search Filters (GeneLab Only)

Project Type Factors Organisms Assay Type Clear

Page 1 of 8 (Total Studies: 191) Next

Studies Per Page: 25



STS-135 Cerebellum Transcriptomics

Organisms	Factors	Assay Types	Release Date	Description
<i>Mus musculus</i>	Spaceflight Absorbed Radiation Dose	Transcription profiling	28-Nov-2010	Mice were from orbiting STS-135 and returned to Earth for analysis. Cerebellums were collected within 2-4 hours of landing and snap frozen in liquid nitrogen. Samples were shipped to UCI Genomics Hg...

Methylome Analysis of Arabidopsis Seedlings Exposed to Microgravity

Organisms	Factors	Assay Types	Release Date	Description
<i>Arabidopsis thaliana</i>	Spaceflight	DNA methylation profiling	13-Jul-2010	DNA methylation is a very important kind of epigenetic modification and participates in many biological functions. Although many previous studies have addressed various plant species, the study of p...

Impact of Antithrostatic Suspension on Mouse response to Tumor and CpG: bone marrow of Biological Omics data

File Launch View Manage Help Tools

Galaxy

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Public

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 - GLDS-119
 - GLDS-12
 - GLDS-120
 - GLDS-121

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GeneLab

Open Science for Exploration

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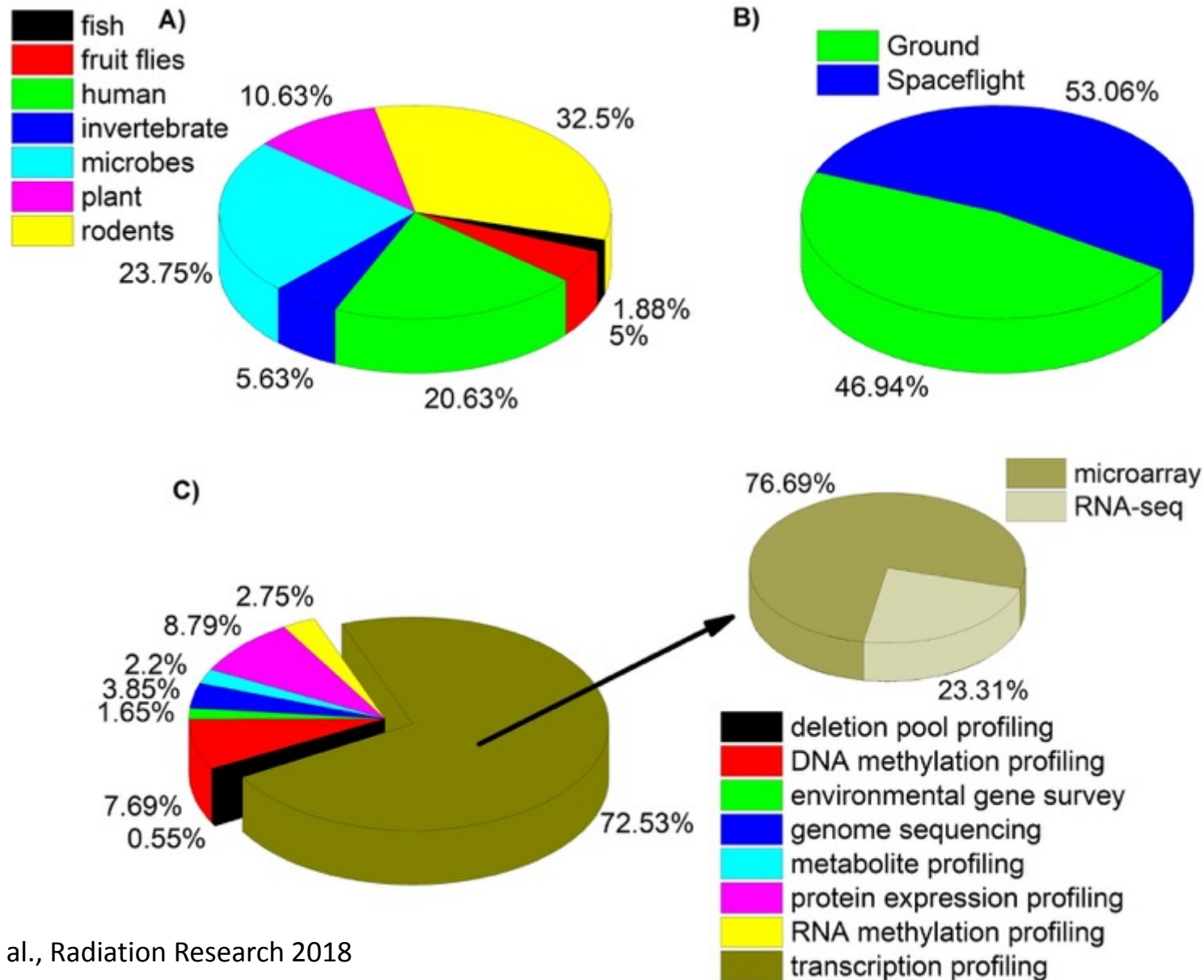
upload datasets

Environmental Data
Data collected

Collaborative Workspace
Share, organize and store

October 2019 will be the release for GeneLab's Visualization Portal!

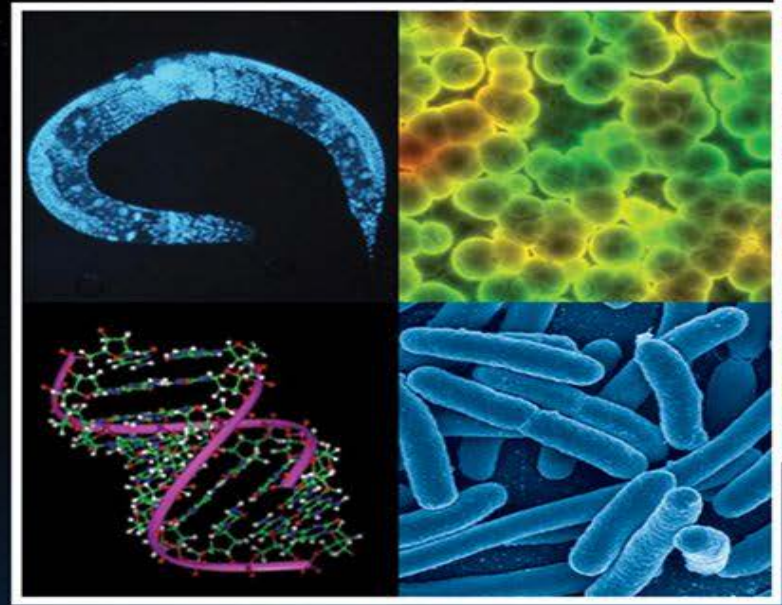
analyze unique genomics data from spaceflight



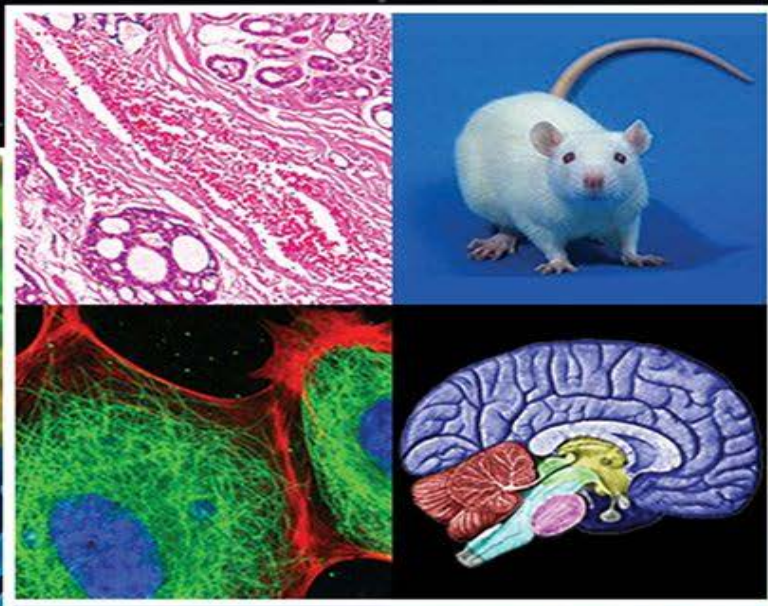
Biological Systems

Human Health

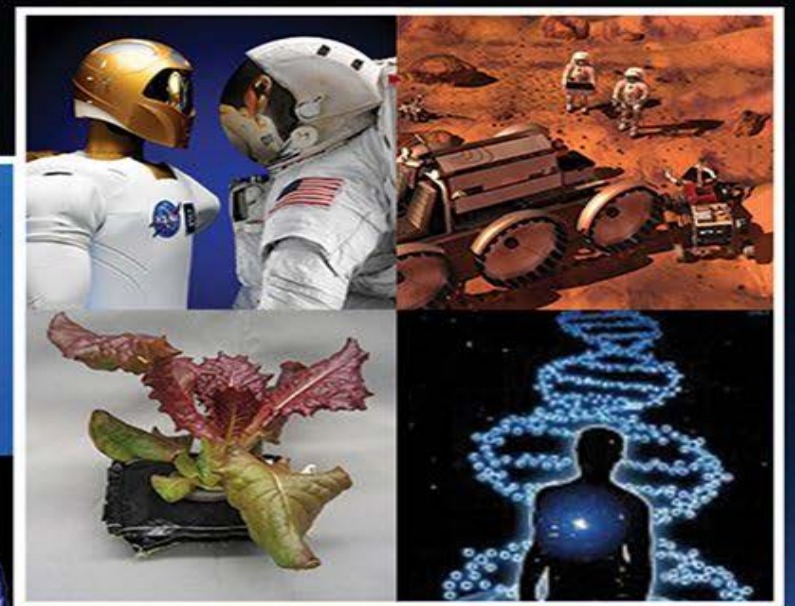
Human Exploration



- Model Organisms
- Cell and Microbial Biology
- Biomolecules



- Mammalian Cells
- Model Organisms



- Exploration Subsystems
- Bioregenerative Life Support

npj | Microgravity www.nature.com/npjmicrogr

PERSPECTIVE OPEN

From the bench to exploration medicine: NASA life sciences translational research for human exploration and habitation missions

Joshua S. Alwood¹, April E. Ronca^{2,3}, Richard C. Mains⁴, Mark J. Shelhamer⁵, Jeffrey D. Smith¹ and Thomas J. Goodwin¹

NASA's Space Biology and Human Research Program entities have recently spearheaded communications both internally and externally to coordinate the agency's translational research efforts. In this paper, we strongly advocate for translational research at NASA, provide recent examples of NASA sponsored early-stage translational research, and discuss options for a path forward. Our overall objective is to help in stimulating a collaborative research across multiple disciplines and entities that, working together, will more effectively and more rapidly achieve NASA's goals for human spaceflight.

npj Microgravity (2017)3:5; doi:10.1038/n41526-016-0002-8

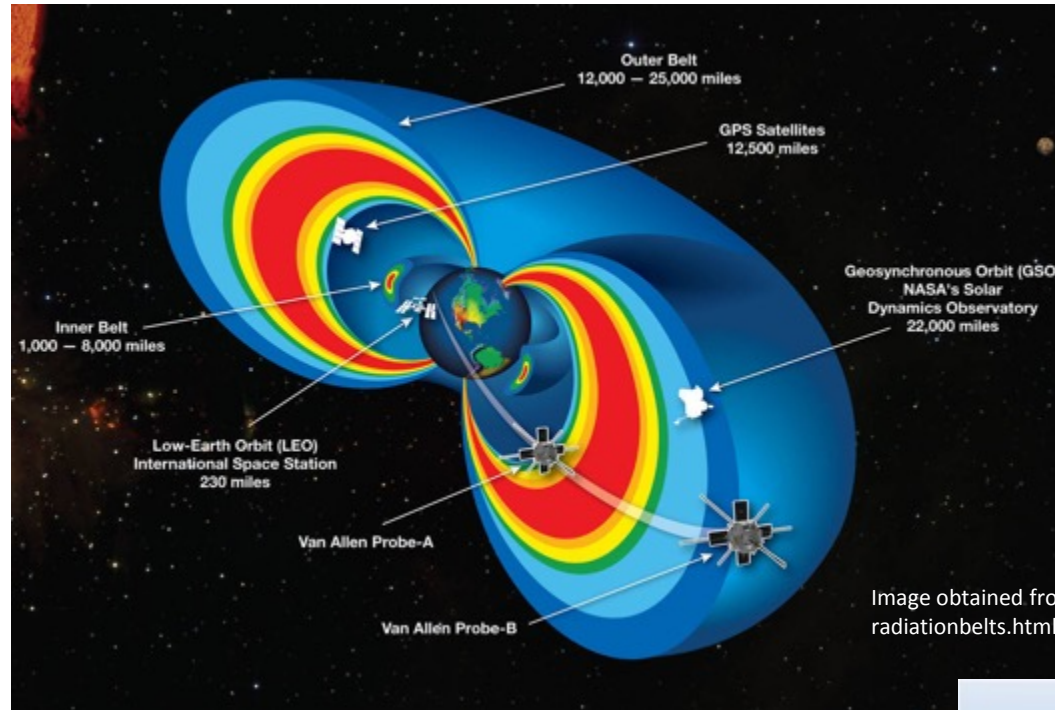


Image obtained from radiationbelts.html

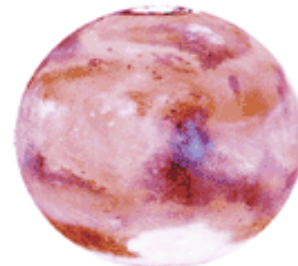


	MILLIREM:
CHEST X-RAY	8 to 50
AVG. YEARLY RADON DOSE	200
U.S. AVG. YEARLY DOSE	350
PET SCAN	1,000
1 YEAR IN KERALA, INDIA	1,300
U.S. NUCLEAR WORKER LIMIT PER YEAR	5,000
APOLLO 14 (9 DAYS)	1,140
SHUTTLE 41-C (18 DAYS)	5,600
SKYLAB 4 (84 DAYS)	17,800
MARS MISSION TOTAL	130,000

2½ Years, 2,600 X-Rays

Americans on average absorb the radiation equivalent of at least 7 chest X-rays each year.

Space missions, outside of Earth's protective atmosphere and magnetic field, expose astronauts to many times more.



NASA

Source: Brookhaven National Laboratory, U.S. Department of Energy



Isolation/
Confinement

Distance from
Earth

Hostile/closed
environments



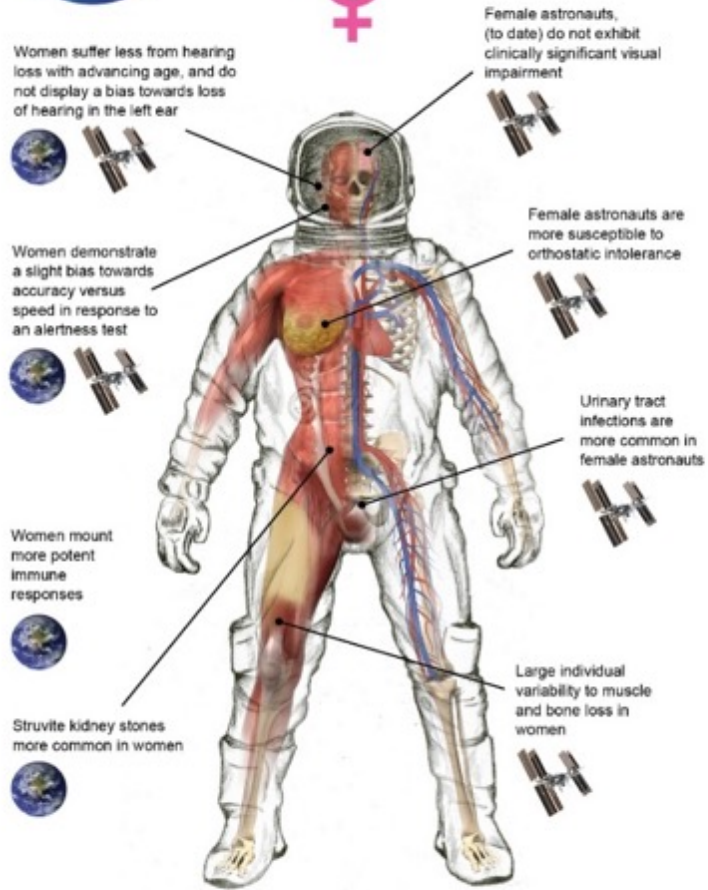
Space
Radiation

Gravity Fields

Credits: NASA

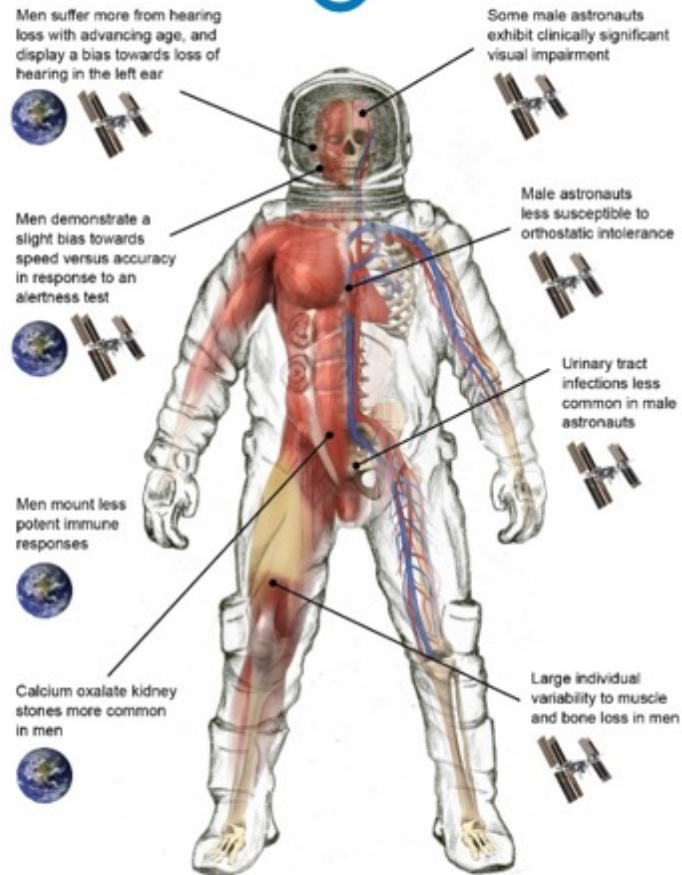


FEMALE ASTRONAUT

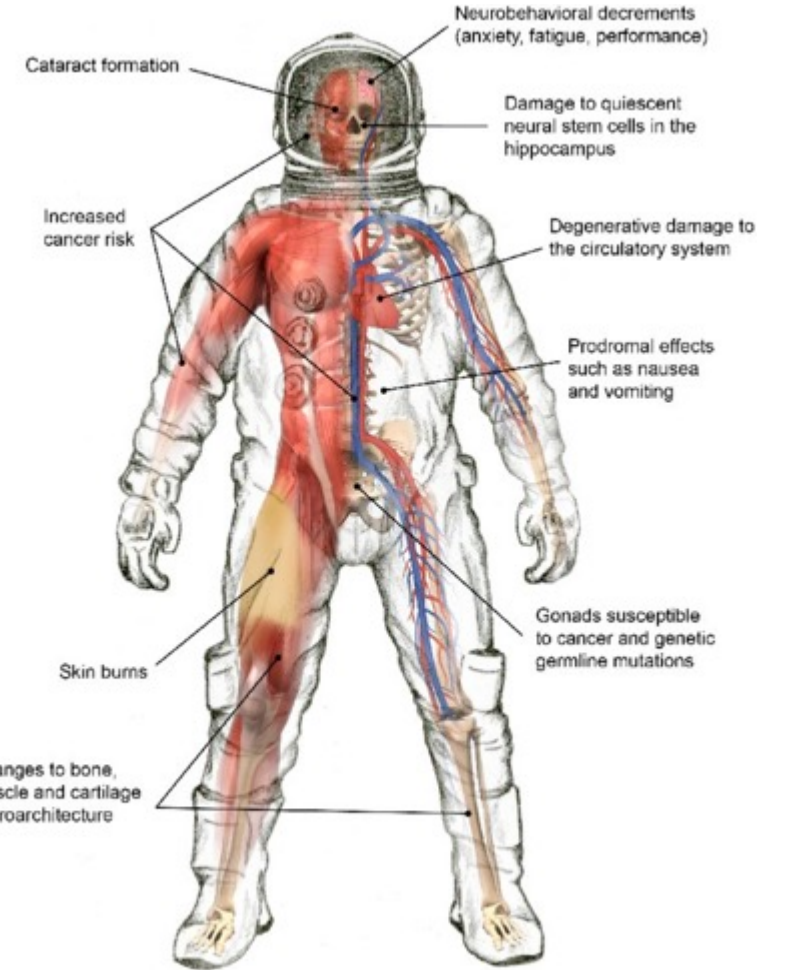


Health effect observed on Earth

MALE ASTRONAUT



Health effect observed in space



Select health effects due to space radiation exposures.

From: J. Chancellor et al., Space Radiation: The Number One Risk to Astronaut Health beyond Low Earth Orbit. *Life*, 4(3), 491-510;

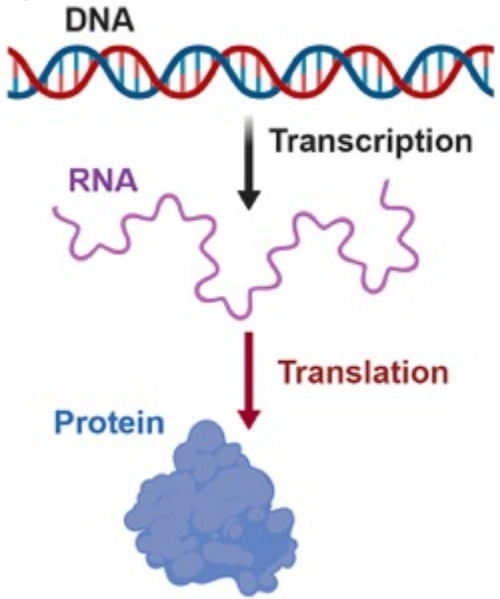
- Circulating miRNA Signature Predicts Health Risks Associated with Radiation and Microgravity
- Multi-Omics Analysis using GeneLab database recognizes Mitochondrial Dysfunction as a mediator of spaceflight health risks

The screenshot shows the Jove website interface. At the top, there is a search bar with the text "Search 10,142 video articles" and a "LOG IN" button. Below the search bar are navigation tabs: "ABOUT JOVE", "FOR LIBRARIANS", "PUBLISH", "VIDEO JOURNAL", and "SCIENCE EDUCATION". A secondary navigation bar includes "ABSTRACT", "INTRODUCTION", "PROTOCOL", "RESULTS", "DISCUSSION", "MATERIALS", "REFERENCES", and "DOWNLOADS". The main content area features a "GENETICS" category tag. The article title is "Exploring the Effects of Spaceflight on Mouse Physiology using the Open Access NASA GeneLab Platform". Below the title, the authors are listed: Afshin Beheshti¹, Yasaman Shirazi-Fard², Sungshin Choi¹, Daniel Berrios³, Samrawit G. Gebre¹, Jonathan M. Galazka², Sylvain V. Costes². The affiliations are: ¹WYLE Labs, Space Biosciences Division, NASA Ames Research Center, ²Space Biosciences Division, NASA Ames Research Center, ³USRA, NASA Ames Research Center. The article has 1,725 views. A video player is embedded, showing a thumbnail of the article title and authors. To the right of the video player is a "CHAPTERS" table of contents.

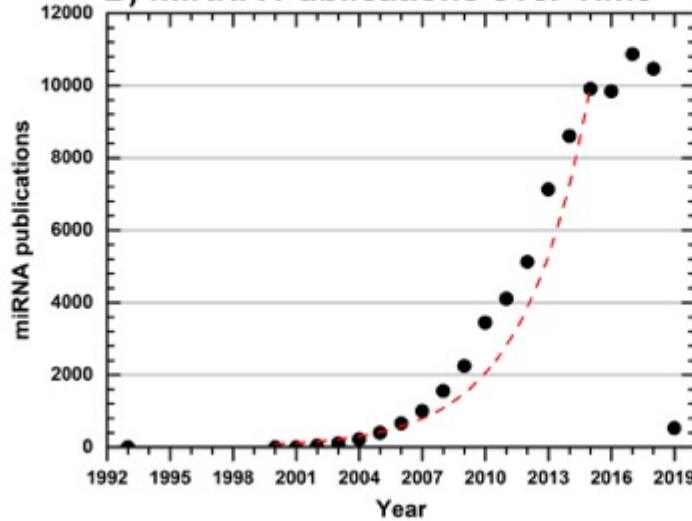
CHAPTERS	
0:04	Title
0:46	Rodent Handling for Spaceflight Experiments
4:52	Dataset Analysis
6:35	Metadata Access and Study Description and Transcriptomic Data Analysis
8:35	Results: Determining Key Genes Between Rodent Habitat- and Vivarium-housed Mice
10:06	Conclusion



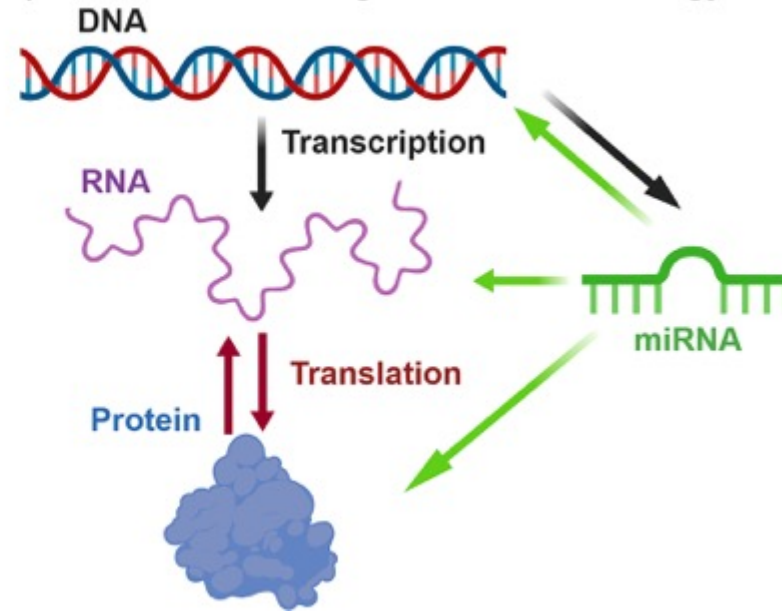
A) Classical View of Molecular Biology



B) miRNA Publications over Time



C) New Understanding of Molecular Biology

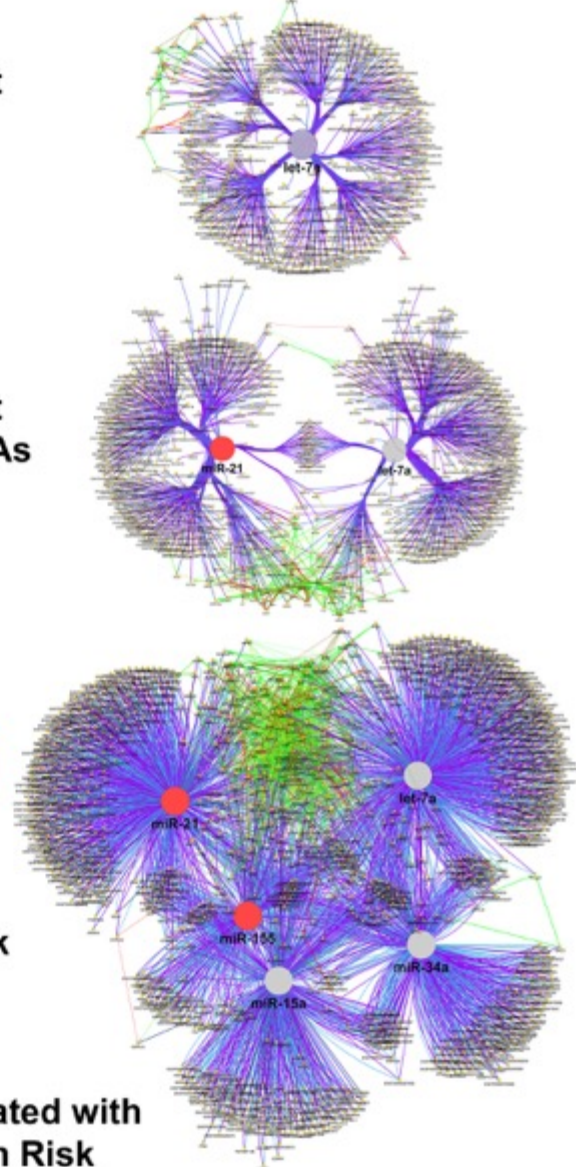
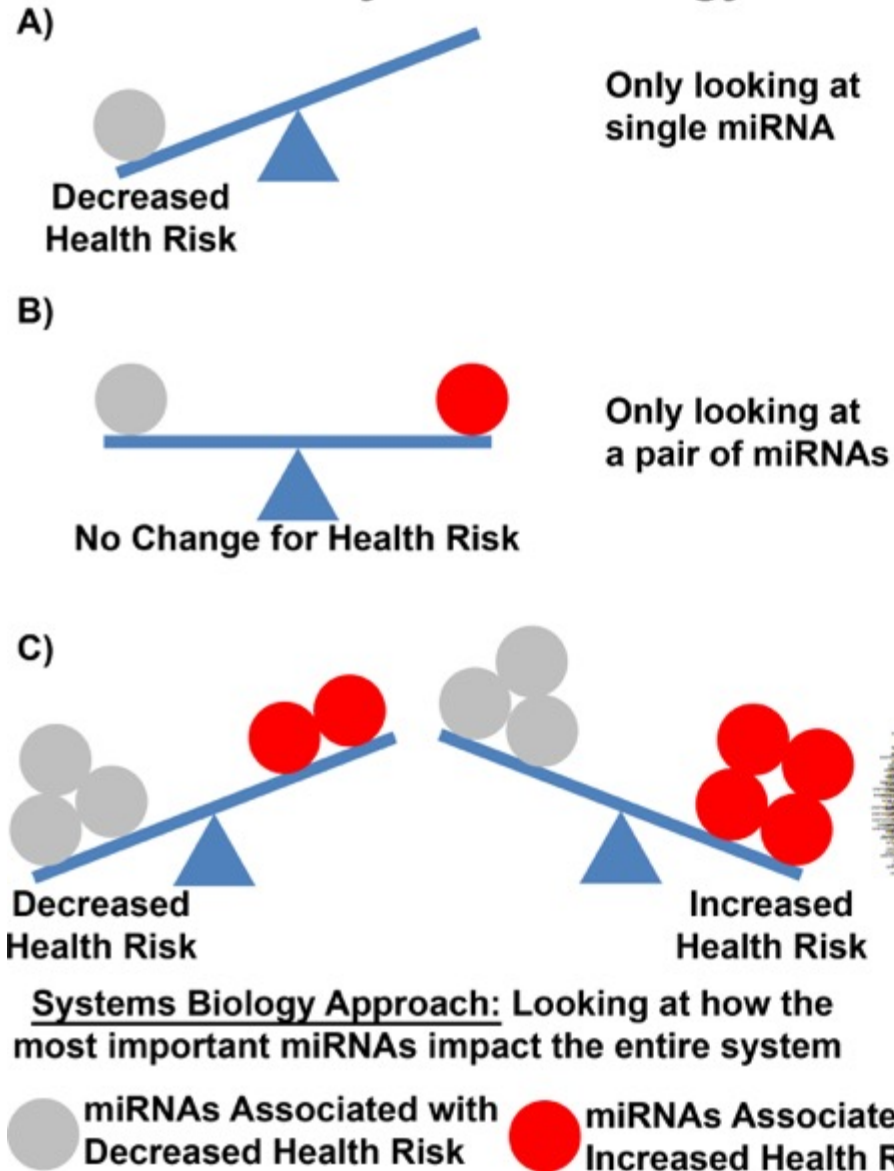


- A single miRNA has been estimated to regulate up to 500 mRNAs.
- miRNAs are ~22nt
- **Due to the size and stability of the miRNAs, it can float freely in the blood.**
- miRNAs are now known to be involved in all aspects of diseases.
- miRNA are not only found in mammals, but everything else living: plants, microbes, fish, C. Elegans, fruit flies, insects, etc...
- miRNAs play a big role in radiation response (which also relates to space radiation).

Saliva	Colostrum	Amniotic Fluid	Vaginal Secretion	Venous Blood	Cerebrospinal Fluid	Tears	Peritoneal Fluid	Semen	Menstrual Blood	Plasma					
miR-26a ^[1] miR-96 ^[1] miR-135b ^[1] miR-141 ^[1] miR-145 ^[1] miR-182 ^[1]	miR-10b ^[1] miR-150 ^[1] miR-193b ^[1] miR-217 ^[1] miR-518c ^[1] miR-924 ^[1]	miR-26b ^[1] miR-92a-1 ^[1] miR-363 ^[1] miR-376b ^[1] miR-556-5p ^[1] miR-593 ^[1]	miR-144 ^[1] miR-124a ^[1] miR-372 ^[1] miR-617 ^[1]	miR-16 ^[1] miR-20a ^[1] miR-106a ^[1] miR-126 ^[1]	miR-577 ^[1]	miR-637 ^[1]	miR-29b-1 ^[1] miR-129 ^[1]	miR-223 ^[1] miR-583 ^[1]	miR-10a ^[1] miR-10b ^[1] miR-17 ^[1] miR-29b-2 ^[1] miR-135a ^[1]	miR-135b ^[1] miR-340 ^[1] miR-380 ^[1] miR-507 ^[1]	miR-508-5p ^[1] miR-644 ^[1] miR-891a ^[1] miR-943 ^[1]	miR-145 ^[1] miR-185 ^[1] miR-412 ^[1] miR-451 ^[1]	miR-135a ^[1] miR-139-3p ^[1] miR-182 ^[1] miR-224 ^[1] miR-299-5p ^[1]	miR-330-5p ^[1] miR-369-3p ^[1] miR-373 ^[1] miR-483-3p ^[1] miR-508-3p ^[1]	miR-518f ^[1] miR-519d ^[1] miR-551b ^[1] miR-801 ^[1]

Silva, S.S., et al., *Forensic miRNA: potential biomarker for body fluids?* Forensic Sci Int Genet, 2015, 14: p. 1-10.

Systems Biology View of miRNAs



RESEARCH ARTICLE

A microRNA signature and TGF- β 1 response were identified as the key master regulators for spaceflight response

Afshin Beheshti^{1,2*}, Shayoni Ray^{2,3}, Homer Fogle¹, Daniel Berrios², Sylvain V. Costes^{2,3*}

1 WYLE, NASA Ames Research Center, Moffett Field, California, United States of America, **2** USRA, NASA Ames Research Center, Moffett Field, California, United States of America, **3** NASA Ames Research Center, Space Biosciences Division, Moffett Field, California, United States of America

* These authors contributed equally to this work.
* afshin.beheshti@nasa.gov (AB); sylvain.v.costes@nasa.gov (SVC)



Abstract

Translating fundamental biological discoveries from NASA Space Biology program into health risk from space flights has been an ongoing challenge. We propose to use NASA GeneLab database to gain new knowledge on potential systemic responses to space. Unbiased systems biology analysis of transcriptomic data from seven different rodent datasets reveals for the first time the existence of potential “master regulators” coordinating a systemic response to microgravity and/or space radiation with TGF- β 1 being the most common regulator. We hypothesized the space environment leads to the release of biomolecules circulating inside the blood stream. Through datamining we identified 13 candidate microRNAs (miRNA) which are common in all studies and directly interact with TGF- β 1 that can be potential circulating factors impacting space biology. This study exemplifies the utility of the

OPEN ACCESS

Citation: Beheshti A, Ray S, Fogle H, Berrios D, Costes SV (2018) A microRNA signature and TGF- β 1 response were identified as the key master regulators for spaceflight response. PLOS ONE 13 (7): e0199621. <https://doi.org/10.1371/journal.pone.0199621>

Editor: Andre van Wijnen, University of Massachusetts Medical School, UNITED STATES

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Accepted: May 3, 2018

Published: July 25, 2018



Article

GeneLab Database Analyses Suggest Long-Term Impact of Space Radiation on the Cardiovascular System by the Activation of FYN Through Reactive Oxygen Species

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Received: 15 January 2019; Accepted: 30 January 2019; Published: 3 February 2019



PLOS ONE

RESEARCH ARTICLE
A microRNA signature and TGF- β 1 response were identified as the key master regulators for spaceflight response

Alshin Beheshti^{1*}, Shayoni Ray^{2*}, Homer Fogle³, Daniel Berrios³, Sylvain V. Costes^{3*}

¹ WYLE, NASA Ames Research Center, Moffett Field, California, United States of America, ² USRA, NASA Ames Research Center, Moffett Field, California, United States of America, ³ NASA Ames Research Center, Space Sciences Division, Moffett Field, California, United States of America

* These authors contributed equally to this work.
 * alshin.beheshti@nasa.gov (AB); shayoni.v.costes@nasa.gov (SVC)



Abstract

Translating fundamental biological discoveries from NASA Space Biology program into health risk from space flights has been an ongoing challenge. We propose to use NASA GeneLab database to gain new knowledge on potential systemic responses to space. Unbiased systems biology analysis of transcriptomic data from seven different rodent datasets reveals for the first time the existence of potential "master regulators" coordinating a systemic response to microgravity and/or space radiation with TGF- β 1 being the most common regulator. We hypothesized the space environment leads to the release of biomolecules circulating inside the blood stream. Through datamining we identified 13 candidate microRNAs (miRNA) which are common in all studies and directly interact with TGF- β 1 that can be potential circulating factors impacting space biology. This study exemplifies the utility of the GeneLab data repository to aid in the process of performing novel hypothesis-based research.

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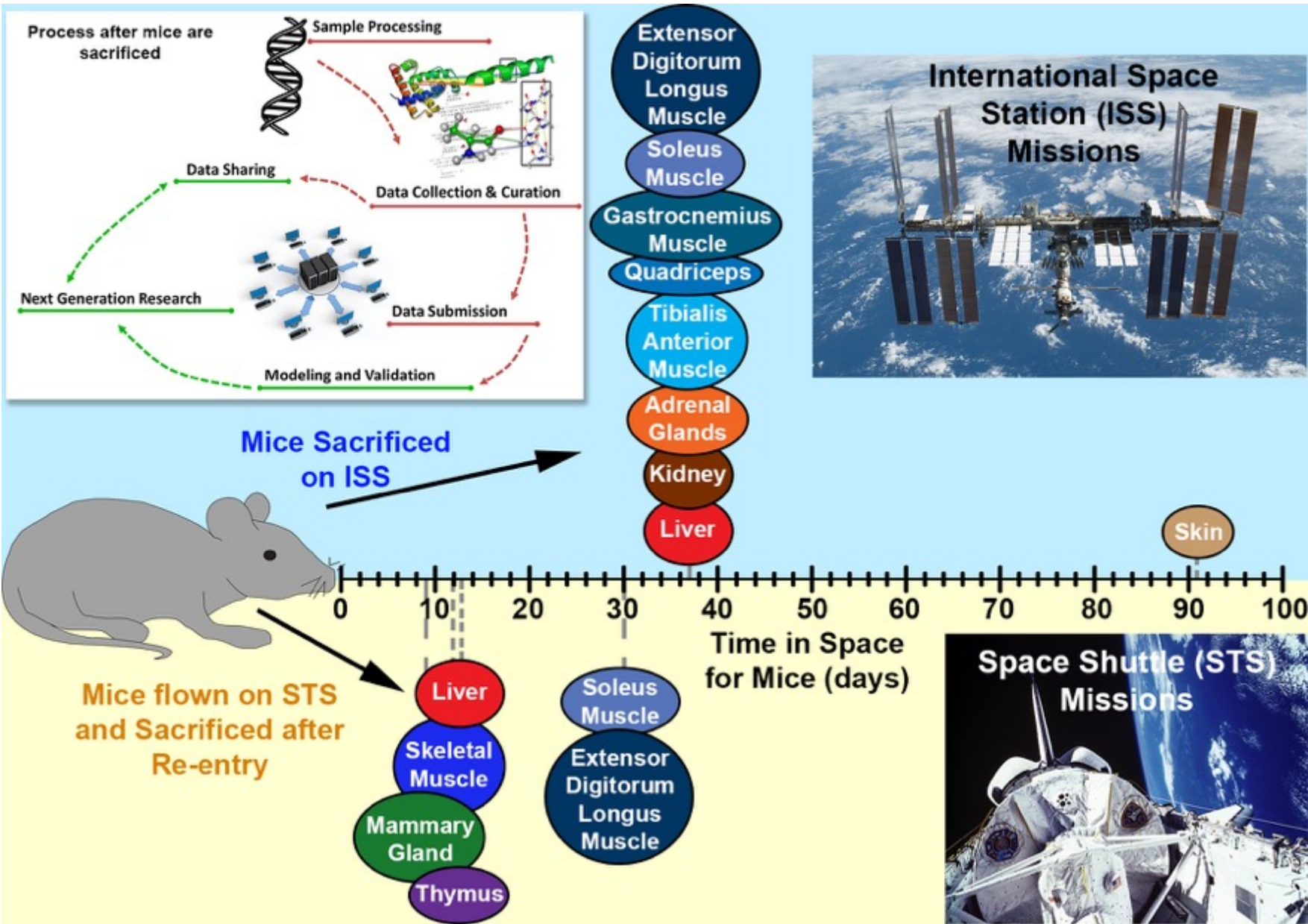
Citation: Beheshti A, Ray S, Fogle H, Berrios D, Costes SV (2018) A microRNA signature and TGF- β 1 response were identified as the key master regulators for spaceflight response. PLOS ONE 13(7): e0198621. <https://doi.org/10.1371/journal.pone.0198621>

Editor: Andre van Wijnen, University of Massachusetts Medical School, UNITED STATES

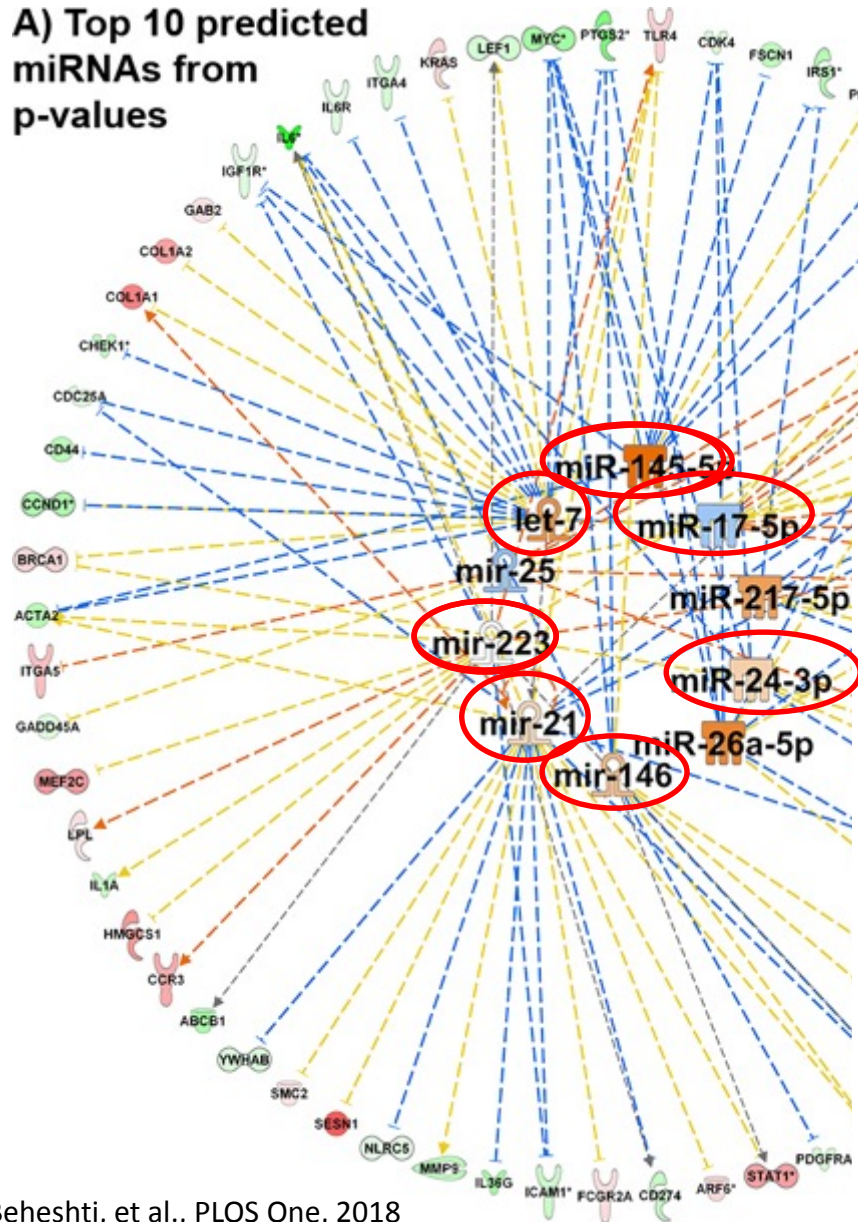
Received: March 5, 2018

Accepted: May 3, 2018

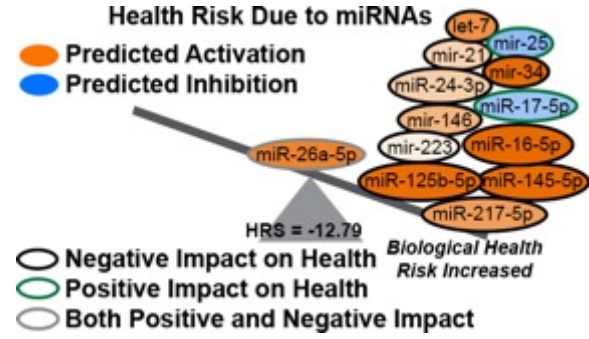
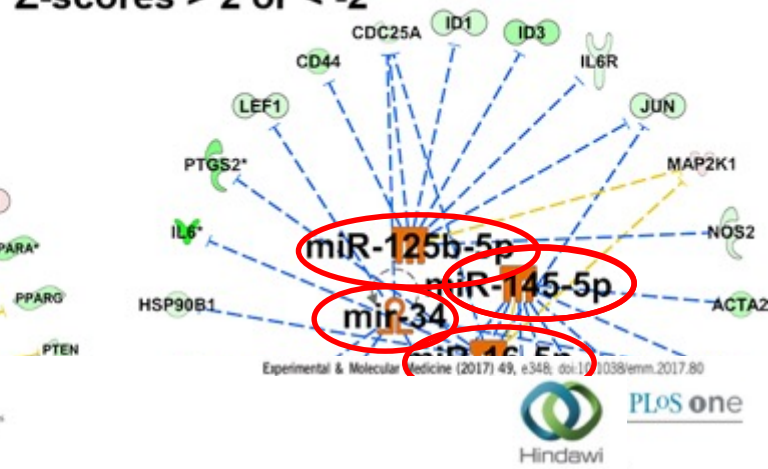
Published: July 25, 2018



A) Top 10 predicted miRNAs from p-values



B) All miRNAs with Z-scores > 2 or < -2



Research Article
Integration Analysis of MicroRNA and mRNA Expression Profiles in Human Peripheral Blood Lymphocytes Cultured in Modeled Microgravity

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¹ Dipartimento di Biologia, Università degli Studi di Padova, Via U. Bassi 58/B, 35131 Padova, Italy
² Laboratori Nazionali di Legnaro, INFN, Viale dell'Università 2, Legnaro, 35020 Padova, Italy

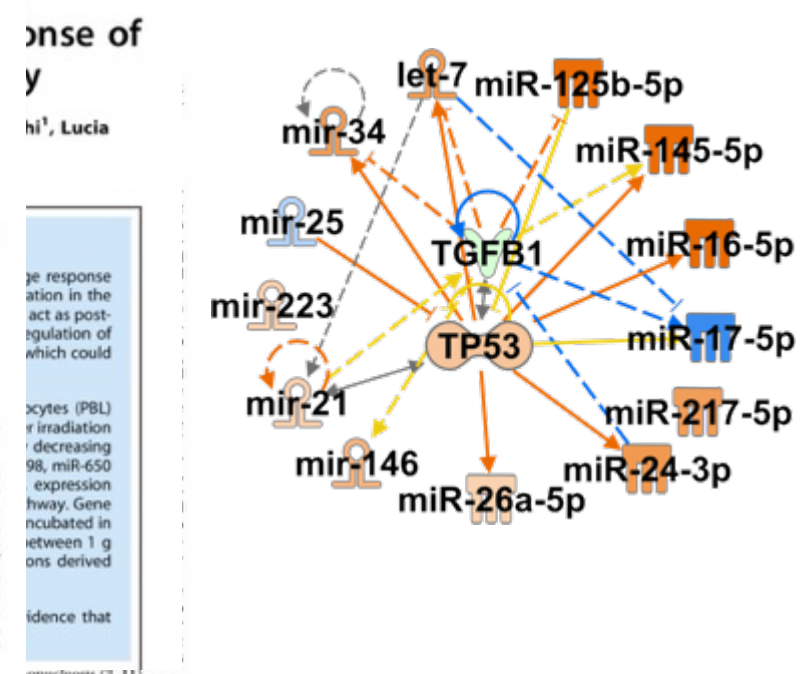
Correspondence should be addressed to L. Celotti; lucia.celotti@unipd.it and M. Mognato; maddalena.mognato@unipd.it

Received 16 April 2014; Revised 22 May 2014; Accepted 22 May 2014; Published 23 June 2014

Academic Editor: Mariano Bizzarri

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We analyzed miRNA and mRNA expression profiles in human peripheral blood lymphocytes (PBLs) incubated in microgravity condition, simulated by a ground-based rotating wall vessel (RWV) bioreactor. Our results show that 42 miRNAs were differentially expressed in MMG-incubated PBLs compared with 1g incubated ones. Among these, miR-9-5p, miR-9-3p, miR-155-5p, miR-150-3p, and miR-378-3p were the most dysregulated. To improve the detection of functional miRNA-mRNA pairs, we performed gene expression profiles on the same samples assayed for miRNA profiling and we integrated miRNA and mRNA expression data. The functional classification of miRNA-correlated genes evidenced significant enrichment in the biological processes of immune/inflammatory response, signal transduction, regulation of response to stress, regulation of programmed cell death, and regulation of cell proliferation. We identified the correlation of miR-9-3p, miR-155-5p, miR-150-3p, and miR-378-3p expression with that of genes involved in immune/inflammatory response (e.g., IFNG and IL17F), apoptosis (e.g., PDCD4 and PTEN), and cell proliferation (e.g., NKX3-1 and GADD45A). Experimental assays of cell viability and apoptosis induction validated the results obtained by bioinformatics analyses demonstrating that in human PBLs the exposure to reduced gravitational force increases the frequency of apoptosis and decreases cell proliferation.





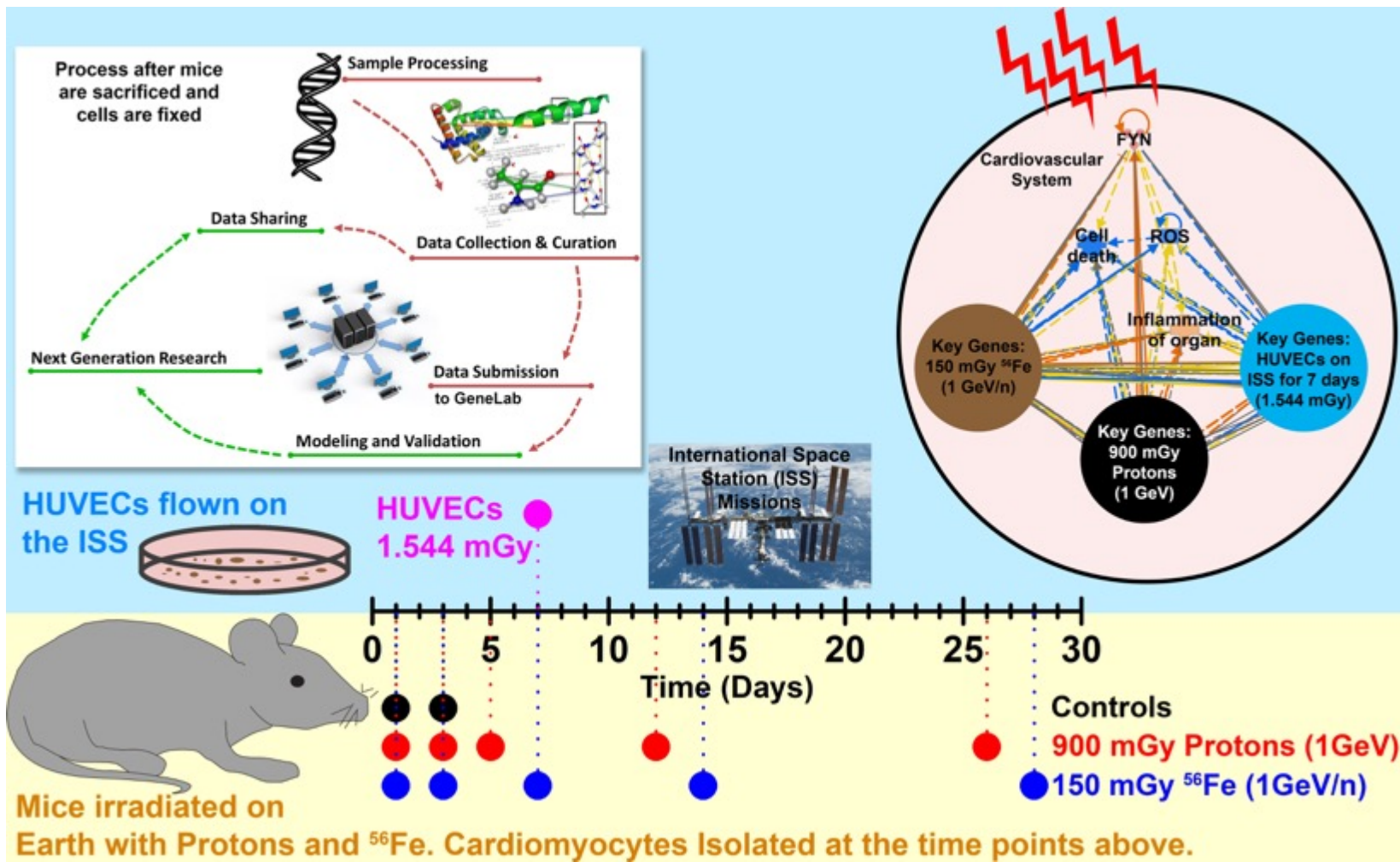
International Journal of
Molecular Sciences

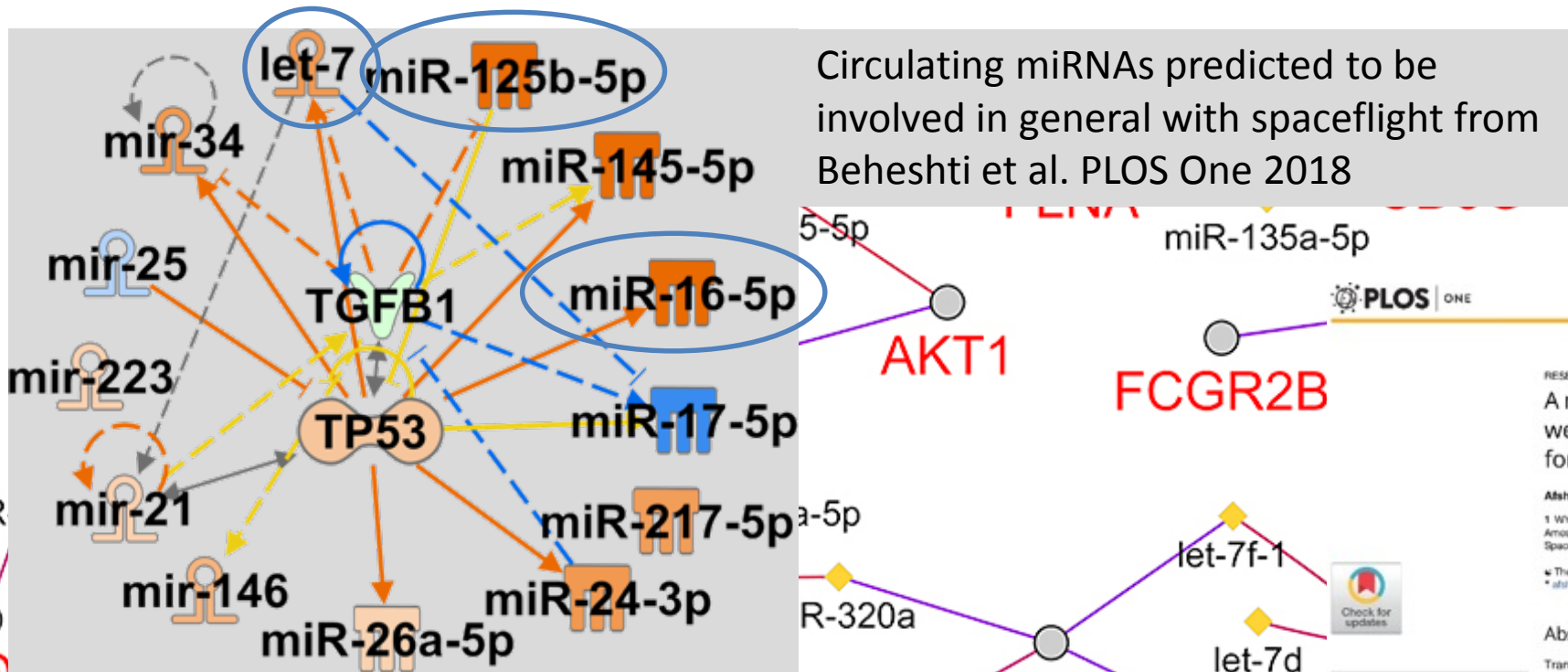


Article
GeneLab Database Analyses Suggest Long-Term Impact of Space Radiation on the Cardiovascular System by the Activation of *FYN* Through Reactive Oxygen Species

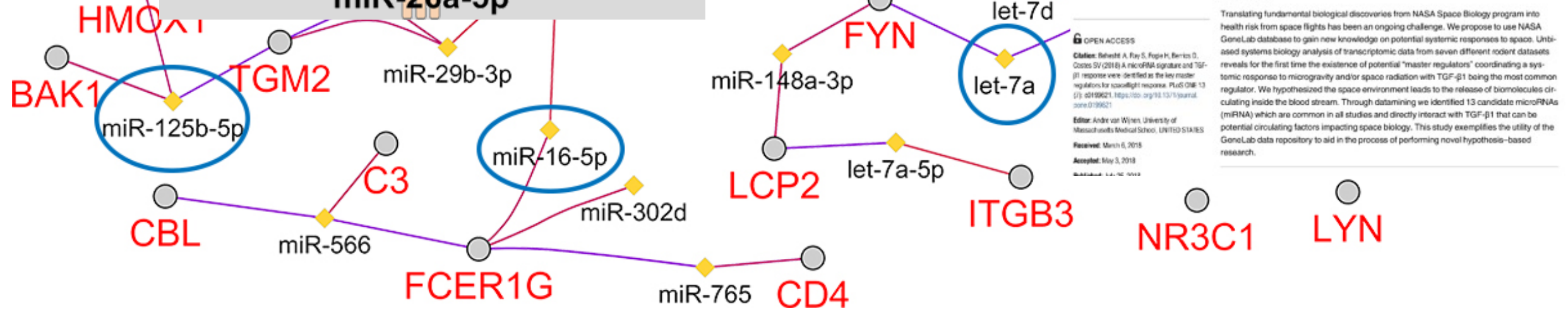
Afshin Beheshti ^{1,*}, J. Tyson McDonald ², Jack Miller ³, Peter Grabham ⁴ and Sylvain V. Costes ^{5,*}

- ¹ WYLE Labs, NASA Ames Research Center, Moffett Field CA 94035, USA
 - ² Department of Physics, Hampton University, Hampton, VA 23668 USA; john.mcdonald@hamptonu.edu
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 - ⁵ NASA Ames Research Center, Space Biosciences Division, Moffett Field, CA 94035, USA
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Circulating miRNAs predicted to be involved in general with spaceflight from Beheshti et al. PLOS One 2018



PLOS ONE

RESEARCH ARTICLE

A microRNA signature and TGF-β1 response were identified as the key master regulators for spaceflight response

Ashish Beheshti^{1*}, Shayoni Ray^{2*}, Homer Fogie¹, Daniel Berrios², Sylvain V. Costes^{3*}

¹ WYLE, NASA Ames Research Center, Moffett Field, California, United States of America, ² USRA, NASA Ames Research Center, Moffett Field, California, United States of America, ³ NASA Ames Research Center, Space Biosciences Division, Moffett Field, California, United States of America

* These authors contributed equally to this work.
* ashish.beheshti@nasa.gov (AB); shayoni.v.costes@nasa.gov (SVC)

Abstract

Translating fundamental biological discoveries from NASA Space Biology program into health risk from space flights has been an ongoing challenge. We propose to use NASA GeneLab database to gain new knowledge on potential systemic responses to space. Unbiased systems biology analysis of transcriptomic data from seven different rodent datasets reveals for the first time the existence of potential "master regulators" coordinating a systemic response to microgravity and/or space radiation with TGF-β1 being the most common regulator. We hypothesized the space environment leads to the release of biomolecules circulating inside the blood stream. Through datamining we identified 13 candidate microRNAs (miRNA) which are common in all studies and directly interact with TGF-β1 that can be potential circulating factors impacting space biology. This study exemplifies the utility of the GeneLab data repository to aid in the process of performing novel hypothesis-based research.

OPEN ACCESS

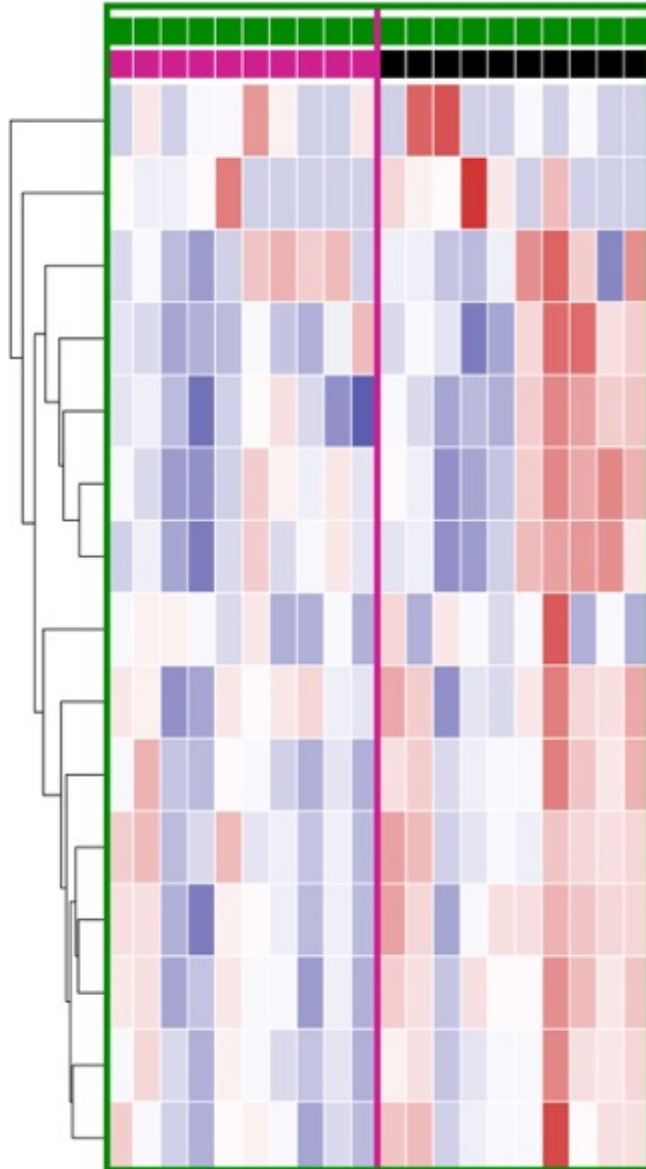
Citation: Beheshti A, Ray S, Fogie H, Berrios D, Costes SV (2018) A microRNA signature and TGF-β1 response were identified as the key master regulators for spaceflight response. PLOS ONE 13(5): e0196271. <https://doi.org/10.1371/journal.pone.0196271>

Editor: Andre van Wijnen, University of Massachusetts Medical School, UNITED STATES

Received: March 6, 2018
Accepted: May 3, 2018
Published: May 10, 2018

Check for updates

miRNA Signature in Serum



Irradiation
Type of Loading

miR-25-5p

miR-217-5p

miR-223-3p

miR-146a-5p

miR-92a-3p

let-7a-5p

let-7c-5p

miR-34a-5p

miR-21-5p

miR-145-5p

miR-17-5p

miR-16-5p

miR-24-3p

miR-125b-5p

miR-26a-5p

Irradiation

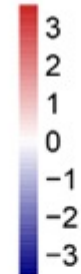
Sham

2Gy Gamma

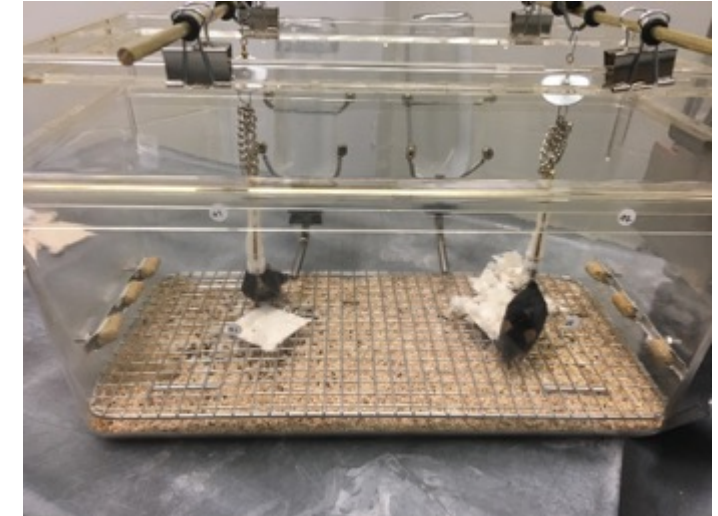
Type of Loading

Normal Loading

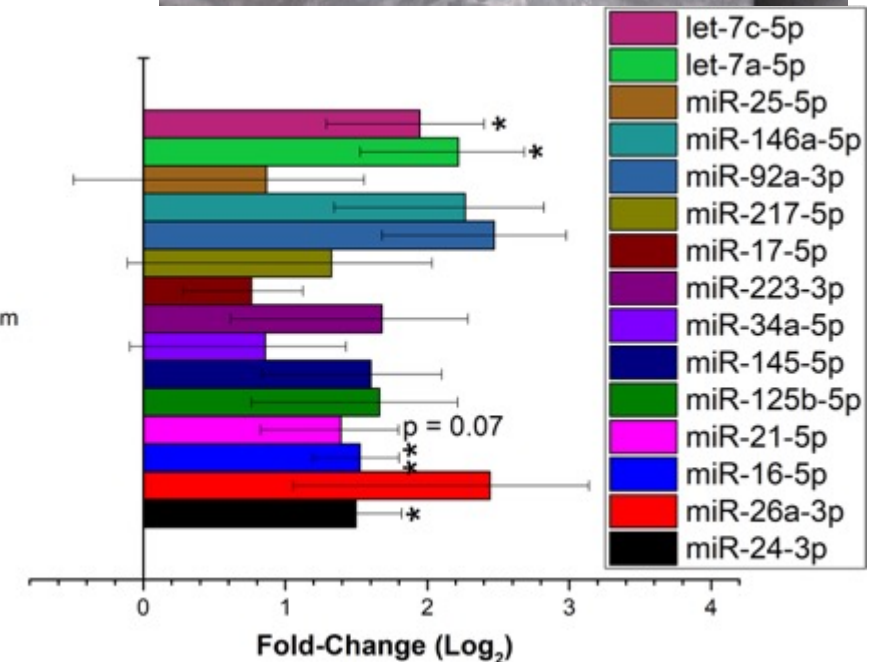
Hindlimb Unloading



Hindlimb Unloading

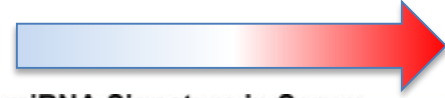


HU vs Sham

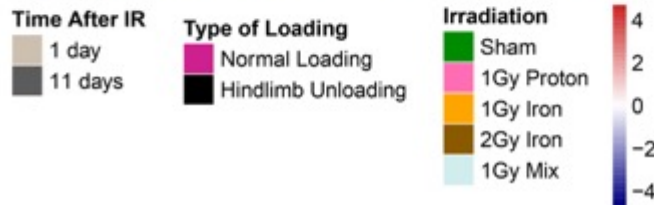
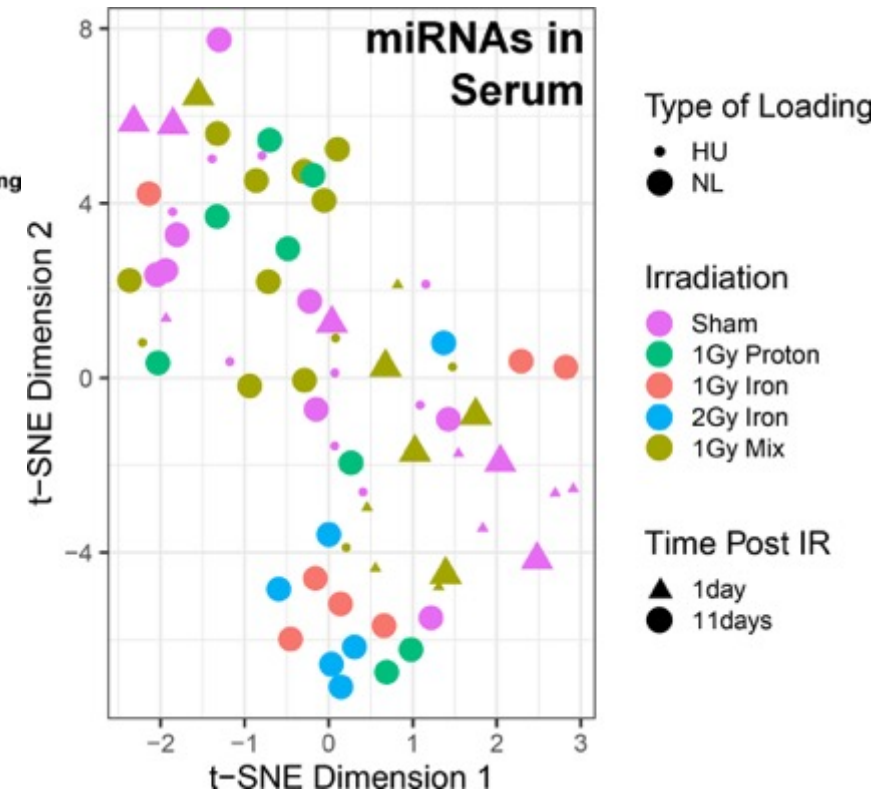
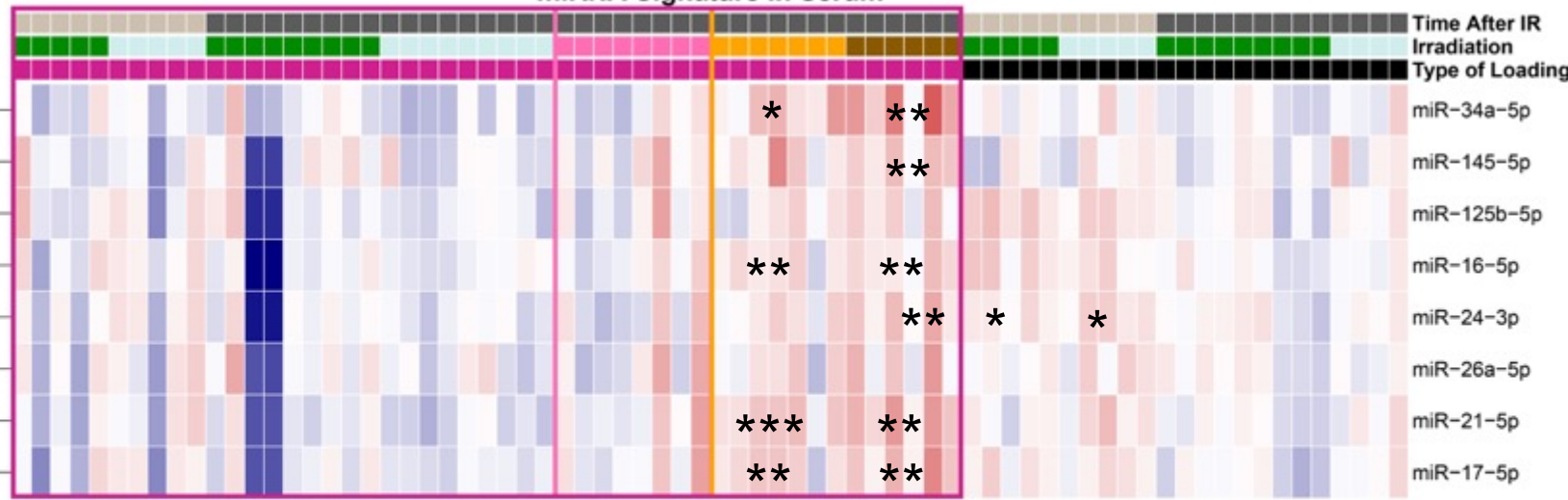


- HU for an initial three days followed by IR and continuation of HU for another 1 or 11 days
- Radiation exposure: Total body irradiation, conscious mice, 600 MeV/n ⁵⁶Fe (1 Gy and 2 Gy), 150 MeV Proton (1Gy) or '1Gy Mix' (0.5Gy ⁵⁶Fe and 0.5Gy Proton)

Increasing Dose and Ions causes increase miRNAs in serum



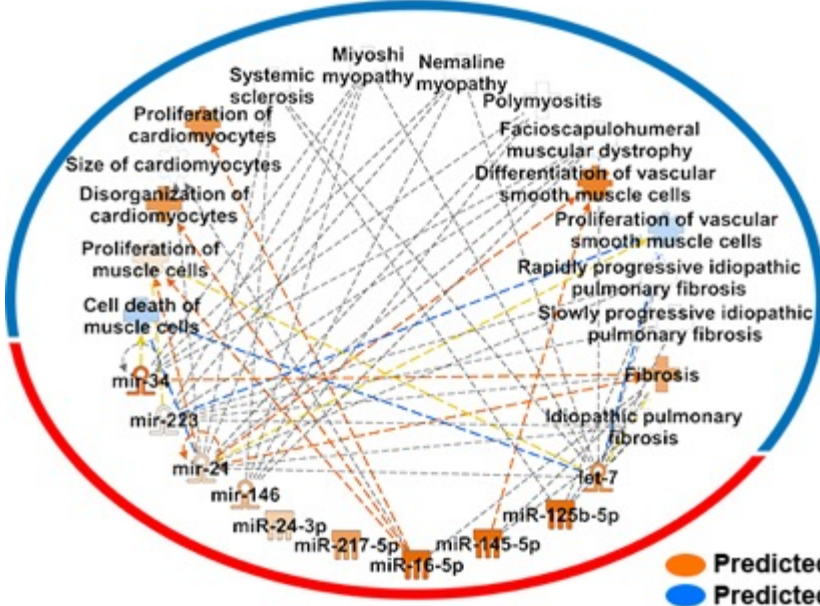
miRNA Signature in Serum



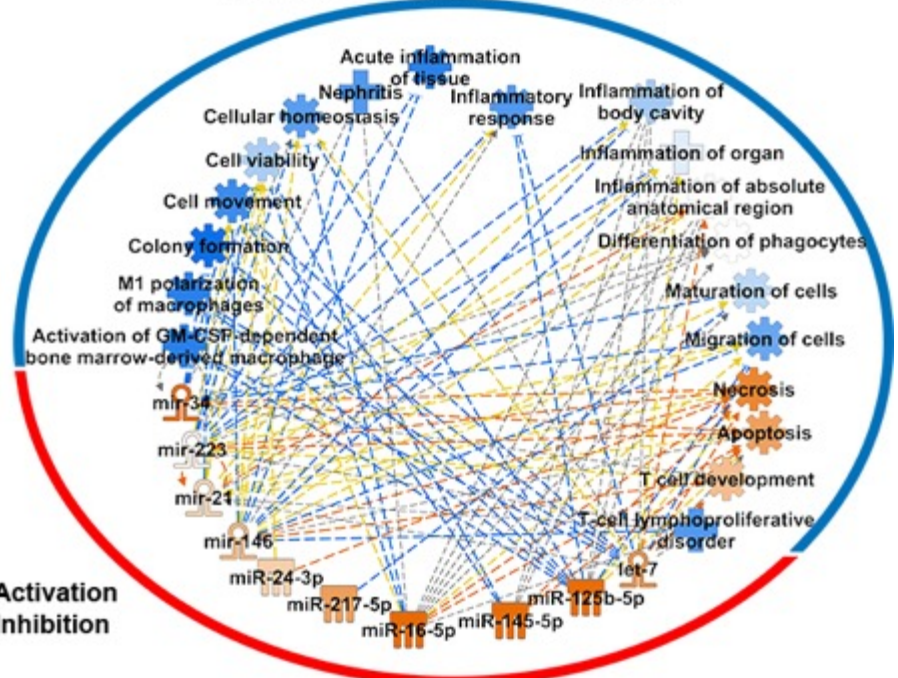
Significance compared to serum from Sham NL (Time Post IR)

- * p-value < 0.05
- ** p-value < 0.01
- *** p-value < 0.001

Predicted Muscle Related Functions

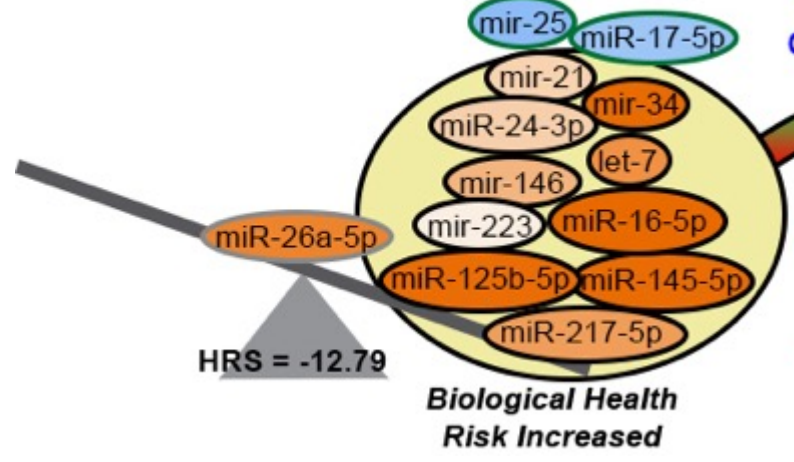


Predicted Immune Related Functions



● Predicted Activation
● Predicted Inhibition

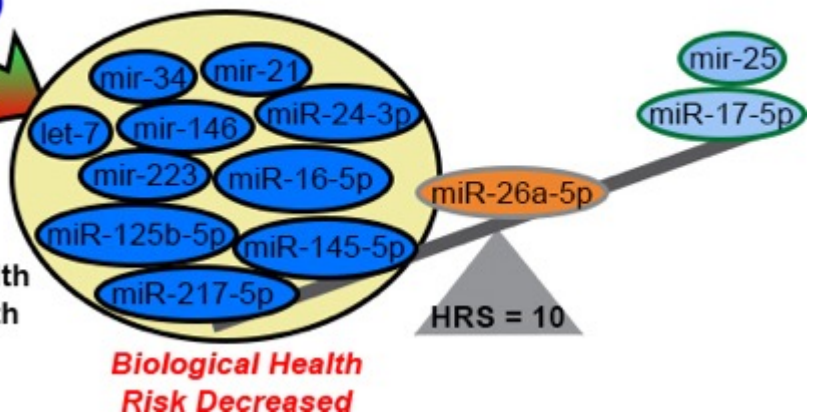
miRNA Targets



Multi-miRNA Detection and Countermeasures (MMRDaC)

● Predicted Activation
● Predicted Inhibition

○ Negative Impact on Health
○ Positive Impact on Health
○ Both Positive and Negative Impact





Sylvain Costes
Space Bio
miRNAs



Egle Cekanaviciute
Quantifying
miRNAs



Sherina Malkani
Quantifying miRNAs



Ann-Sofie
Schreurs
Provided Archived
Tissues



Margareth
Cheng-Campbell
Quantifying
miRNAs



Yasaman
Shirazi
Provided
Archived
Tissues



Ruth Globus
Provided
Archived
Tissues



Elizabeth Blaber
Space Bio miRNAs



J. Tyson McDonald



Charles Vanderburg



Peter Grabham



This work is supported by:

16-ROSBFP GL-0005:
NNH16ZTT001N-FG
Appendix G: Solicitation of
Proposals for Flight and
Ground Space Biology
Research

The Translational Research Institute
through NASA Cooperative Agreement
NNX16AO69A (T-0404)



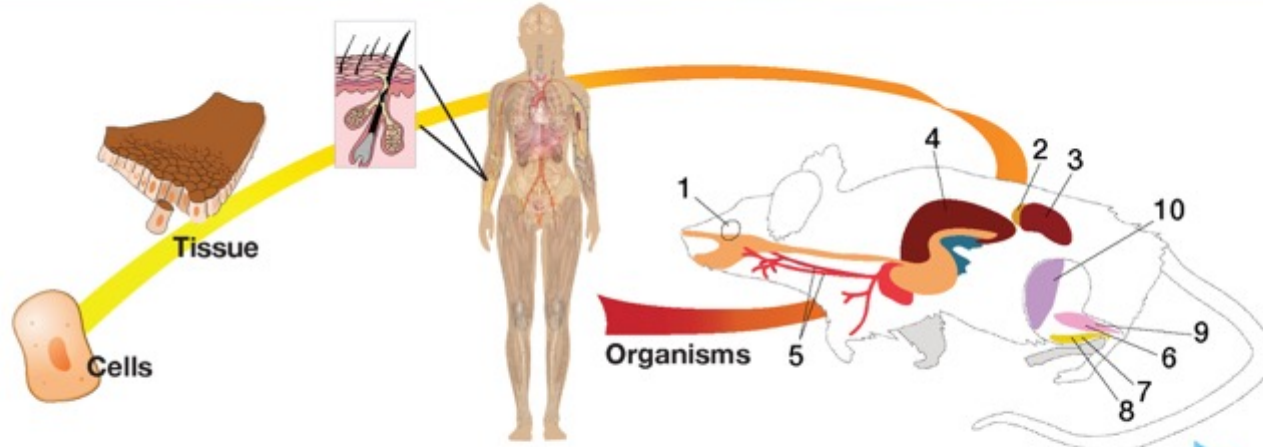
System Complexity

Factors

Earth
Gravity
Low Radiation
Normal air

Space
µGravity
Cosmic Radiation
CO₂ rich air

Variability
Species
Genetic Diversity



Measurements

Transcriptomics, Proteomics, Epigenetics, Metabolomics

Physiological

Human Cell Cultures

- Primary T Cells
- HUVEC cells: Human umbilical vein endothelial cell
- HMVEC-dBL cells: Human Dermal Blood Microvascular Endothelial Cells
- Fibroblasts

Mouse Tissues

1. Eye: Transcriptomics (RR3 and RR1)
2. Adrenal Glands: Transcriptomics, Proteomics, and Epigenetics (RR1 and RR3)
3. Kidney: Transcriptomics, Proteomics, and Epigenetics (RR1 and RR3)
4. Liver: Transcriptomics, Proteomics, and Epigenetics (RR1 and RR3)
5. Carotid Arteries: Transcriptomics (RR3)
6. Soleus Muscle: Transcriptomics (RR1)
7. Extensor Digitorum Longus: Transcriptomics (RR1)
8. Tibialis Anterior: Transcriptomics (RR1)
9. Gastrocnemius: Transcriptomics (RR1) and Metabolomics (RR9)
10. Quadriceps: Transcriptomics (RR1) and Metabolomics (RR9)

Human Tissues

- Hair follicles

Astronaut Physiological Data

- 1,25 Vitamin D
- Antiox Cap
- Cholesterol
- LDL
- HDL
- IGF-1
- IL-1
- IL-α
- IL-1ra
- PGF2-α
- Renin
- VEGF-1
- 8OHdG

- Paper being written
- Plan to submit paper by end of September
- Target journal to submit is *New England Journal of Medicine*
 - Contacted the editor of the journal and he was interested in the paper and encouraged submission to their journal.

AWG Members Involved



Kathleen Fisch



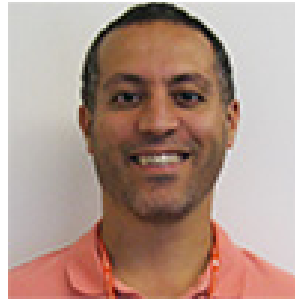
UNIVERSITY of CALIFORNIA, SAN DIEGO
SCHOOL OF MEDICINE



Brin Rosenthal



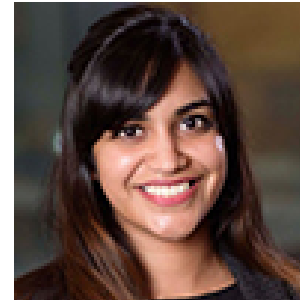
Deanne Taylor



Hossein Fazelinia



Children's Hospital
of Philadelphia™



Komal Rathi



Douglas Wallace



Perelman
School of Medicine
UNIVERSITY of PENNSYLVANIA



Larry Singh



Helio Costa



STANFORD
UNIVERSITY



Kathryn Grabek



J. Tyson McDonald



HAMPTON
UNIVERSITY
THE STANDARD OF EXCELLENCE



Gary Hardiman



QUEEN'S
UNIVERSITY
BELFAST



Willian da Silveira

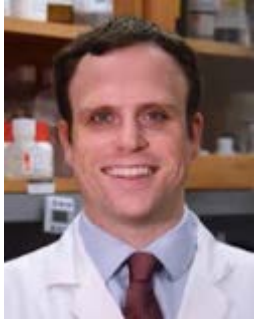


Jeffrey Scott Willey



WAKE FOREST
UNIVERSITY

AWG Members Involved



Chris Mason



Cem Meydan



Jonathan Foox



Flavia Rius



Yared Kidane



Evagelia C. Laiakis



GEORGETOWN UNIVERSITY
Georgetown University Medical Center



Robert Meller,
D.Phil



Cornell University



Susana Zanello



Scott Smith



Sara Zwart



Sonja Schrepfer



University of California
San Francisco



Dong Wang



Afshin Beheshti



Sylvain Costes





FEMALE ASTRONAUT



Women suffer less from hearing loss with advancing age, and do not display a bias towards loss of hearing in the left ear



Women demonstrate a slight bias towards accuracy versus speed in response to an alertness test



Women mount more potent immune responses



Struvite kidney stones more common in women



Female astronauts, (to date) do not exhibit clinically significant visual impairment



Large individual variability to muscle and bone loss in women



Health effect observed on Earth

MALE ASTRONAUT



Men suffer more from hearing loss with advancing age, and display a bias towards loss of hearing in the left ear



Some male astronauts exhibit clinically significant visual impairment



Calcium oxalate kidney stones more common in men

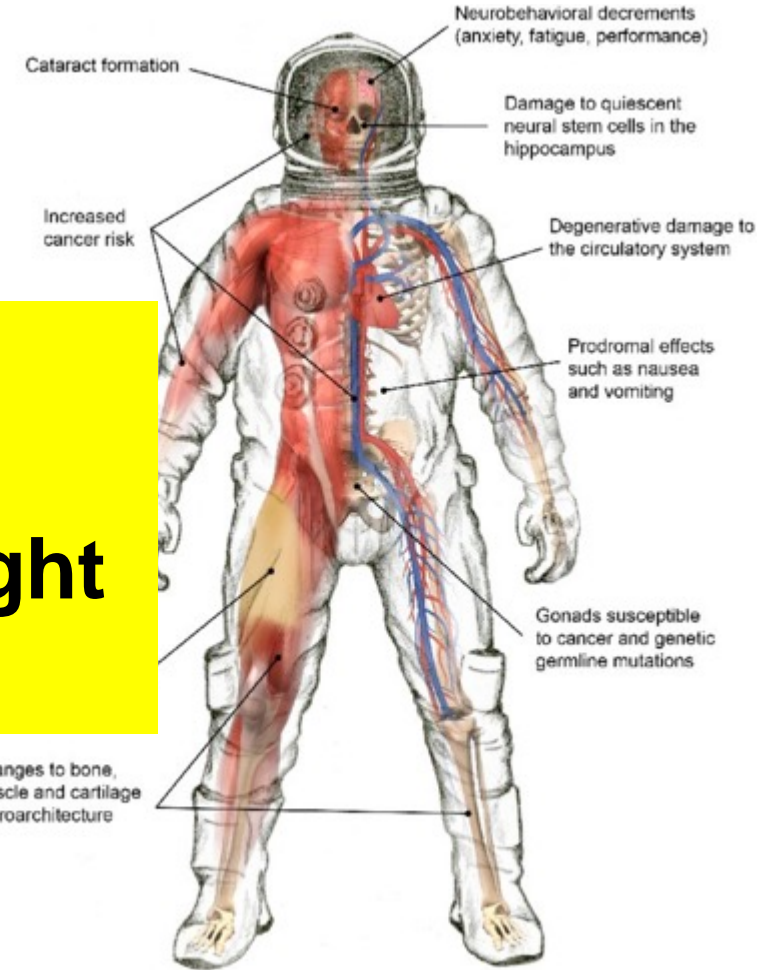


Large individual variability to muscle and bone loss in men



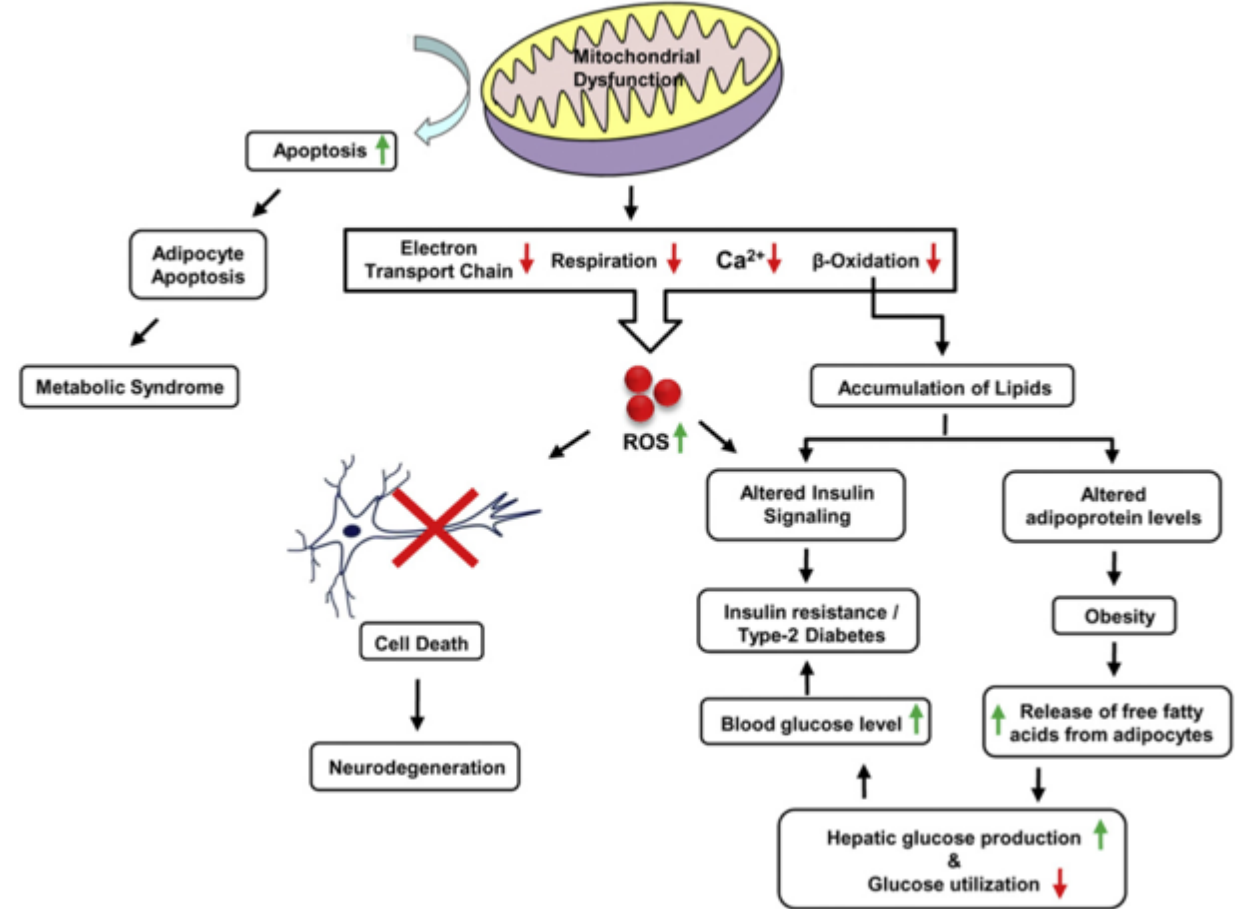
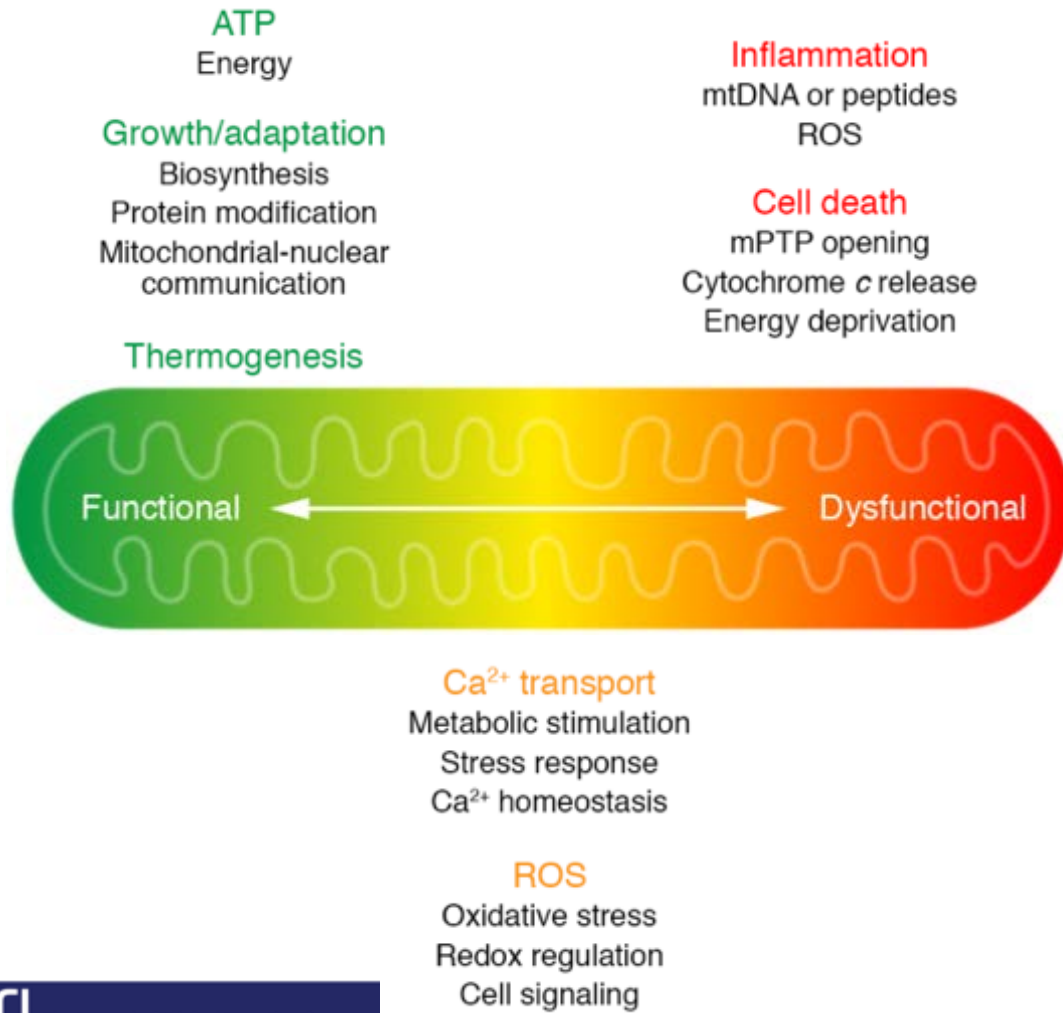
Health effect observed in space

One thing is always missing: LIVER and Mitochondrial as factors of interest for spaceflight related health risks!!



Select health effects due to space radiation exposures.

From: J. Chancellor et al., Space Radiation: The Number One Risk to Astronaut Health beyond Low Earth Orbit. *Life*, 4(3), 491-510;



Technique in Biophysics Acta 1803 (2017) 1152–1160

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

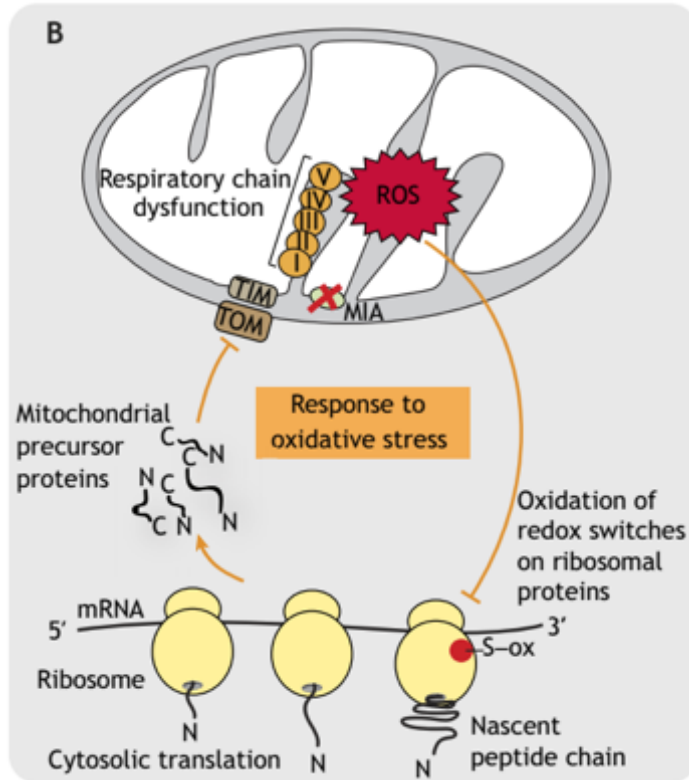
journal homepage: www.elsevier.com/locate/bbaadis

Linking mitochondrial dysfunction, metabolic syndrome and stress signaling in Neurodegeneration*

Saurabh Kumar Jha¹, Niraj Kumar Jha¹, Dhiraj Kumar, Rashmi K. Ambasta, Pravir Kumar*

Mitochondrial Neuroscience and Functional Genomics Laboratory, Department of Biotechnology, Delhi Technological University (Formerly DCE), Delhi 110029, India

Respiratory Chain Dysfunction resulting in halt of translation



Cell arrest in response to oxidative stress

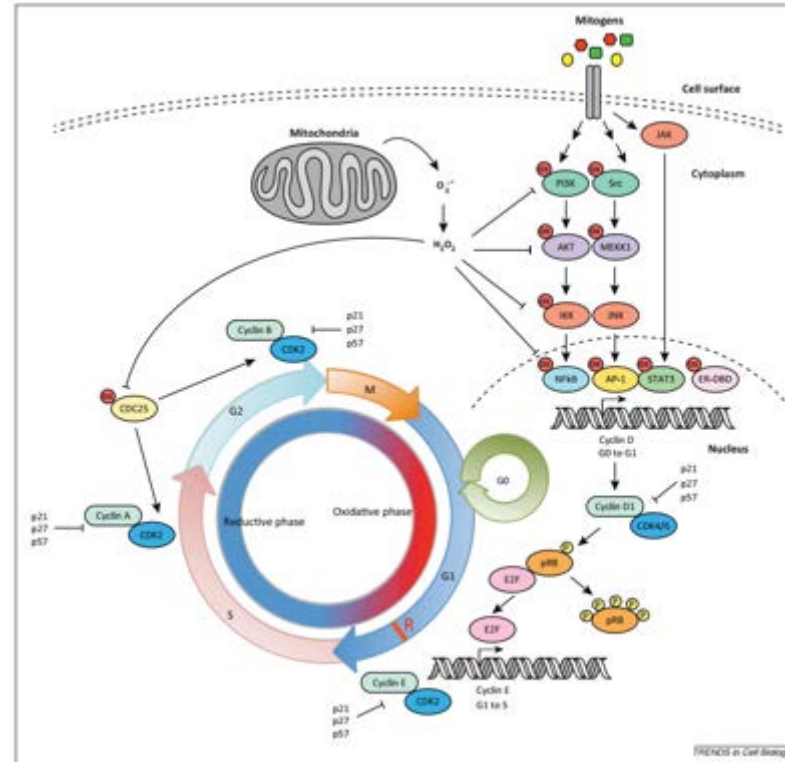
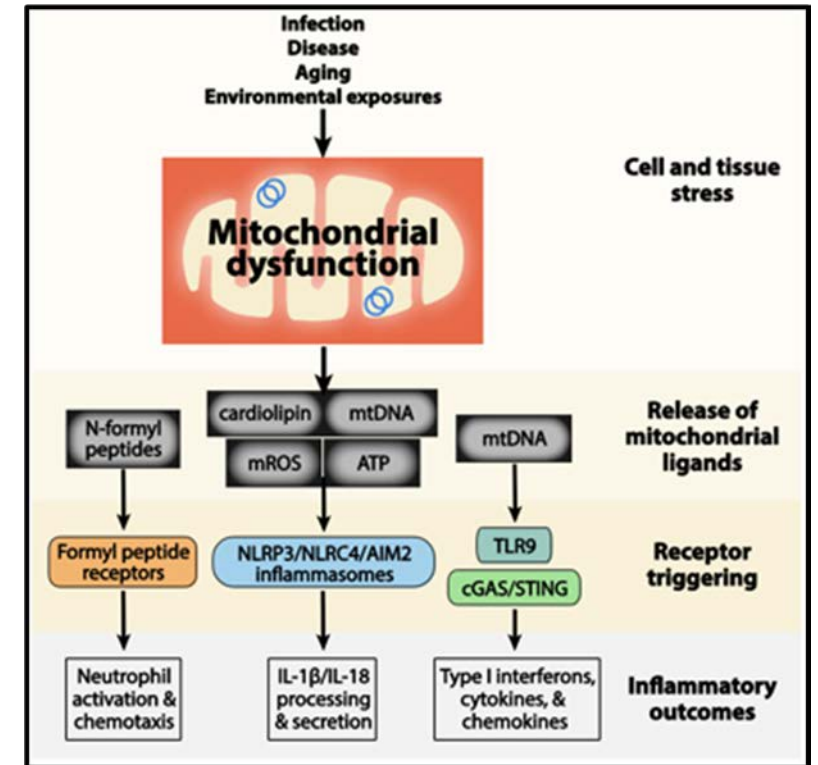


Figure 1. Overview of redox control of the eukaryotic cell-cycle.

Mitochondrial stress as a trigger innate immune responses



Mitochondrial Dysfunction Impacts Many Organs

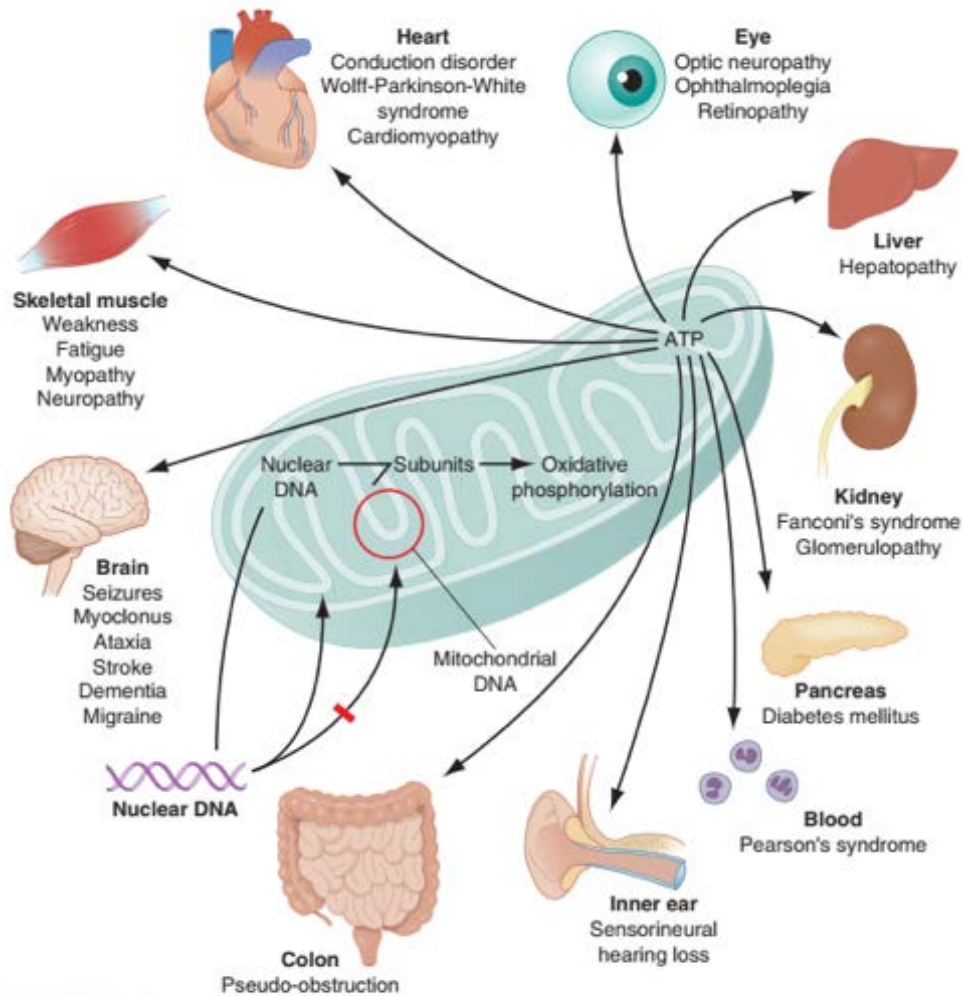


FIGURE 85e-1 Dual genetic control and multiple organ system manifestations of mitochondrial disease. (Reproduced with permission from DR. Johns: Mitochondrial DNA and disease. *N Engl J Med* 333:638, 1995.)

Mitochondrial Dysfunction May Differ Between Organs

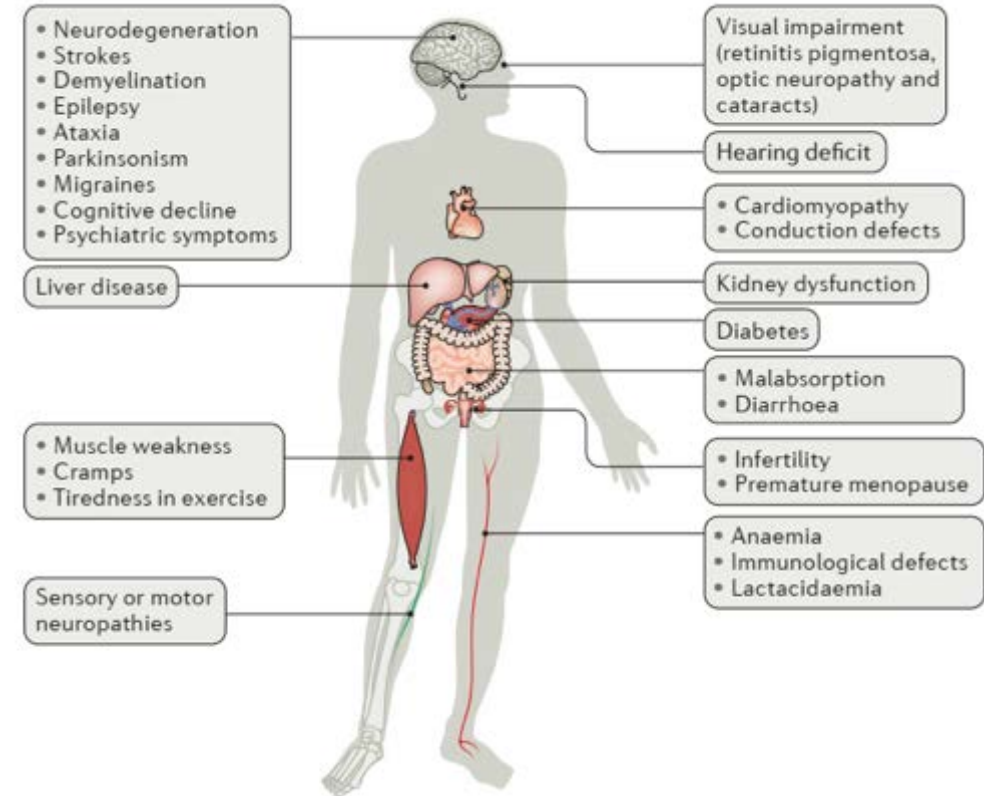
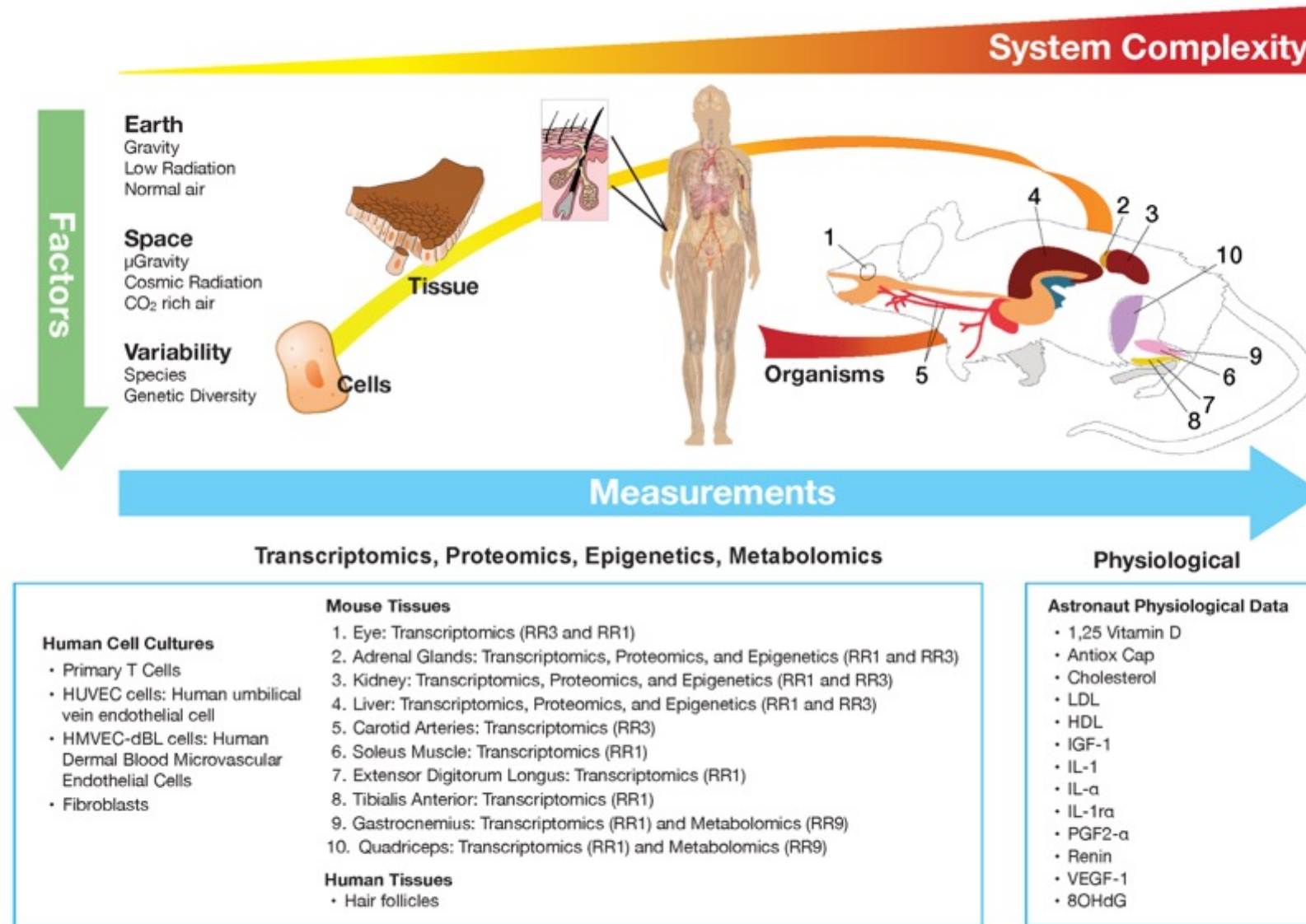
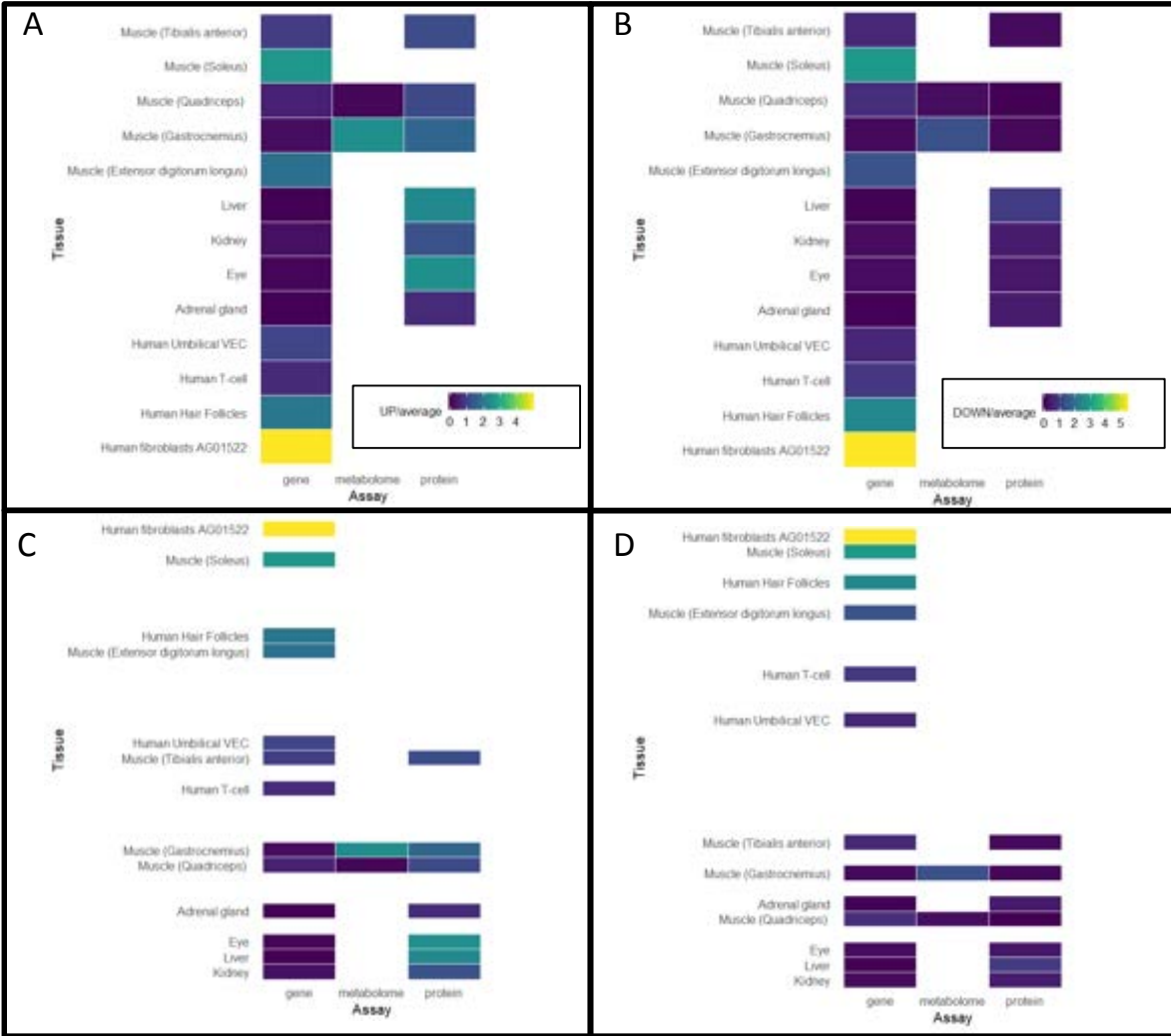


Figure 1 | The variability of mitochondrial disease manifestations. Mitochondrial diseases can manifest both in children and in adults, and can present in various organs, including in multiple organs that may have no apparent functional links to each other, such as the brain and liver, or pancreatic β -cells and the auditory system. Sometimes manifestations only affect one tissue, such as the heart or the optic nerve. Children may recover from one phenotype and later develop another — for example, in Pearson syndrome, the primary manifestation is exocrine pancreatic dysfunction and megaloblastic anaemia, and the survivors may later develop brain disease. Typically, these disorders are progressive.

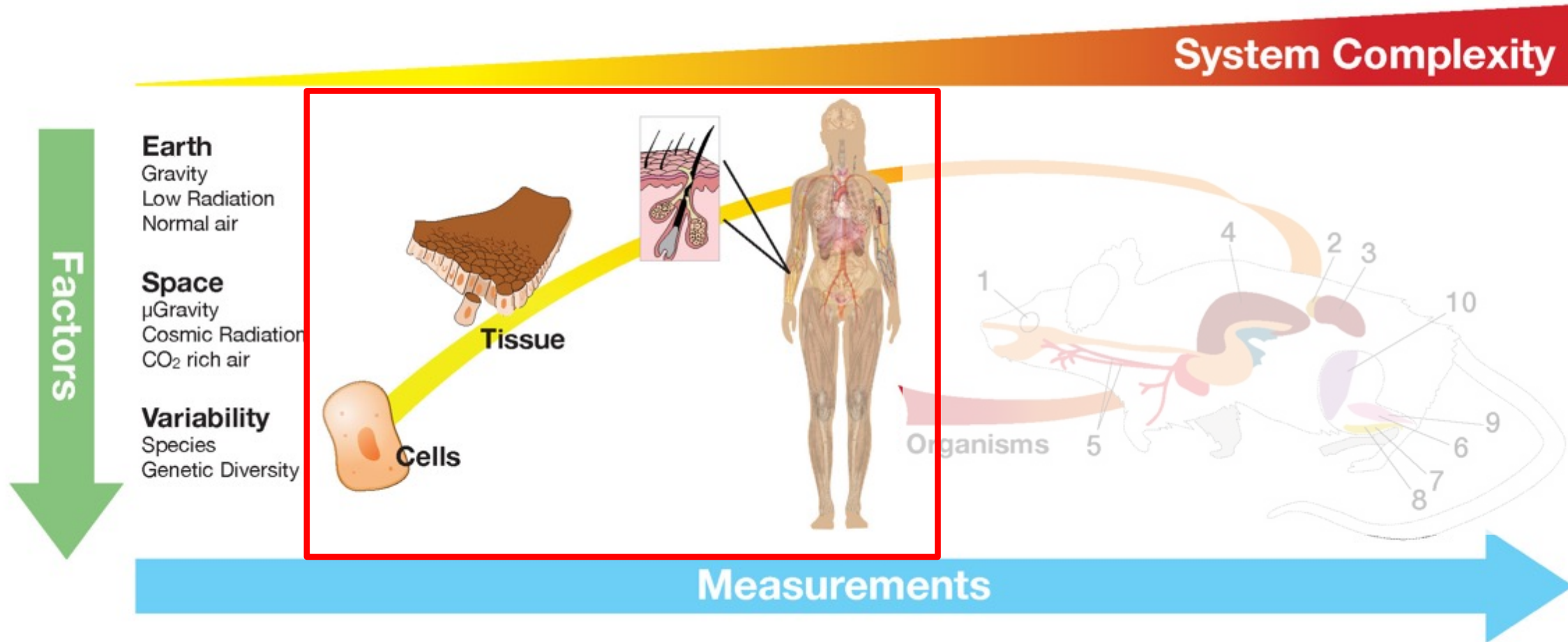


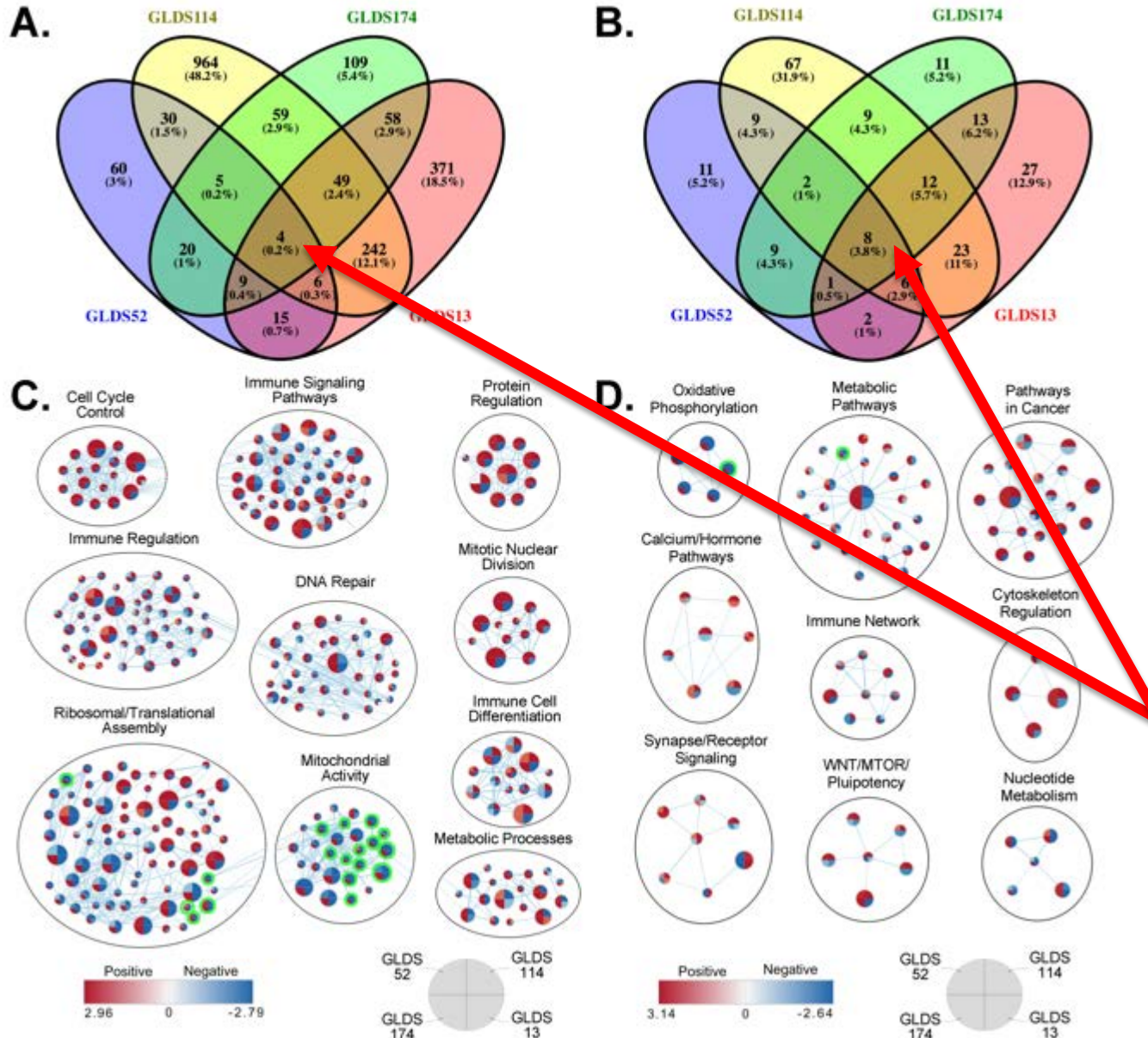


Deanne Taylor Hossein Fazelinia Komal Rathi

Chris Mason Cem Meydan Jonathan Foox

Sylvain Costes





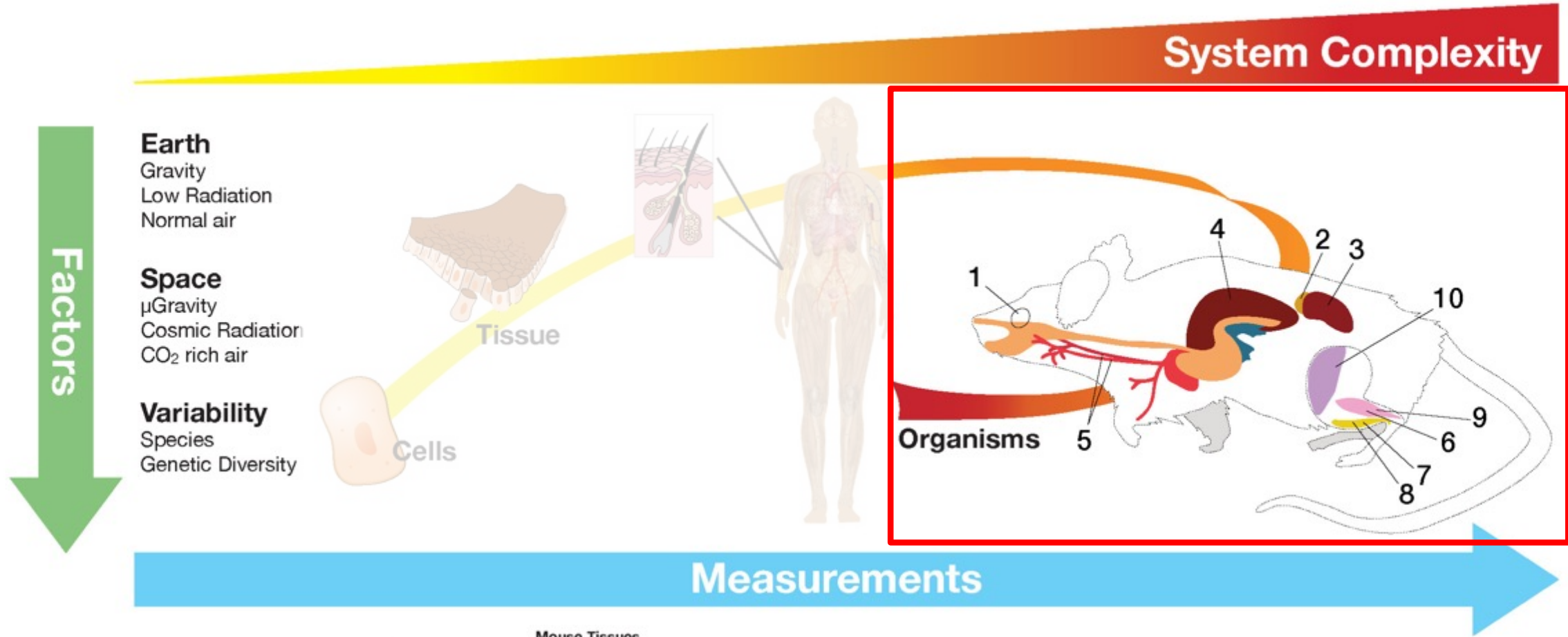
Gene Set Enrichment Analysis (GSEA) of human microarray datasets GLDS-13, GLDS-52, GLDS-114, and GLDS-174 comparing flight to ground treatments. (A,B) Venn diagrams of statistically significant GSEA (A) Gene Ontology (GO) and (B) Kyoto Encyclopedia of Genes and Genomes (KEGG) gene sets with FDR < 10%. (C,D) Cytoscape enrichment maps of (C) GO sets with FDR < 10% in at least two GLDS datasets and (D) KEGG gene sets with FDR < 10% in at least one GLDS dataset. **Green Highlights** indicate all pathways involved with

Common significant dysregulation of the gene ontology genes sets for:

- mitochondrial ATP synthesis
- mitochondrial electron transport
- oxidative phosphorylation
- hydrogen ion transmembrane transportation

Dermal Blood Microvascular Endothelial Cells • Fibroblasts



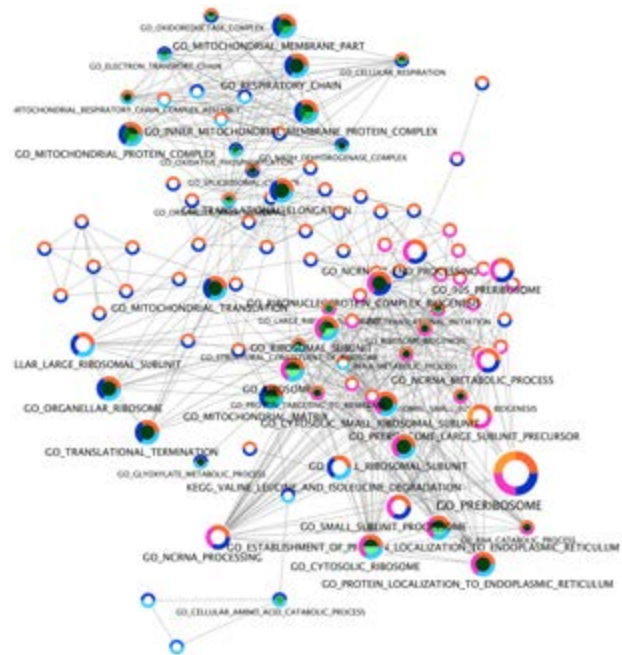


Mouse Tissues

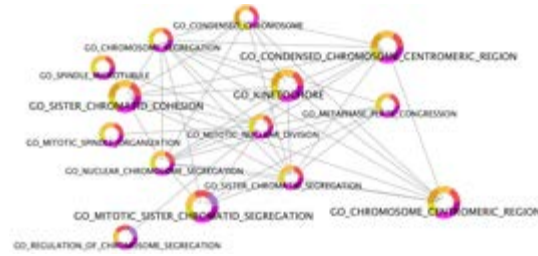
1. Eye: Transcriptomics (RR3 and RR1)
2. Adrenal Glands: Transcriptomics, Proteomics, and Epigenetics (RR1 and RR3)
3. Kidney: Transcriptomics, Proteomics, and Epigenetics (RR1 and RR3)
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5. Carotid Arteries: Transcriptomics (RR3)
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7. Extensor Digitorum Longus: Transcriptomics (RR1)
8. Tibialis Anterior: Transcriptomics (RR1)
9. Gastrocnemius: Transcriptomics (RR1) and Metabolomics (RR9)
10. Quadriceps: Transcriptomics (RR1) and Metabolomics (RR9)

RR1 mice: Female C57BL/6, 32 weeks old at launch
 RR3 mice: Female BALB/C, 18 weeks old at launch
 RR9 mice: Male C57BL/6, 9 weeks old at launch

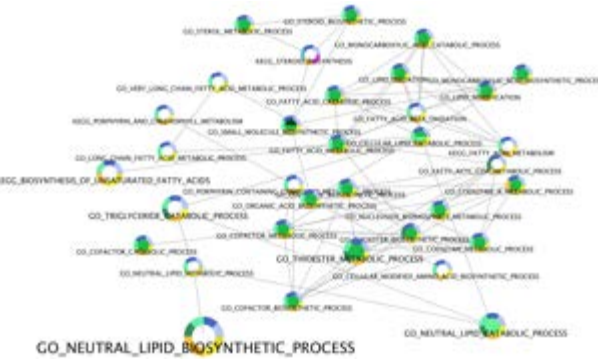
A) Mitochondrial Activity



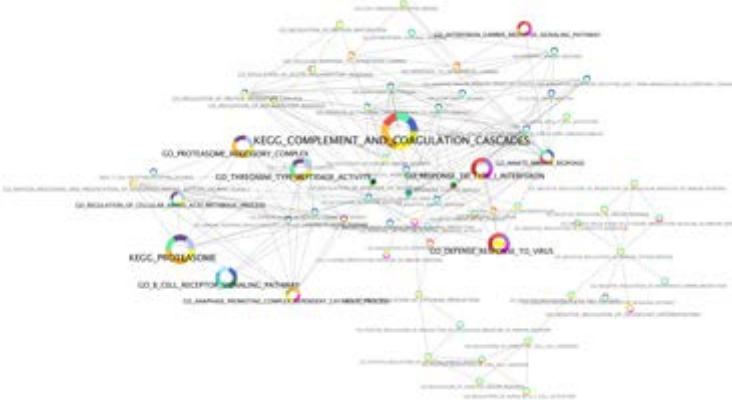
C) Cell Cycle



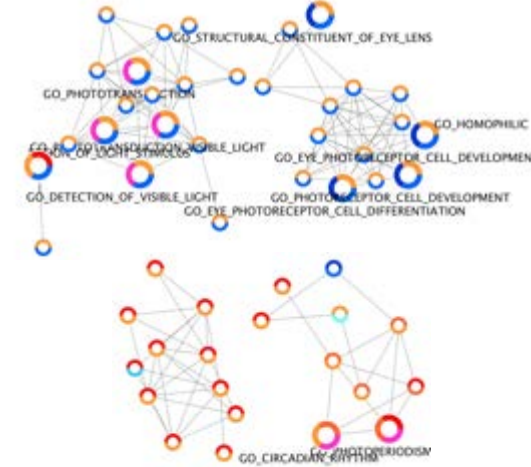
D) Lipid Metabolism



E) Immune Response



F) Photoreceptor Activity / Circadian Rhythm



B) Ribosome and Translation

Node size- RNAseq differential expression (RR1+RR3)

- Pathway enriched in all 8 DE tissues
- Pathway enriched in 7 DE tissues
- Pathway enriched in 7 DE tissues
- Pathway enriched in 5 DE tissues

Node outer colors- RNAseq differential expression (RR1+RR3)

- | | |
|-----------------------|---------------------|
| ● Down in liver RR1 | ● Up in liver RR1 |
| ● Down in liver RR3 | ● Up in liver RR3 |
| ● Down in kidney RR1 | ● Up in kidney RR1 |
| ● Down in kidney RR3 | ● Up in kidney RR3 |
| ● Down in eye RR1 | ● Up in eye RR1 |
| ● Down in eye RR3 | ● Up in eye RR3 |
| ● Down in adrenal RR1 | ● Up in adrenal RR1 |
| ● Down in adrenal RR3 | ● Up in adrenal RR3 |

Node inner colors- Differential proteomics (RR3)

- Enriched in liver proteomics
- Enriched in kidney proteomics
- Enriched in eye proteomics
- Enriched in adrenal proteomics



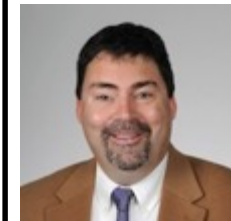
Kathleen Fisch



Brin Rosenthal



UNIVERSITY of CALIFORNIA, SAN DIEGO
SCHOOL OF MEDICINE



Gary Hardiman



Willian da Silveira



Node size- RNAseq differential expression (RR3)

- Pathway enriched in all 4 DE tissues
- Pathway enriched in 3 DE tissues
- Pathway enriched in 2 DE tissues

Node inner colors- Differential proteomics (RR3)

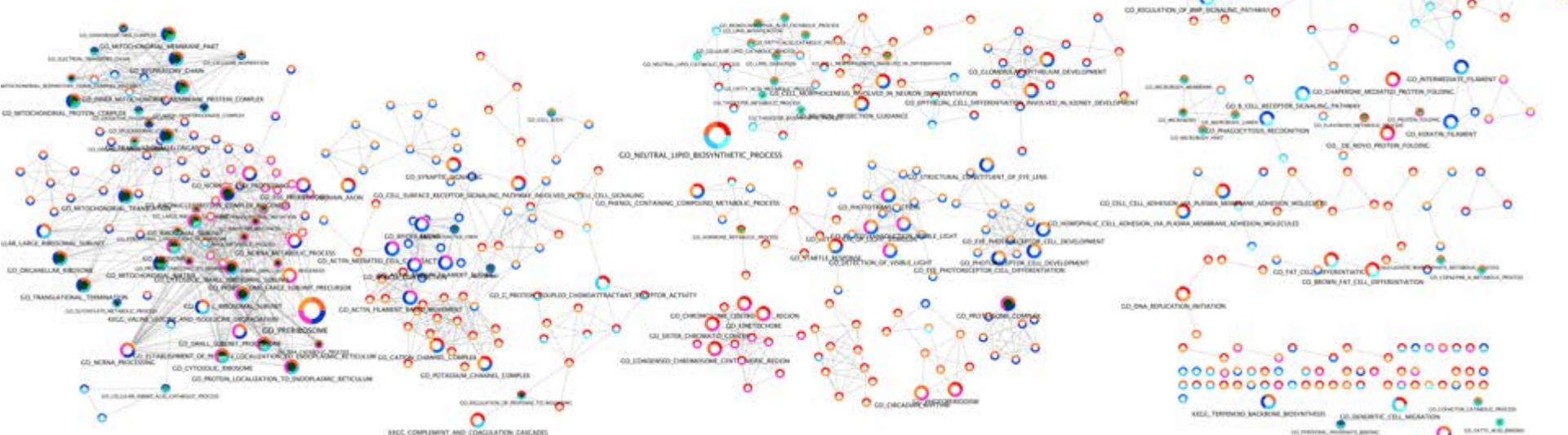
- Enriched in liver proteomics
- Enriched in kidney proteomics
- Enriched in eye proteomics
- Enriched in adrenal proteomics

Node outer colors- RNAseq differential expression (RR3)

- | | |
|--|--|
| Down in liver | Up in liver |
| Down in kidney | Up in kidney |
| Down in eye | Up in eye |
| Down in adrenal | Up in adrenal |



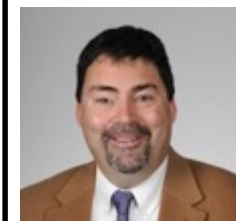
Supplementary Figure in Paper showing the entire pathway multi-omic pathway analysis



Kathleen Fisch



Brin Rosenthal



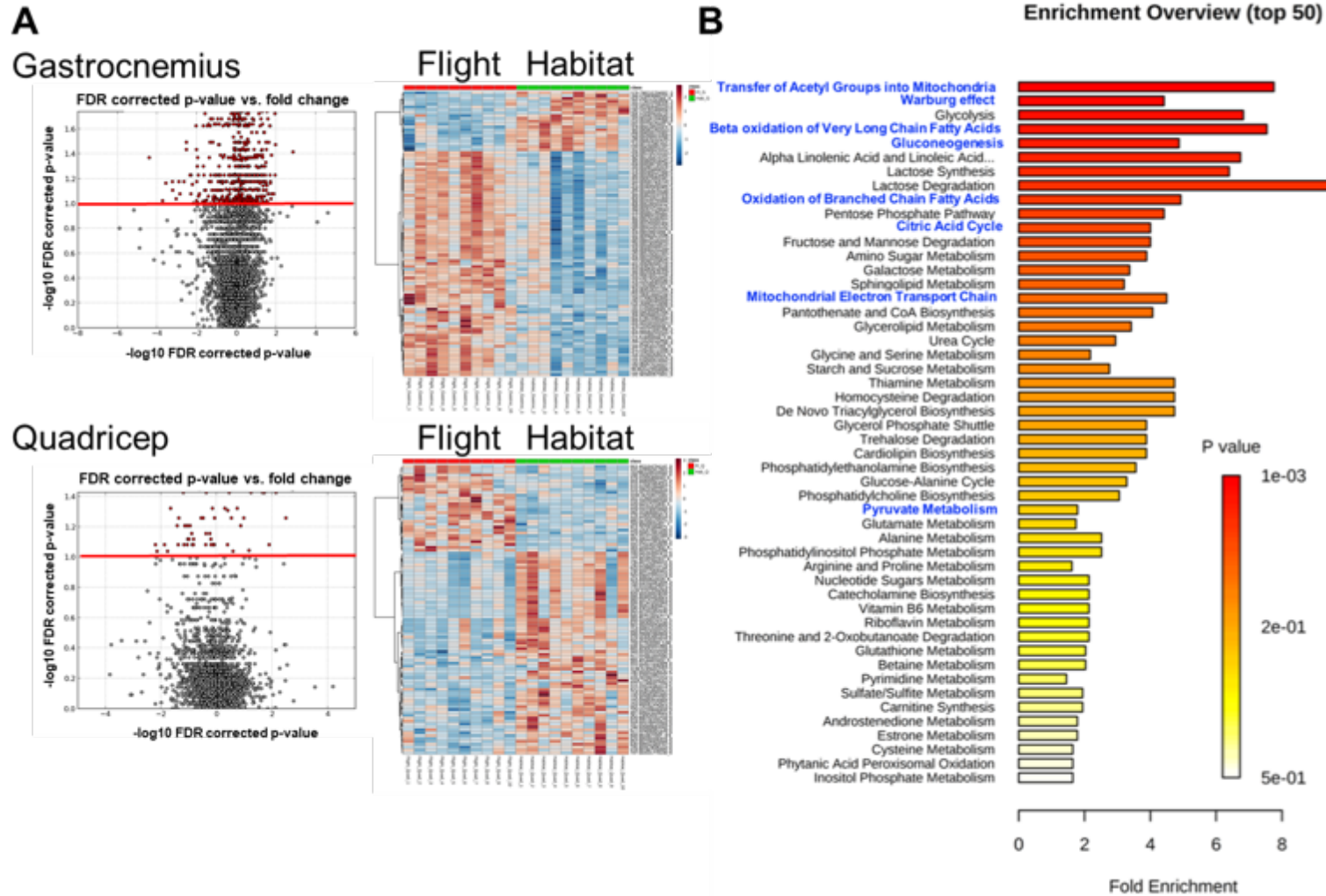
Gary Hardiman



Willian da Silveira



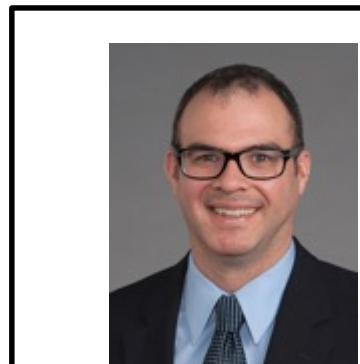
Metabolomics on muscles reveal mitochondrial factors as top biological factors being regulated by spaceflight



- RR1 mice: Female C57BL/6, 32 weeks old at launch
- RR3 mice: Female BALB/C, 18 weeks old at launch
- **RR9 mice: Male C57BL/6, 9 weeks old at launch**



Evagelia C. Laiakis



Jeffrey Scott Willey



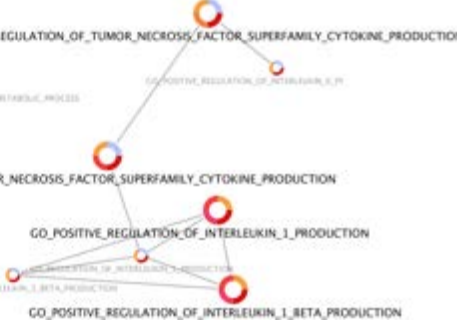
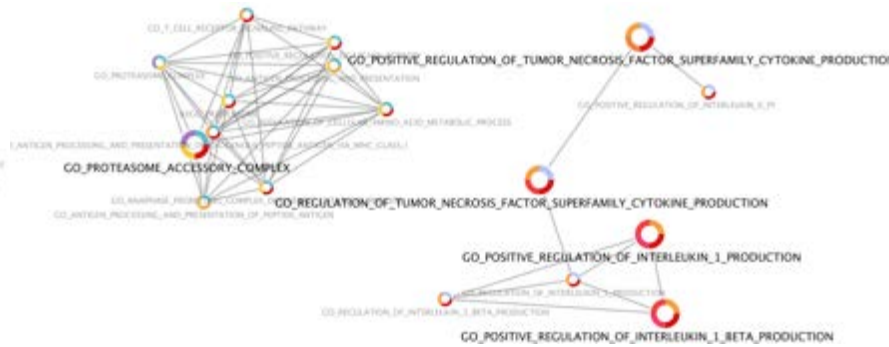
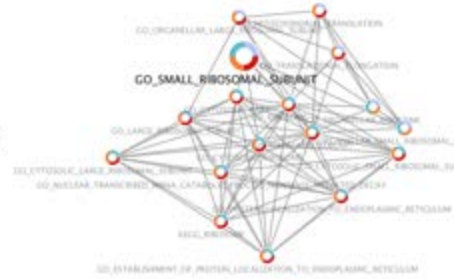
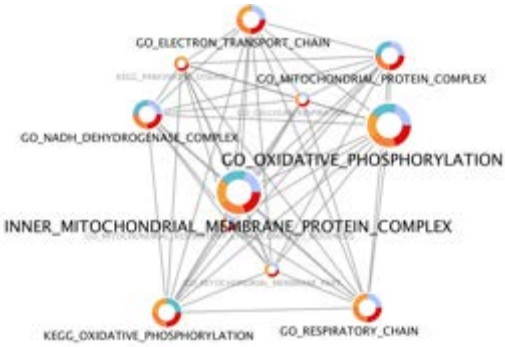
Panel A - Volcano plots and heatmaps from analysis of habitat ground control versus flight samples. Panel B – Enrichment pathway analysis based on the subset of putative metabolites from Supplementary Table 2. Blue letters highlight pathways with mitochondrial involvement.

C) Mitochondrial Activity

D) Ribosome and Translation

E) Proteasome

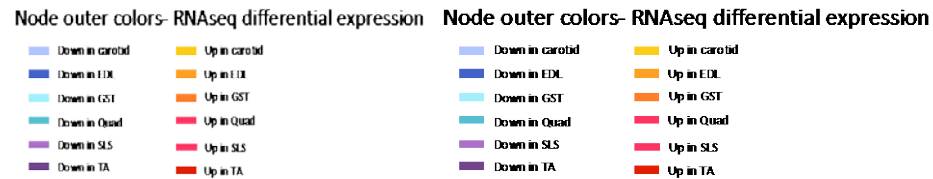
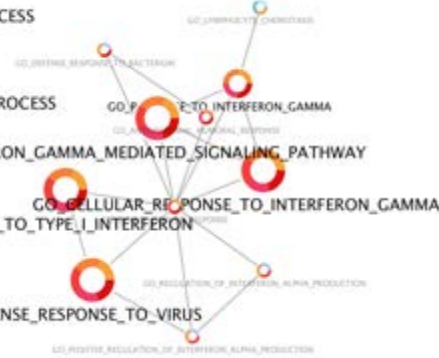
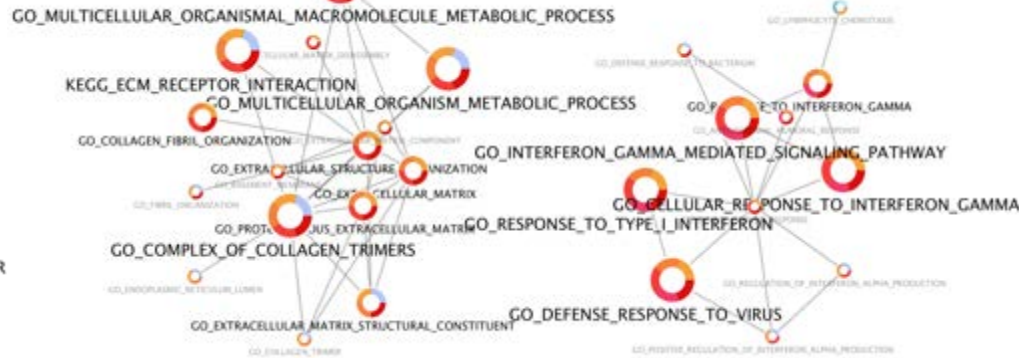
F) TNF/IL1 Response



G) Sympathetic and Feeding Behavior

H) Metabolism and ECM

I) Interferon Response



Kathleen Fisch



Brin Rosenthal



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SCHOOL OF MEDICINE

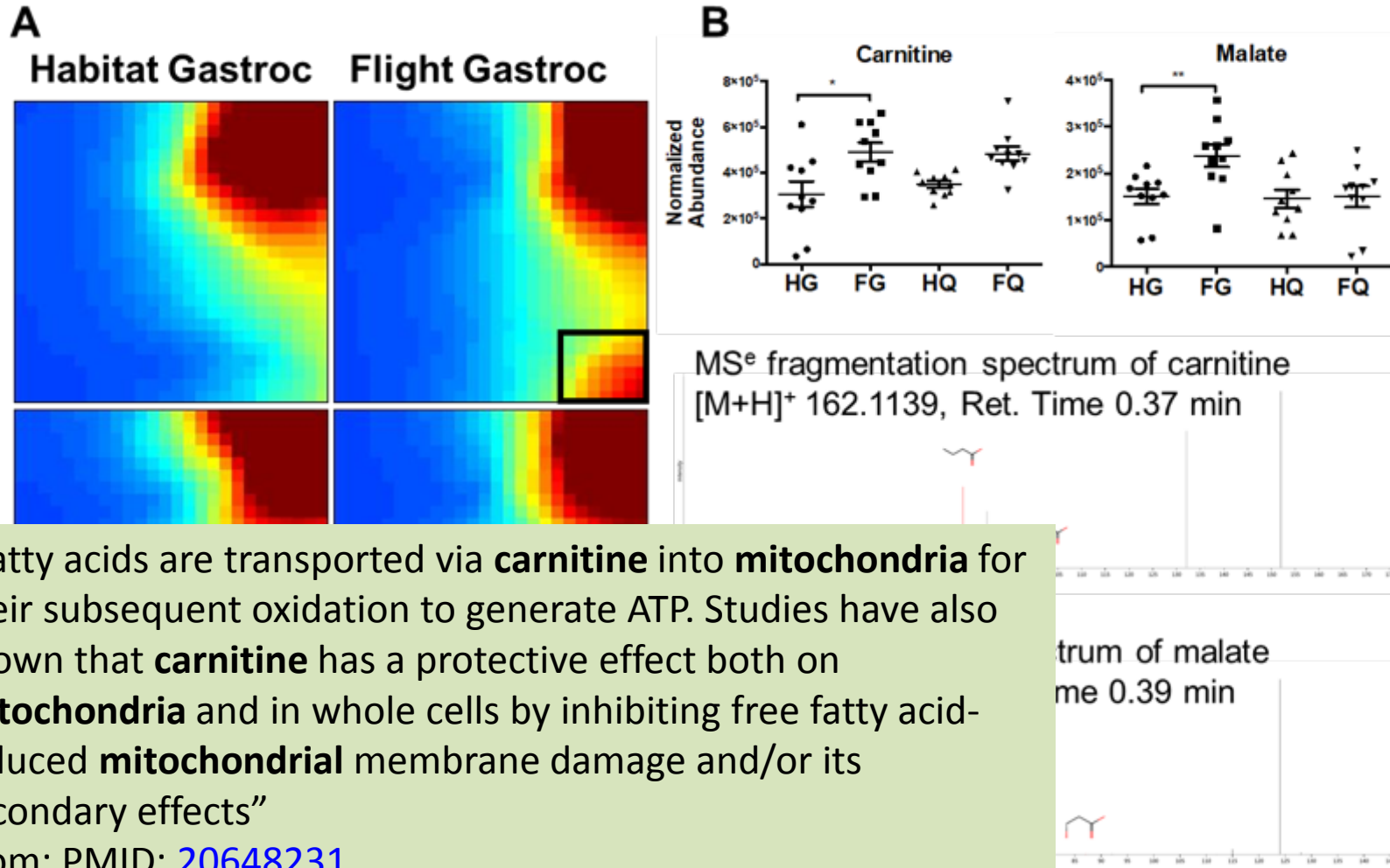


Gary Hardiman



Willian da Silveira





“Fatty acids are transported via **carnitine** into **mitochondria** for their subsequent oxidation to generate ATP. Studies have also shown that **carnitine** has a protective effect both on **mitochondria** and in whole cells by inhibiting free fatty acid-induced **mitochondrial** membrane damage and/or its secondary effects”

From: PMID: [20648231](https://pubmed.ncbi.nlm.nih.gov/20648231/)

Supplementary Figure 2: Panel A – GEDI self organizing maps showing global metabolomic shifts due to the effects of spaceflight. Panel B - Carnitine and malate levels with their theoretical fragmentation spectra from Progenesis Q1. Levels are depicted as mean ± standard error of the mean. * p<0.05, ** p<0.01.



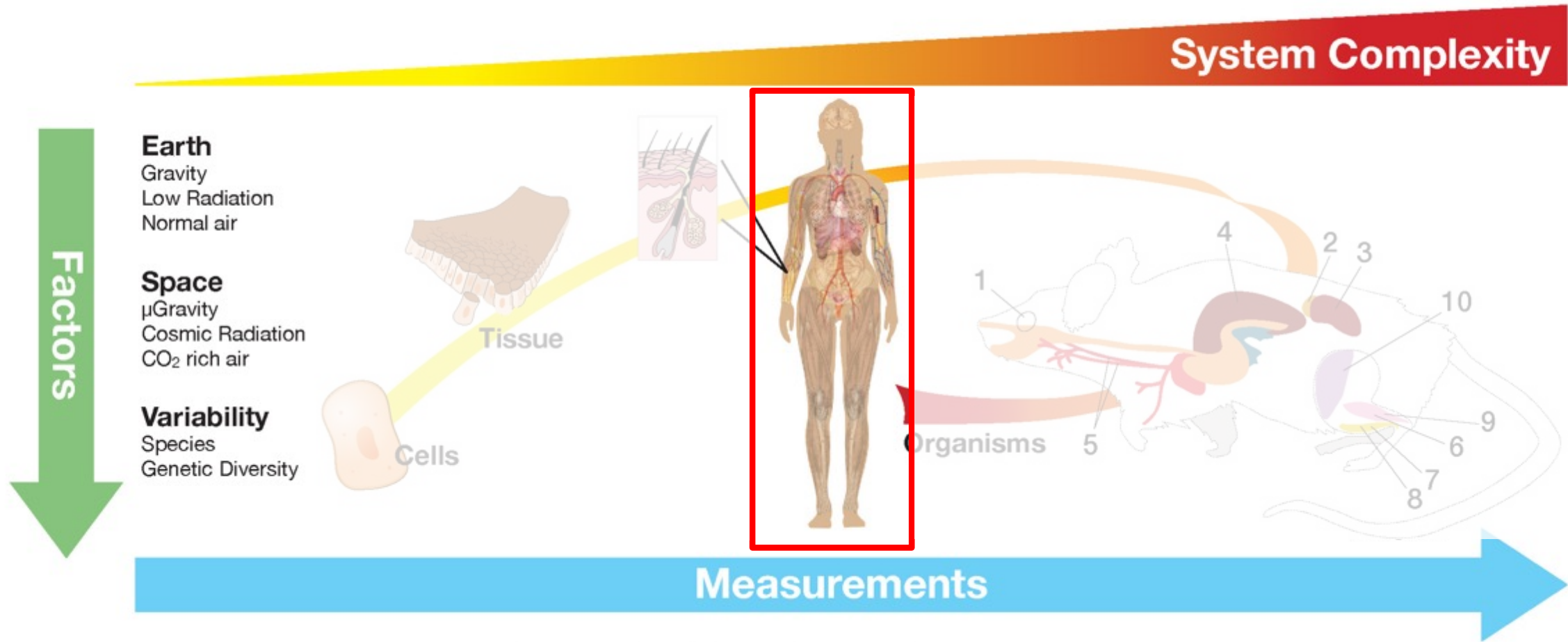
Evagelia C. Laiakis



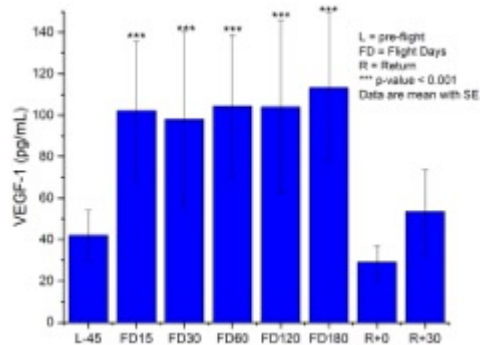
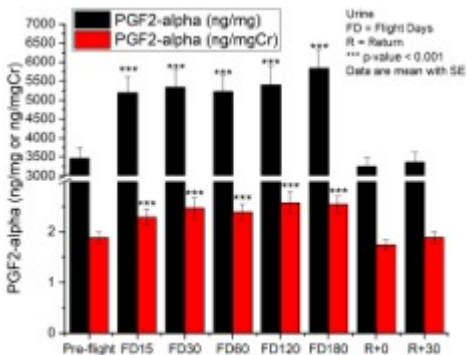
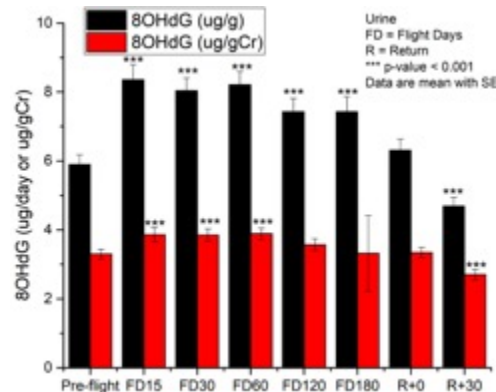
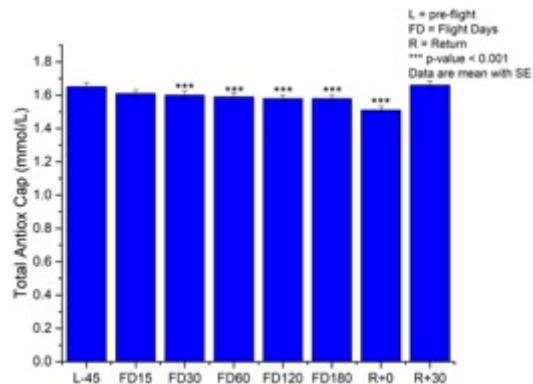
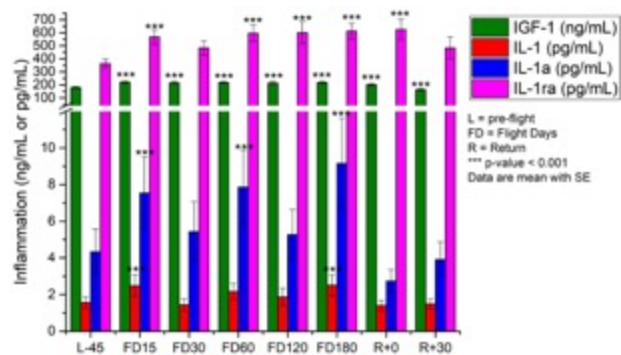
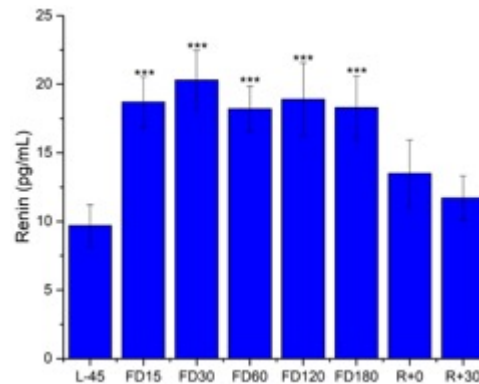
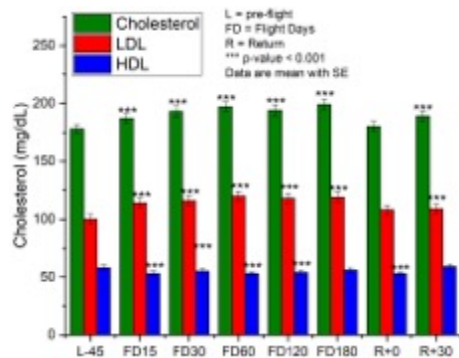
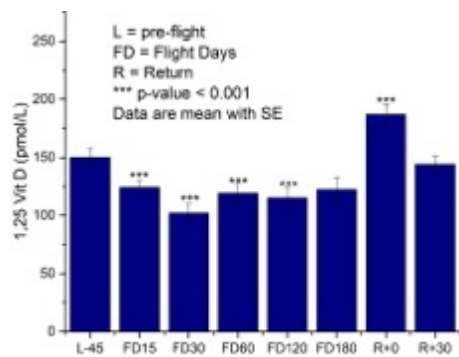
Jeffrey Scott Willey



Astronaut Physiological Factors Confirm Omics *in vitro* and *in vivo* analysis!



Can cause bone loss





Scott Smith



Sara Zwart



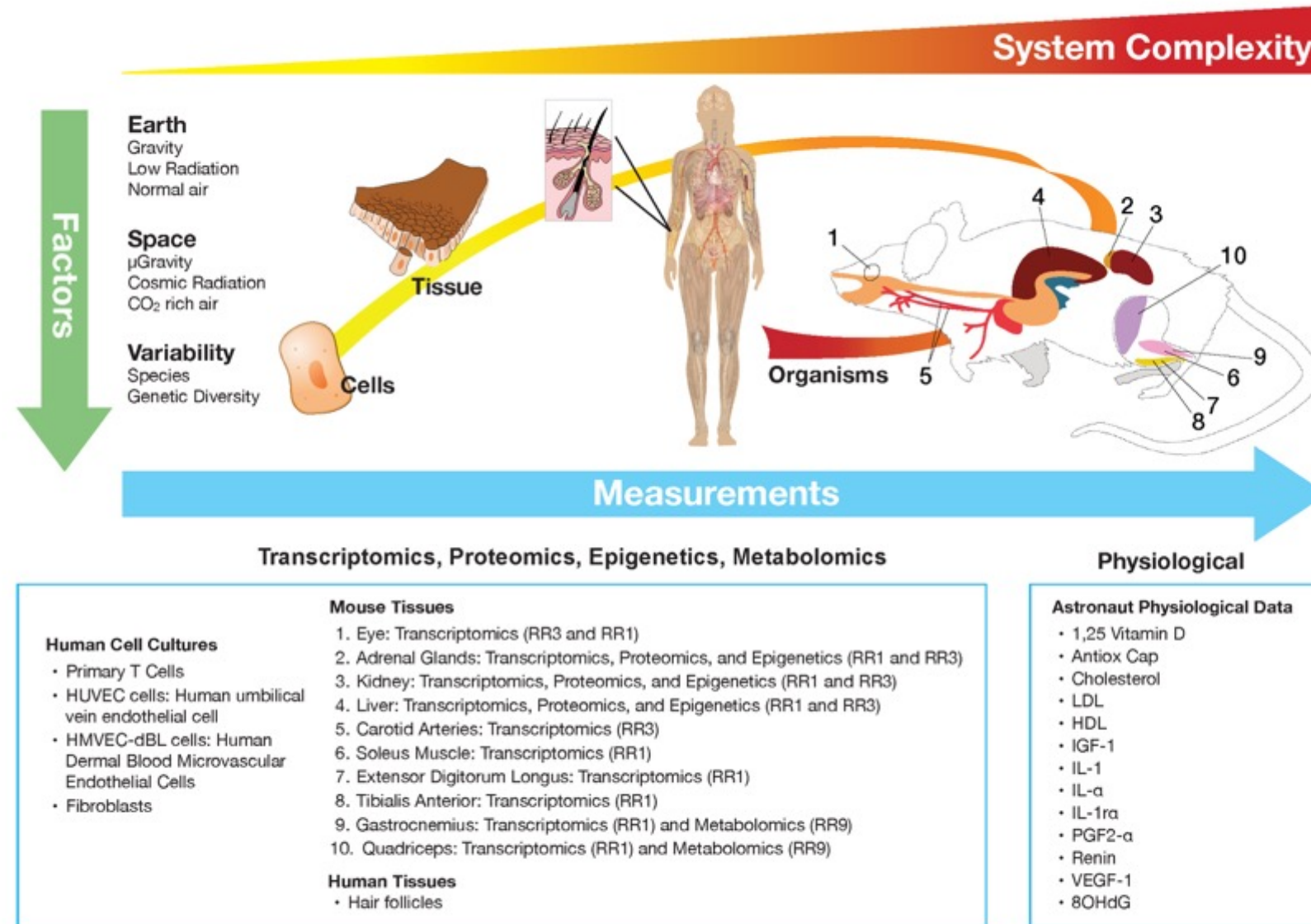

Manned Space Flight Education Foundation



Afshin Beheshti




Mitochondrial Driven Factors Might be Key to Systemic Spaceflight Associated Increase in Health Risk



- **GeneLab was instrumental to determine this universal response!**
- **No other possible way to piece the puzzle together without the power of GeneLab**
- **The large collaborative nature of the AWG was essential to drive this work!!**



Many Space Biology Questions and Challenges Still Need to Addressed!



HUMAN EXPLORATION *NASA's Path to Mars*

EARTH RELIANT
MISSION: 6 TO 12 MONTHS
RETURN TO EARTH: HOURS

PROVING GROUND
MISSION: 1 TO 12 MONTHS
RETURN TO EARTH: DAYS

MARS READY
MISSION: 2 TO 3 YEARS
RETURN TO EARTH: MONTHS



Mastering fundamentals aboard the International Space Station

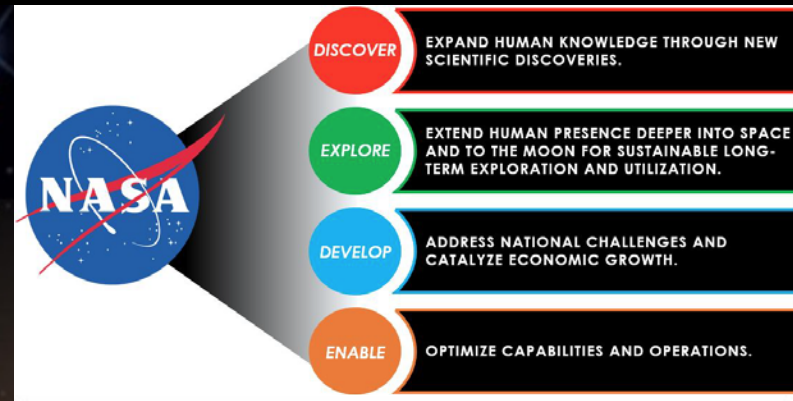
U.S. companies provide access to low-Earth orbit



Expanding capabilities by visiting an asteroid redirected to a lunar distant retrograde orbit

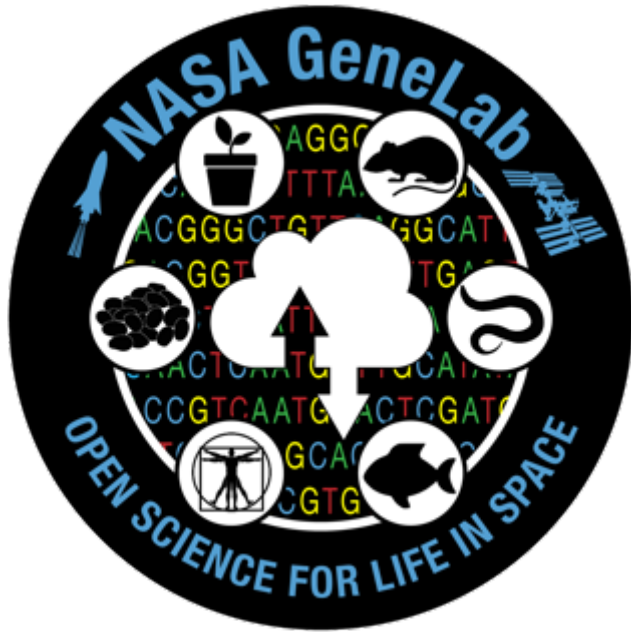
The next step: traveling beyond low-Earth orbit with the Space Launch System rocket and Orion spacecraft

Developing planetary independence by exploring Mars, its moons and other deep space destinations



NASA 2018 Strategic Plan Framework		
Theme	Strategic Goal	Strategic Objective
DISCOVER	EXPAND HUMAN KNOWLEDGE THROUGH NEW SCIENTIFIC DISCOVERIES.	1.1: Understand the Sun, Earth, Solar System, and Universe. 1.2: Understand Responses of Physical and Biological Systems to Spaceflight.
EXPLORE	EXTEND HUMAN PRESENCE DEEPER INTO SPACE AND TO THE MOON FOR SUSTAINABLE LONG-TERM EXPLORATION AND UTILIZATION.	2.1: Lay the Foundation for America to Maintain a Constant Human Presence in Low Earth Orbit Enabled by a Commercial Market. 2.2: Conduct Exploration in Deep Space, including to the Surface of the Moon.
DEVELOP	ADDRESS NATIONAL CHALLENGES AND CATALYZE ECONOMIC GROWTH.	3.1: Develop and Transfer Revolutionary Technologies to Enable Exploration Capabilities for NASA and the Nation. 3.2: Transform Aviation Through Revolutionary Technology Research, Development, and Transfer. 3.3: Inspire and Engage the Public in Aeronautics, Space, and Science.
ENABLE	OPTIMIZE CAPABILITIES AND OPERATIONS.	4.1: Engage in Partnership Strategies. 4.2: Enable Space Access and Services. 4.3: Assure Safety and Mission Success. 4.4: Manage Human Capital. 4.5: Ensure Enterprise Protection. 4.6: Sustain Infrastructure Capabilities and Operations.





<https://genelab.nasa.gov/>

