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

National Aeronautics and Space Administration

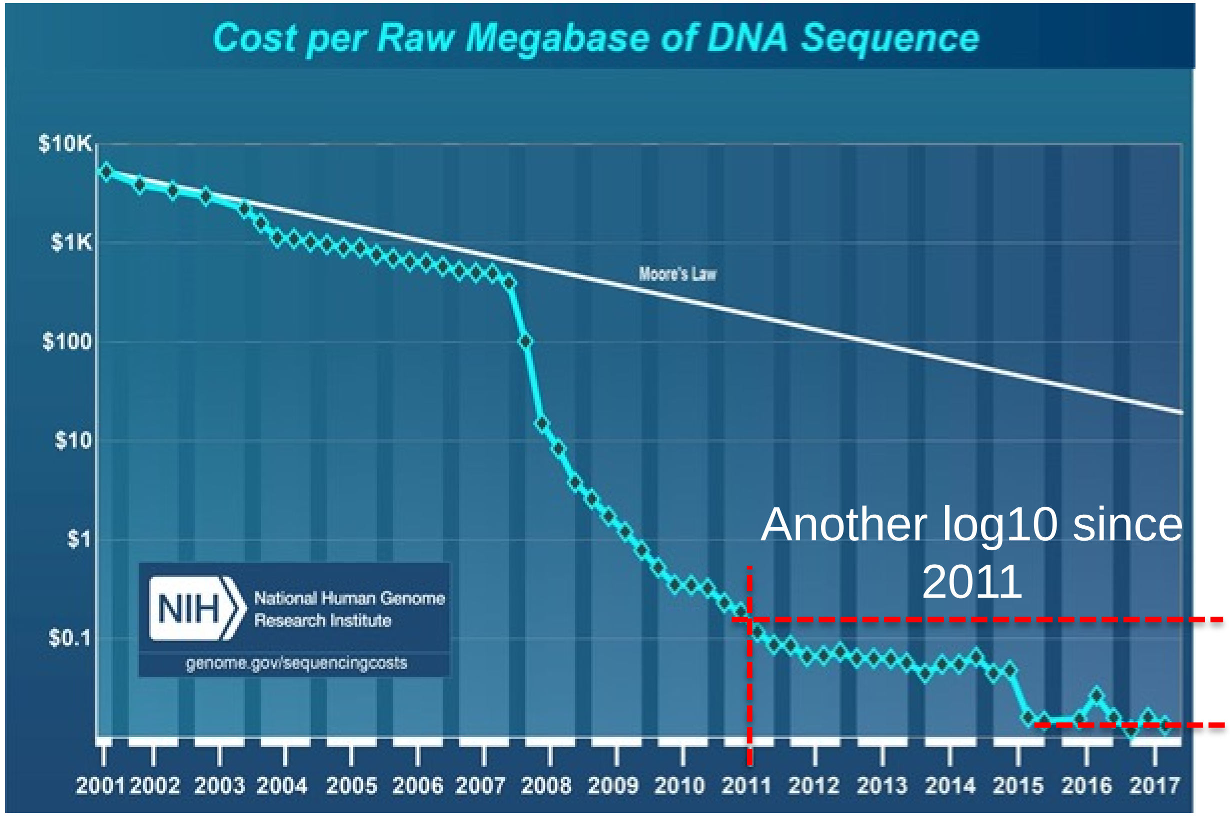
Afshin Beheshti, PhD
Bioinformatician at GeneLab
Principal Investigator
Space Biosciences Division, KBRWyle
NASA Ames Research Center, Moffett Field, CA

Adjunct Assistant Professor at Department of Medicine
Rutgers Robert Wood Johnson Medical School

Visiting Researcher at Broad Institute
Cambridge, MA

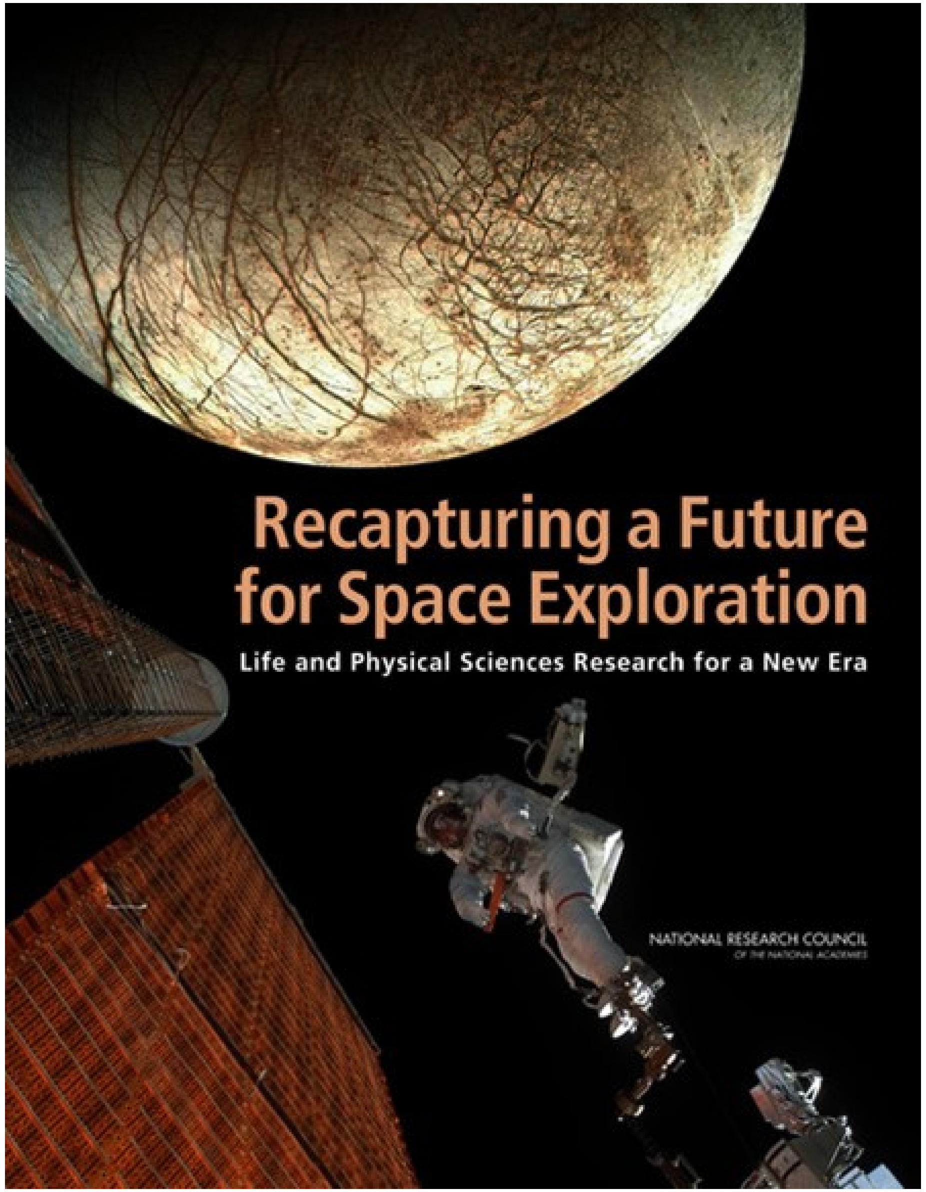
afshin.beheshti@nasa.gov
abehesht@broadinstitute.org

2011 NRC Decadal Survey and the Sequencing Paradigm Shift



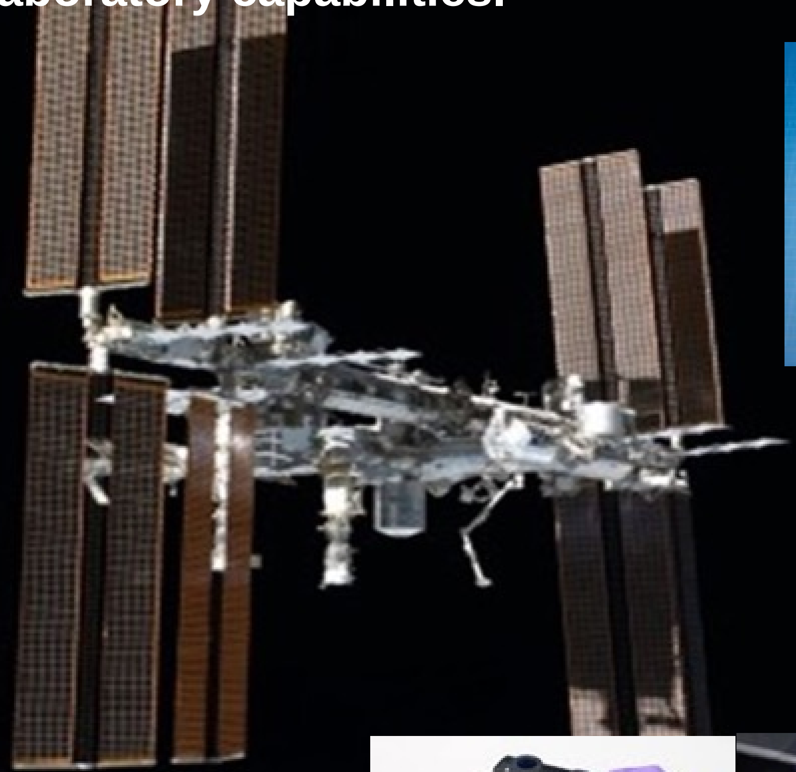
*"…**genomics, transcriptomics, proteomics, and metabolomics** offer an immense opportunity to understand the effects of spaceflight on biological systems…"*

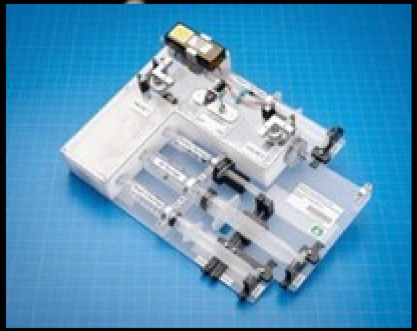
*"…Such techniques generate considerable amounts of **data that can be mined and analyzed** for information by multiple researchers…"*



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.



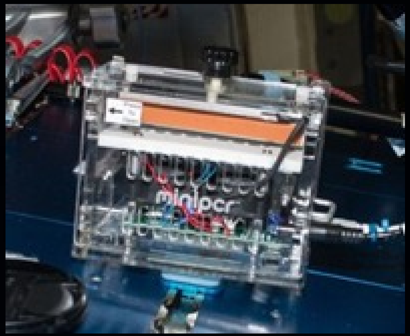


Sample Preparation Module

Oxford Nanopore MinION Gene Sequencer

Cepheid Smart Cycler qRT-PCR

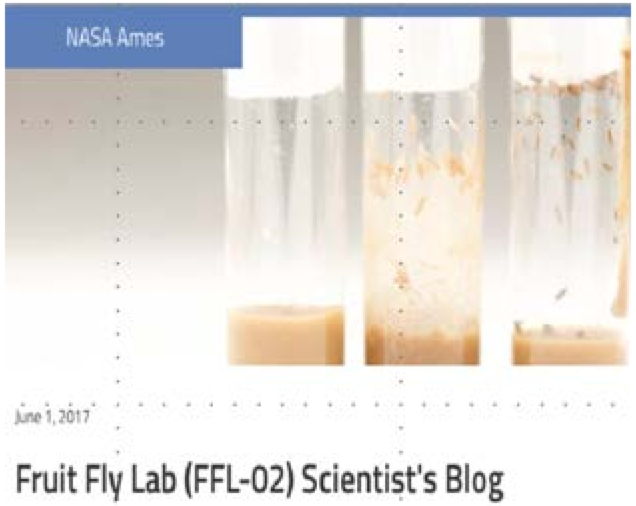
Reaction tube containing lyophilized chemical assay bead (proprietary)

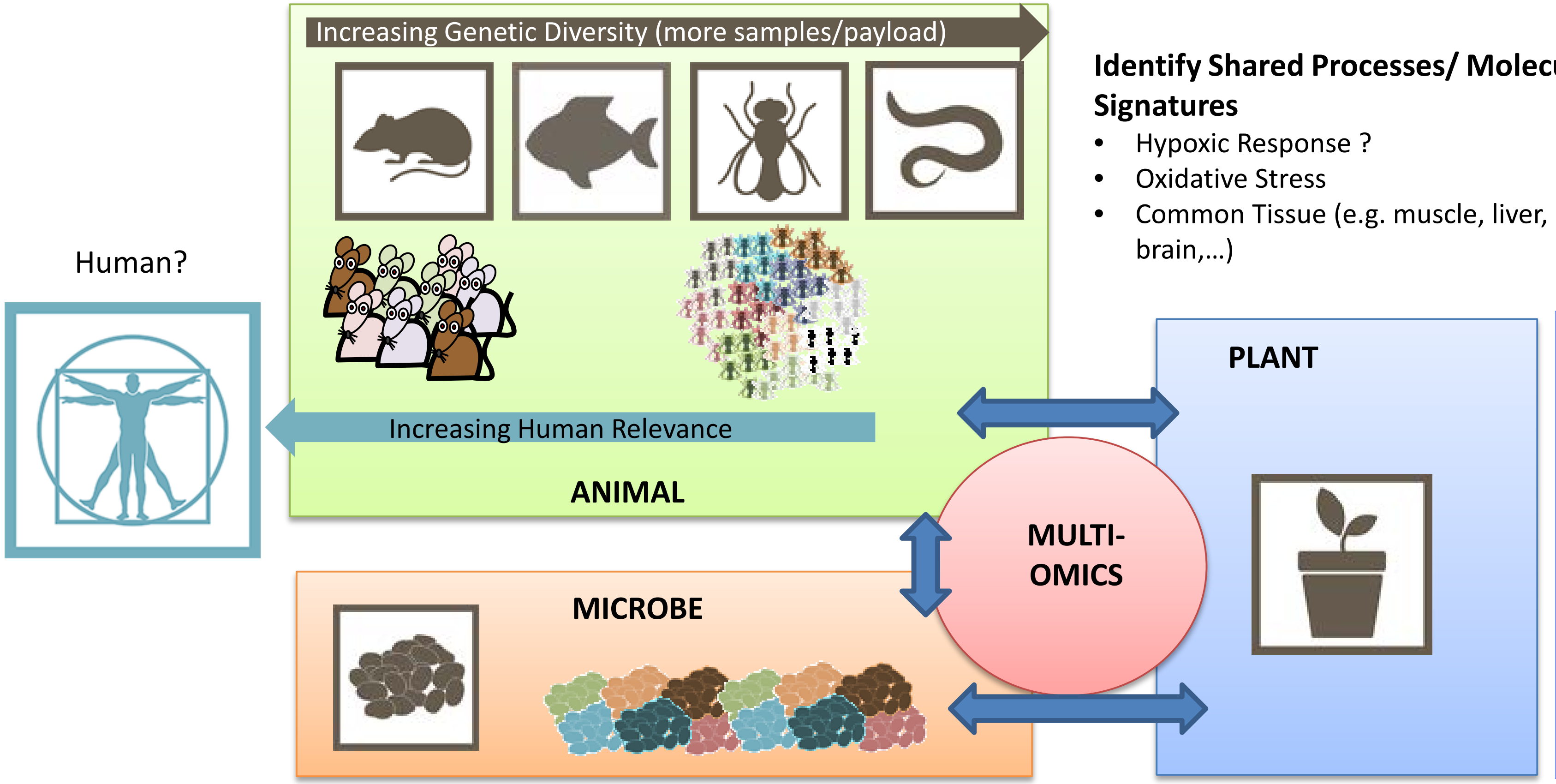


Mini-PCR

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





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

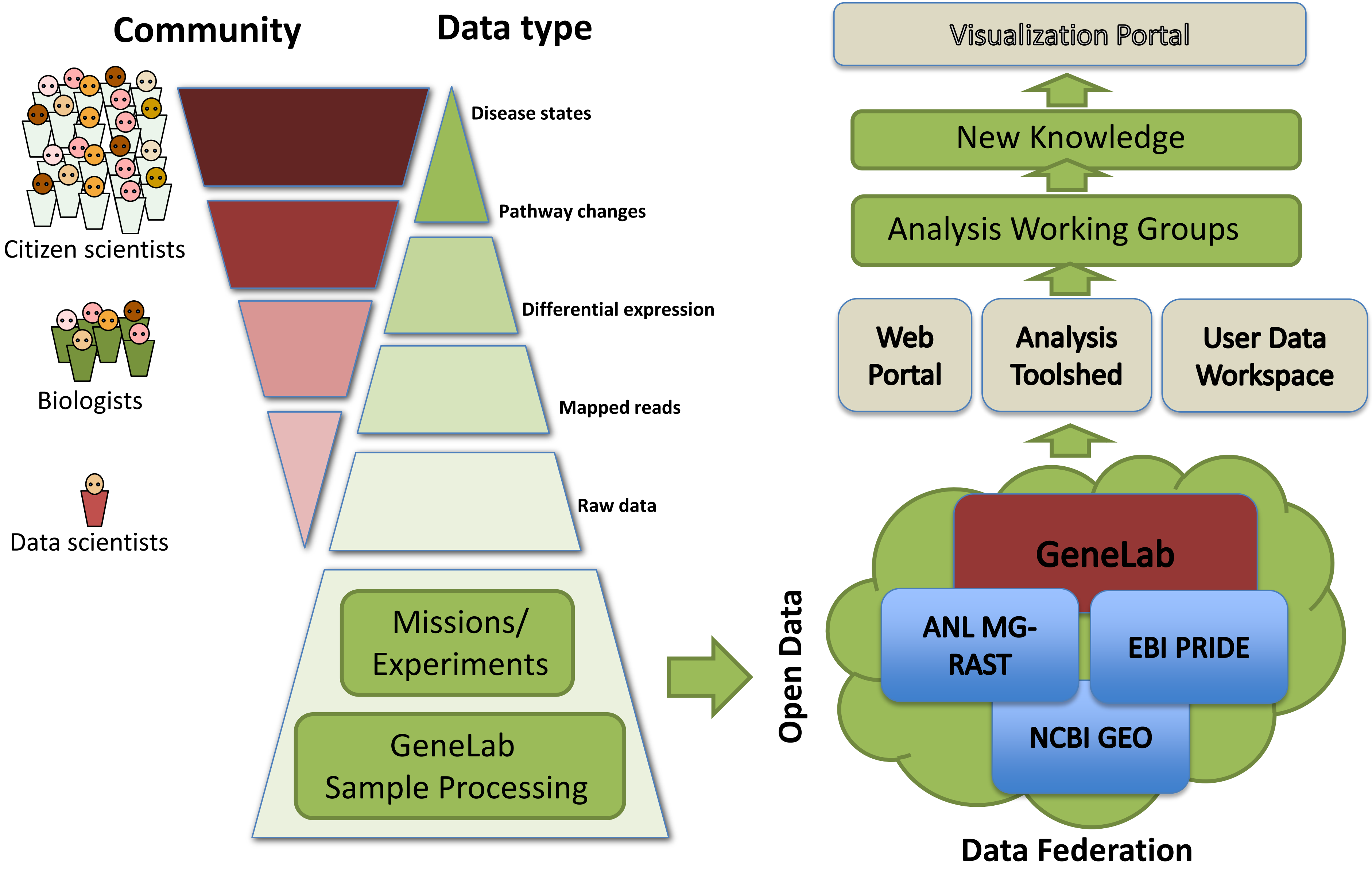
•Low resource requirements

•Short life cycle - multiple generations

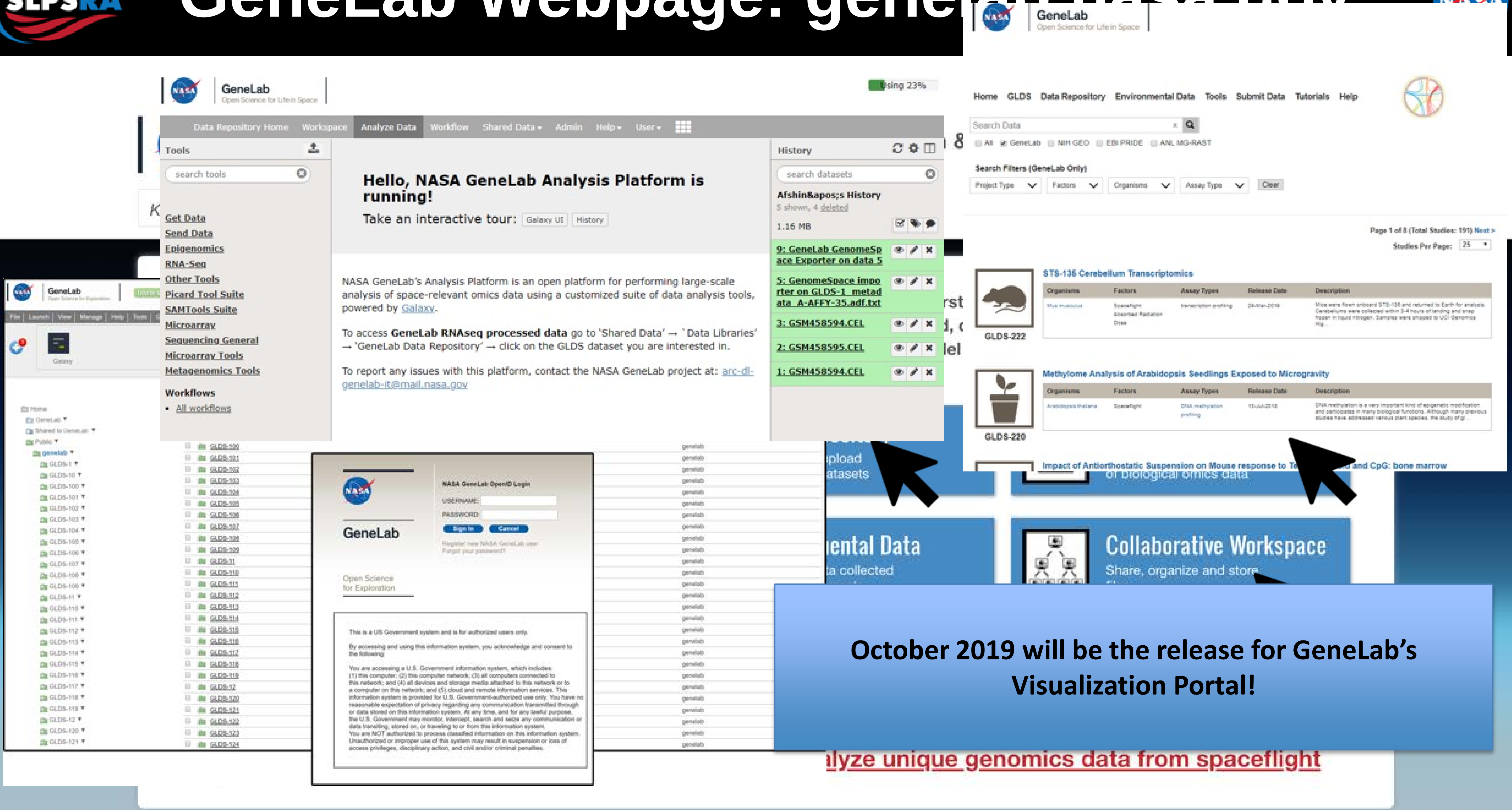
•Measure response of a whole multicellular animal

•Flies used as a model for humans for innate immunity, circadian rhythm, oxidative stress, neurobehavior, development, genetics, GWAS, "omics" studies etc.

GeneLab Data Democratization

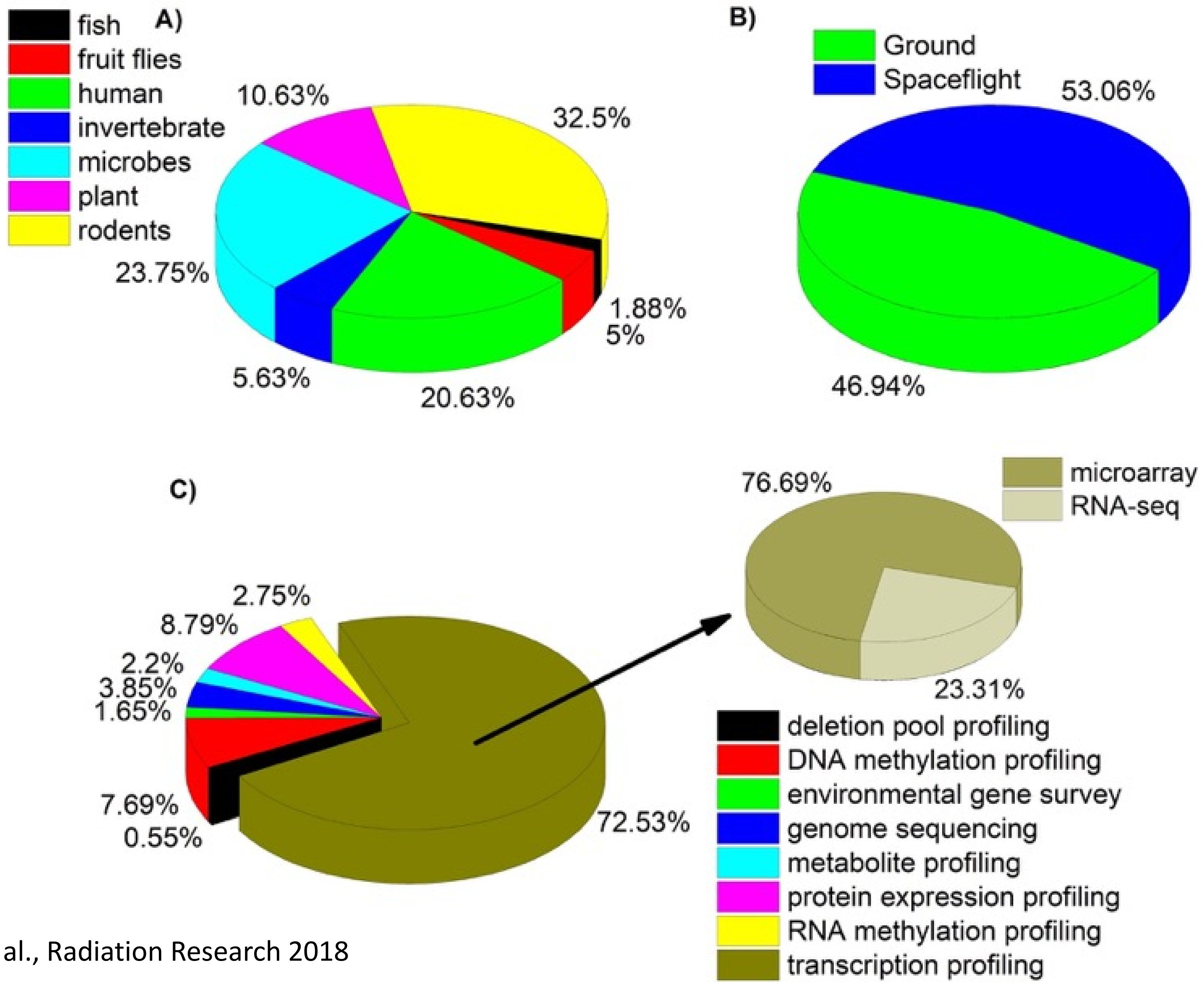


GeneLab Webpage: genelab.nasa.gov



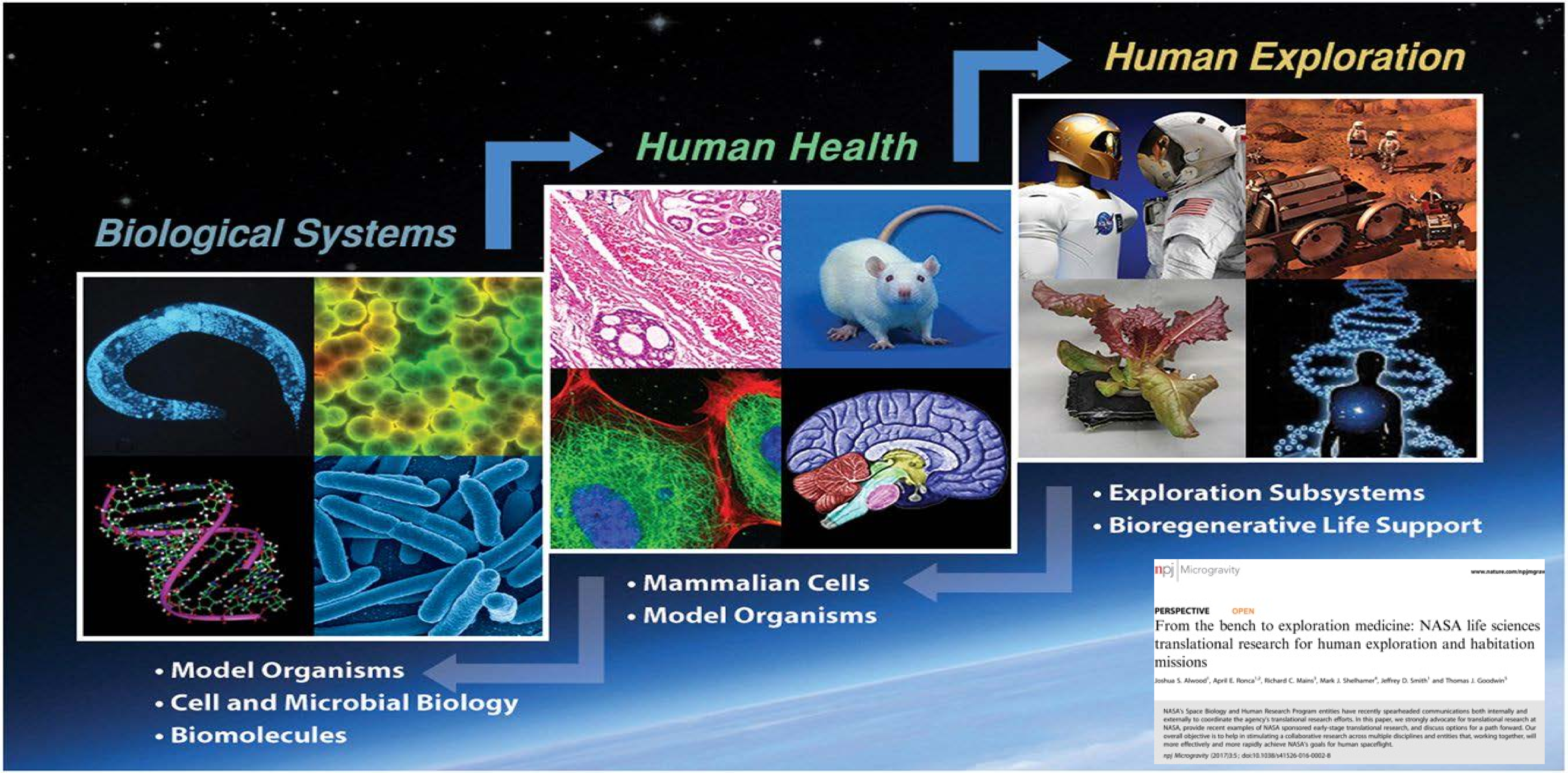
October 2019 will be the release for GeneLab's Visualization Portal!

GeneLab Database: >200 data sets

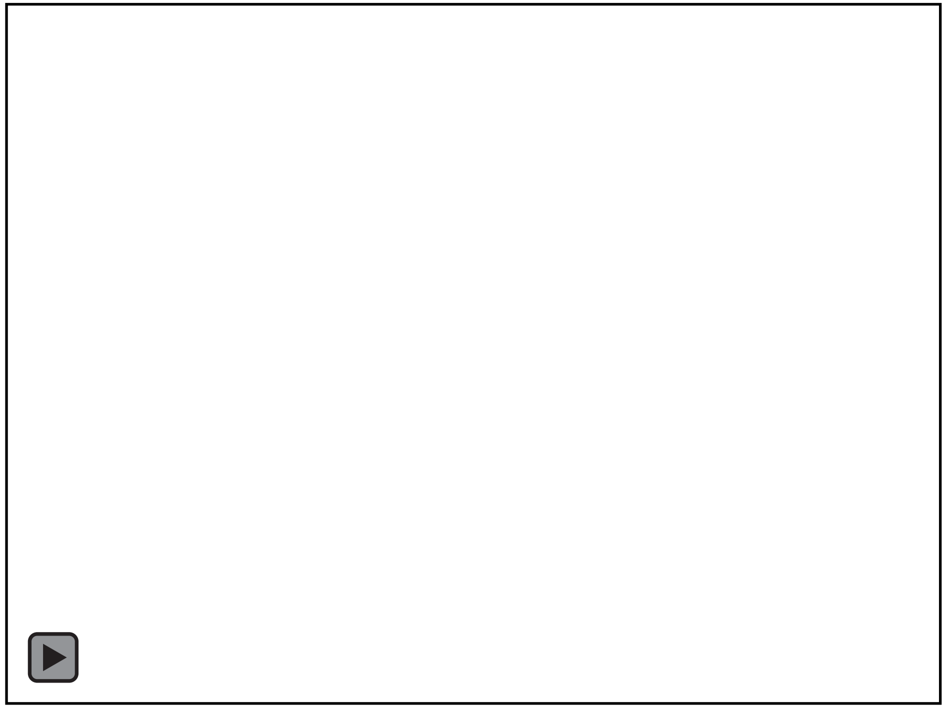


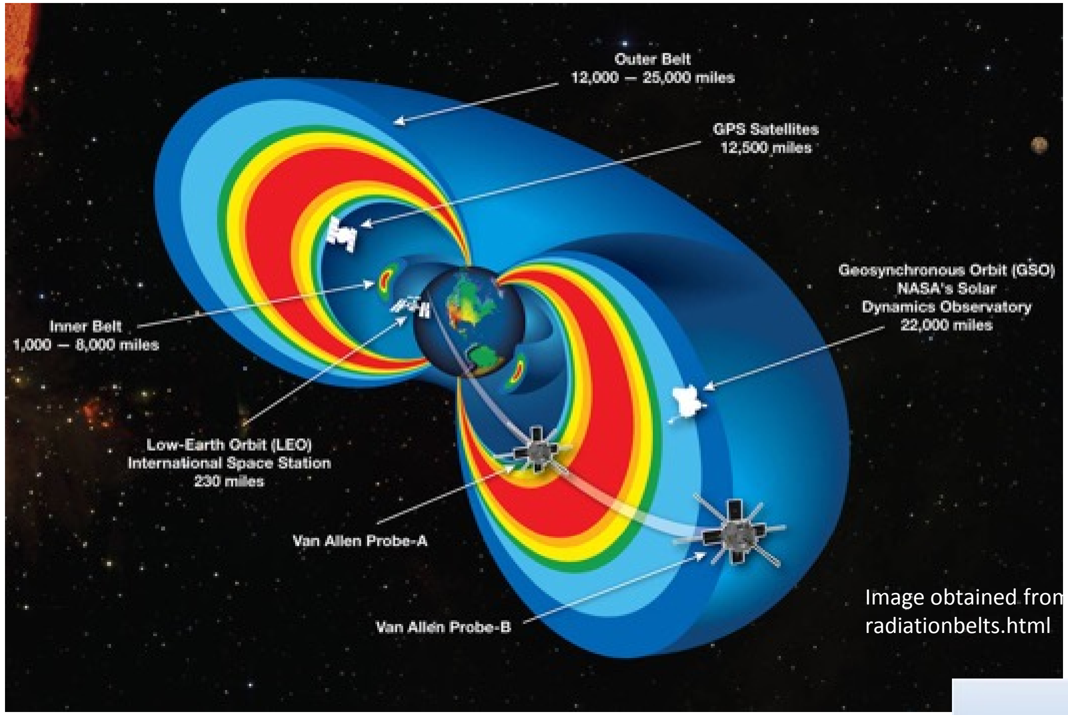
Beheshti et al., Radiation Research 2018

Space Biology Interest for NASA



Space Environment





2½ Years, 2,600 X-Rays

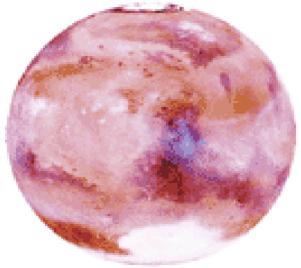
Americans on average absorb the radiation equivalent of at least 7 chest X-rays each year.

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

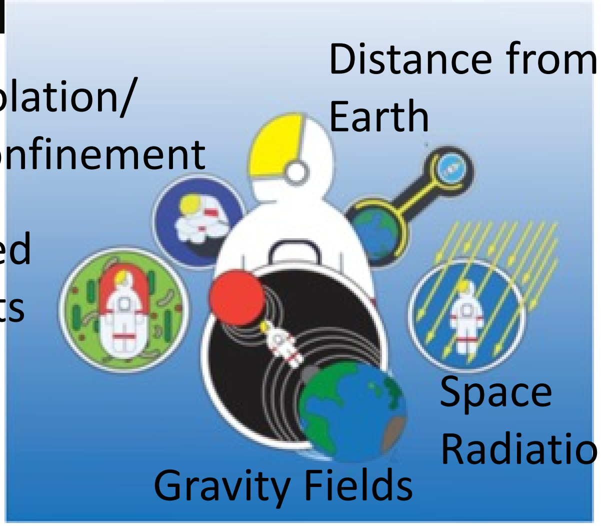
	MILLIREM:
CHEST X-RAY	8 to 50
AVG. YEARLY RADON DOSE	200
U.S. AVG. YEARLY DOSE	350
PET SCAN	1,000
1 YEAR IN KERALA, INDIA	1,300
U.S. NUCLEAR WORKER LIMIT PER YEAR	5,000
APOLLO 14 (9 DAYS)	1,140
SHUTTLE 41-C (18 DAYS)	5,600
SKYLAB 4 (84 DAYS)	17,800
MARS MISSION TOTAL	130,000

TRIP TO AND FROM MARS (1 YEAR): 80,000 — ON MARS (1.5 YEARS): 30,000 — FROM SOLAR FLARE: 20,000

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

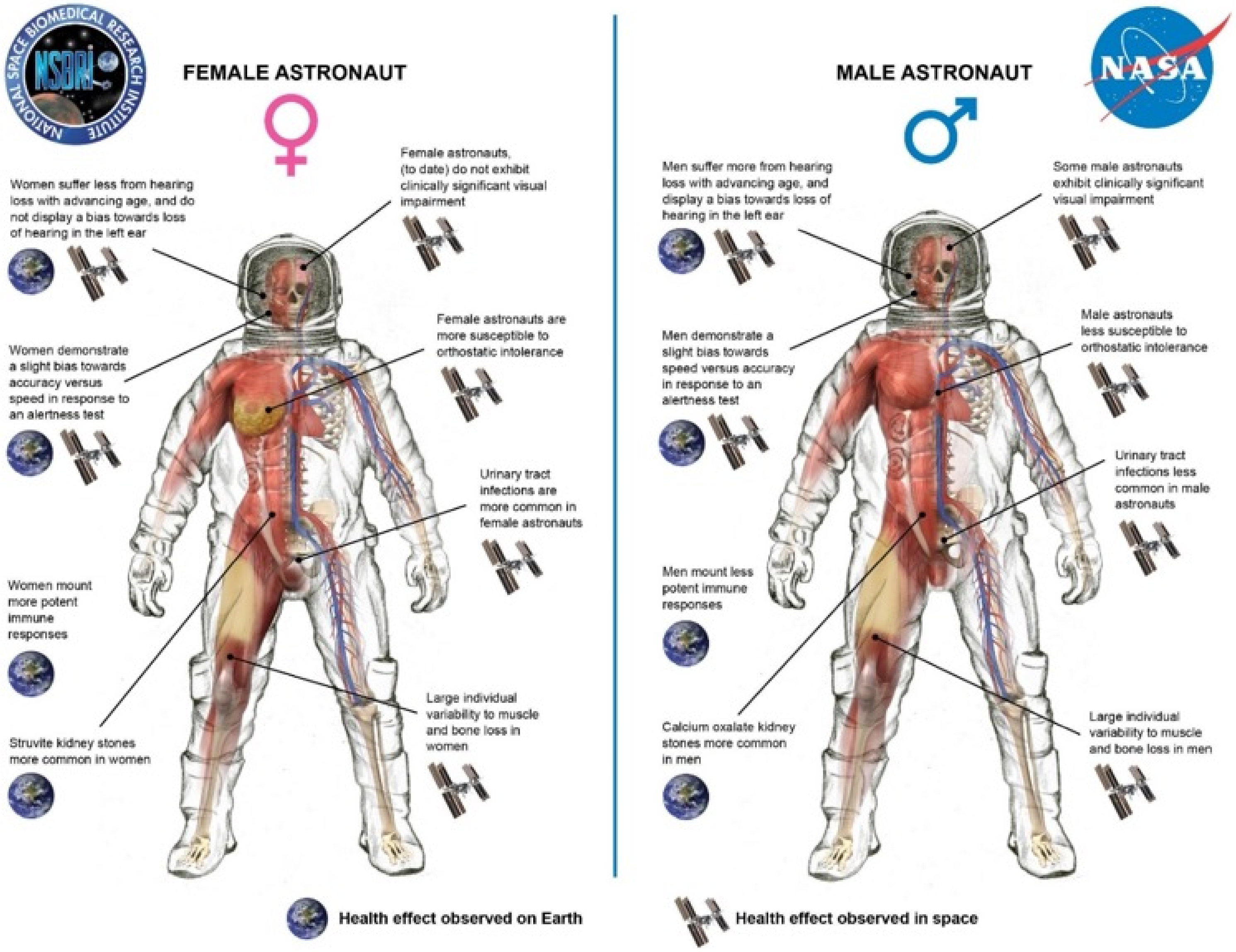


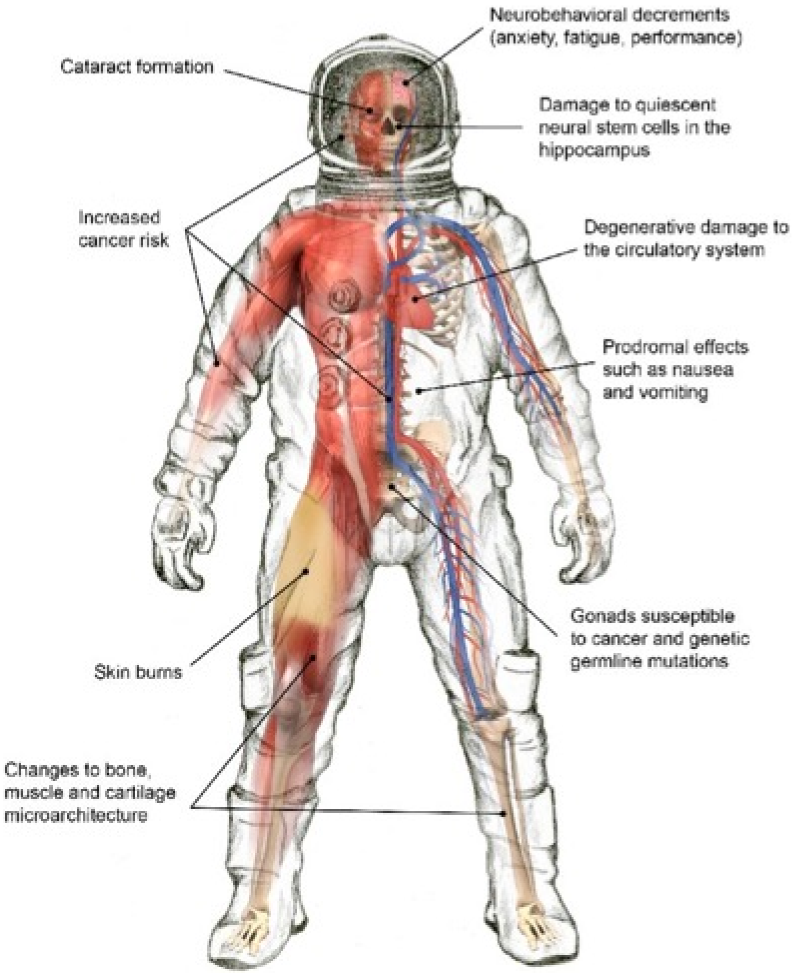
NASA



Credits: NASA

Space Health Risks On Astronauts



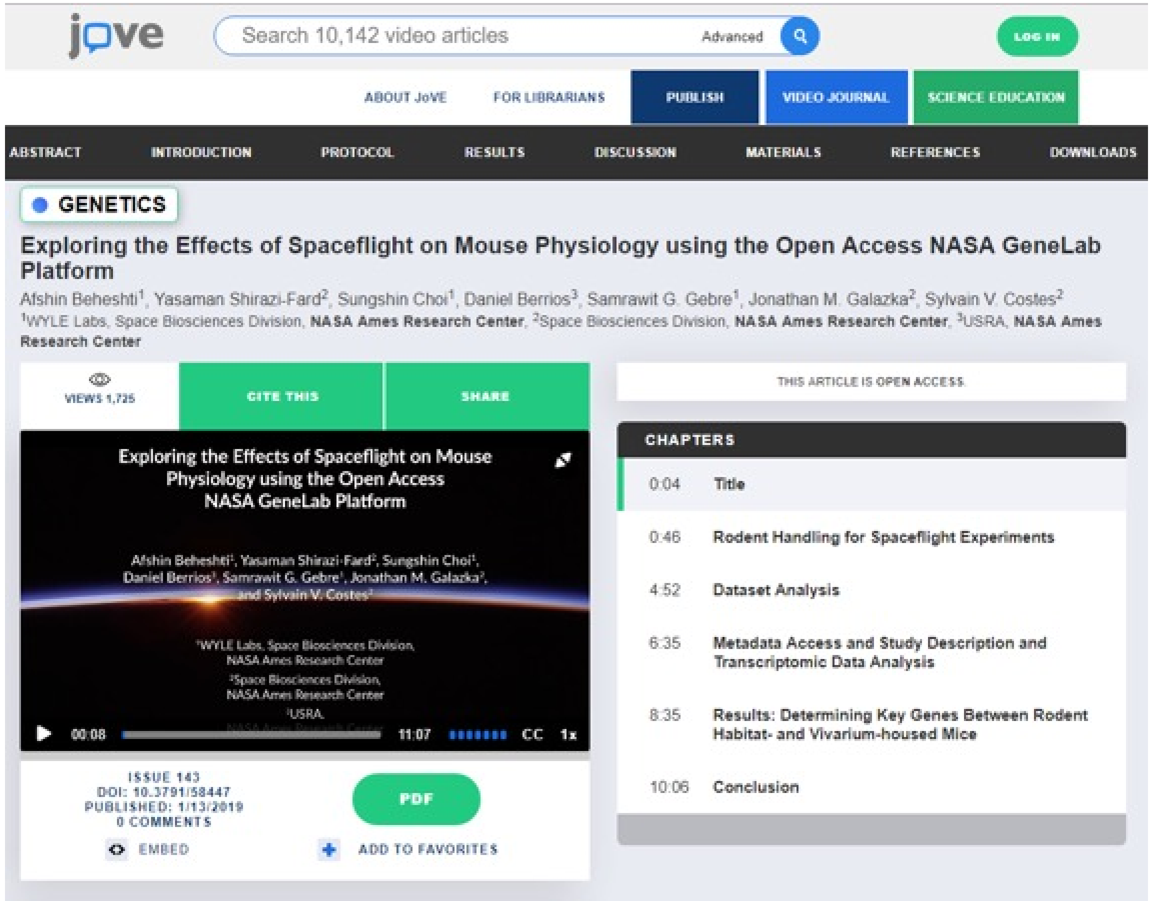


Select health effects due to space radiation exposures.

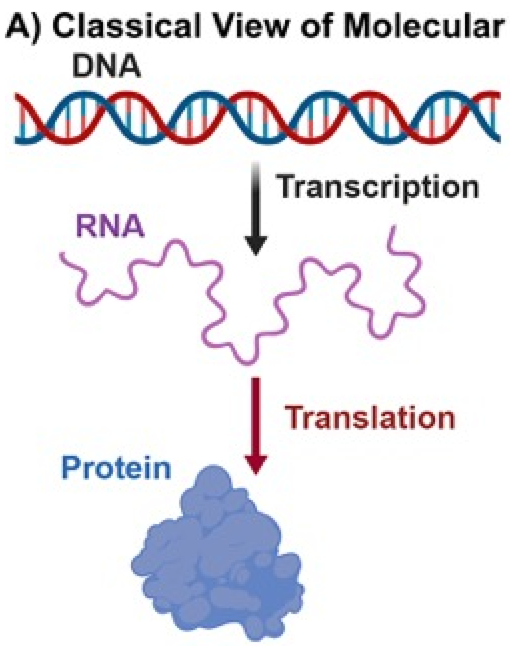
From: J. Chancellor et al., Space Radiation: The Number One Risk to Astronaut Health beyond Low Earth Orbit. *Life,* 4(3), 491-510;

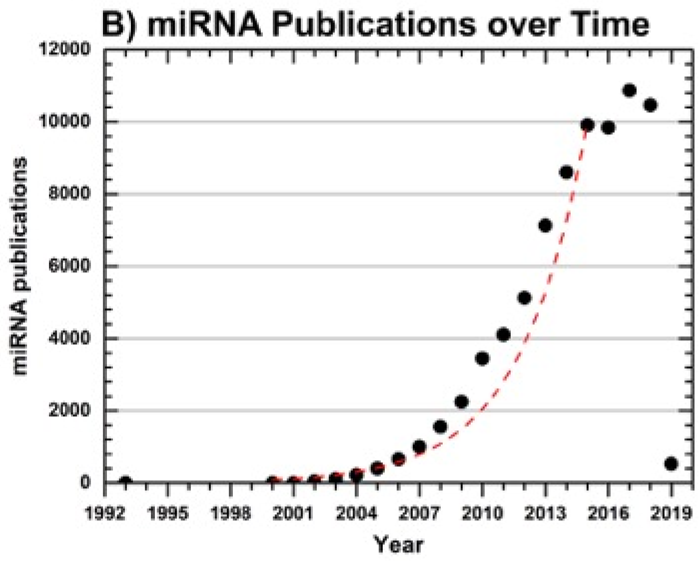
Systemic Alterations with Spaceflight Associated Health Risks: Determined Utilizing GeneLab datasets

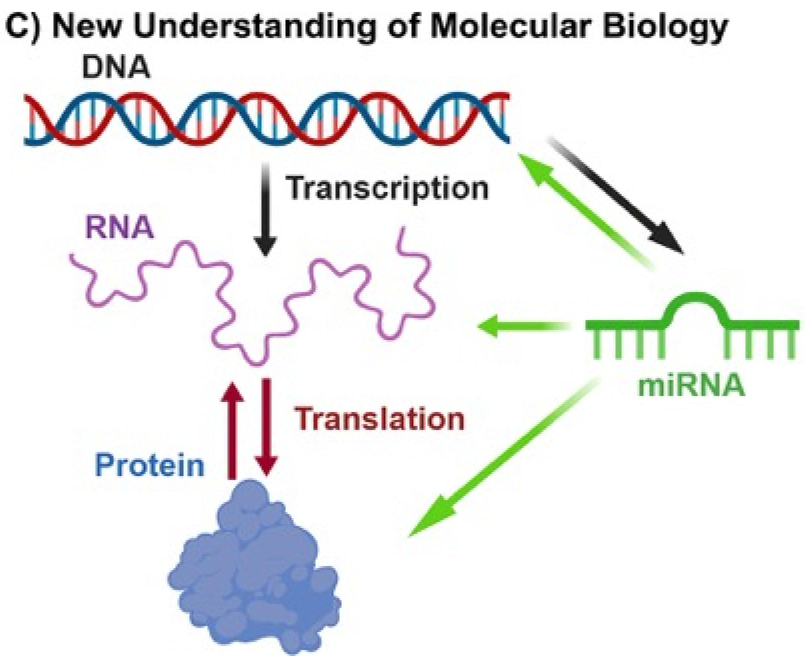
- **Circulating miRNA Signature Predicts Health Risks Associated with Radiation and Microgravity**
- **Multi-Omics Analysis using GeneLab database recognizes Mitochondrial Dysfunction as a mediator of spaceflight health risks**



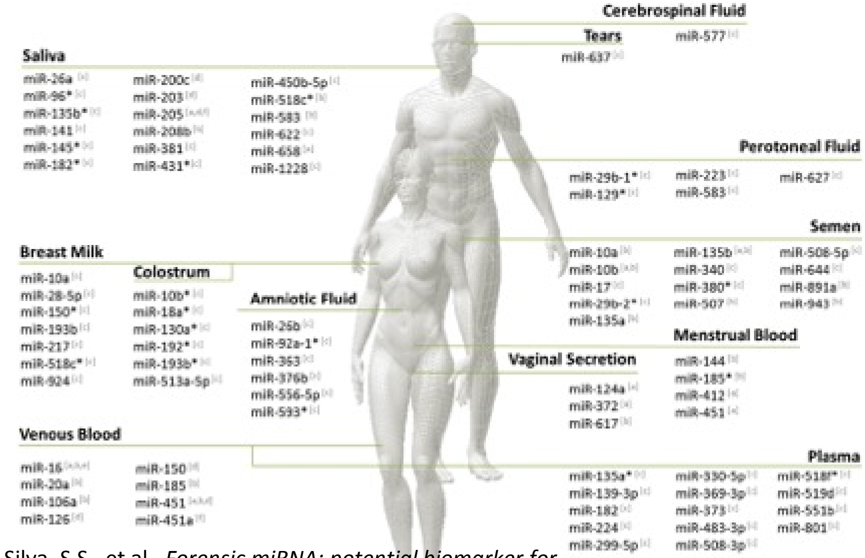
What are miRNAs and why study miRNAs





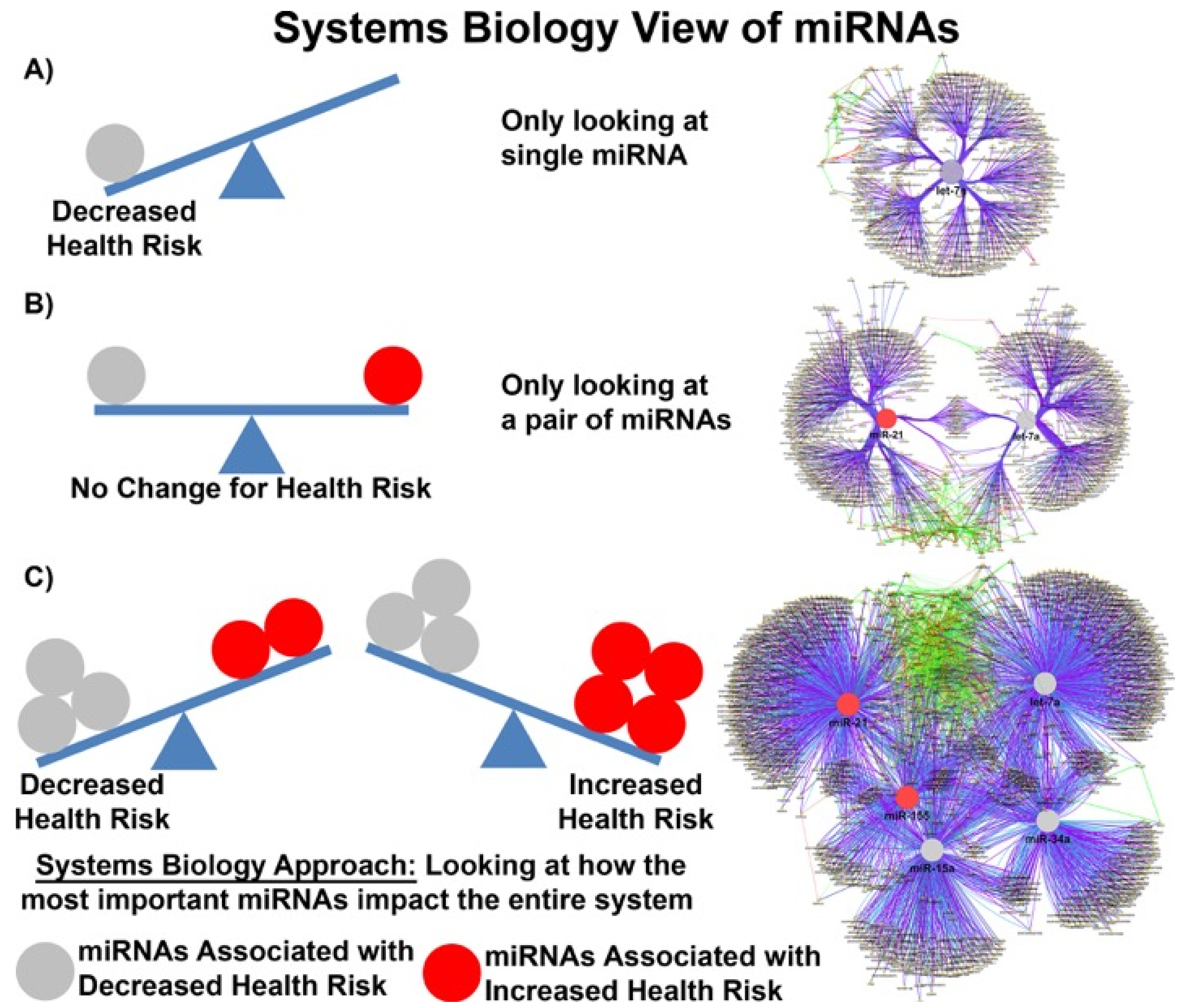


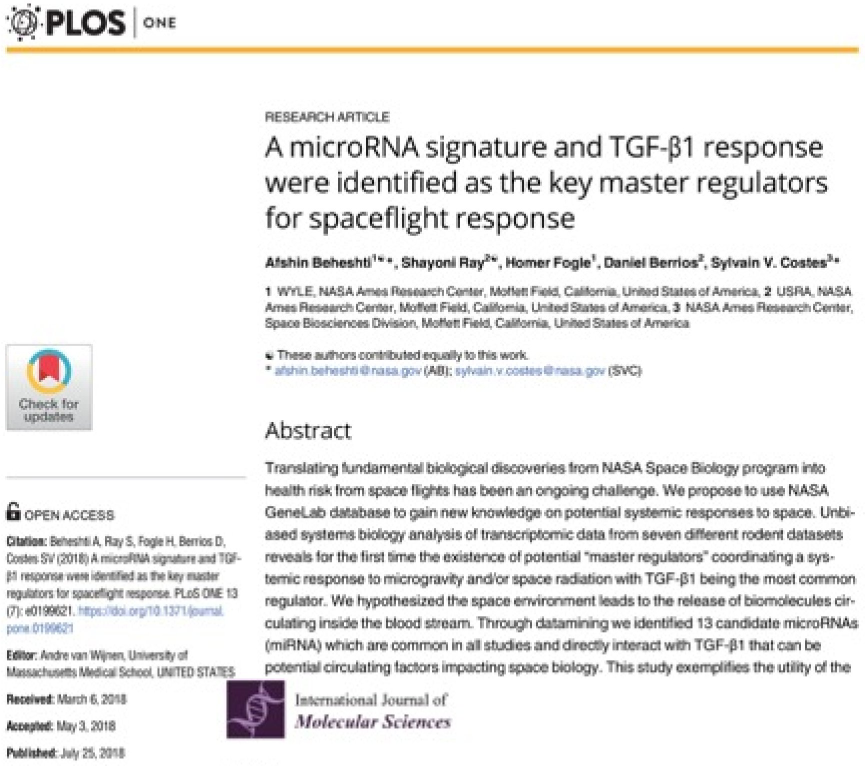
- A single miRNA has been estimated to regulate up to 500 mRNAs.
- miRNAs are ~22nt
- Due to the size and stability of the miRNAs, it can float freely in the blood.
- miRNAs are now known to be involved in all aspects of diseases.
- miRNA are not only found in mammals, but everything else living: plants,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



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





PLOS | ONE

RESEARCH ARTICLE

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

Afshin Beheshti[1☯*], Shayoni Ray[2☯], Homer Fogle[1], Daniel Berrios[2], 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.
* afshin.beheshti@nasa.gov (AB); sylvain.v.costes@nasa.gov (SVC)

Check for updates

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

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Citation: Beheshti A, Ray S, Fogle 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 (7): e0199621. https://doi.org/10.1371/journal.pone.0199621

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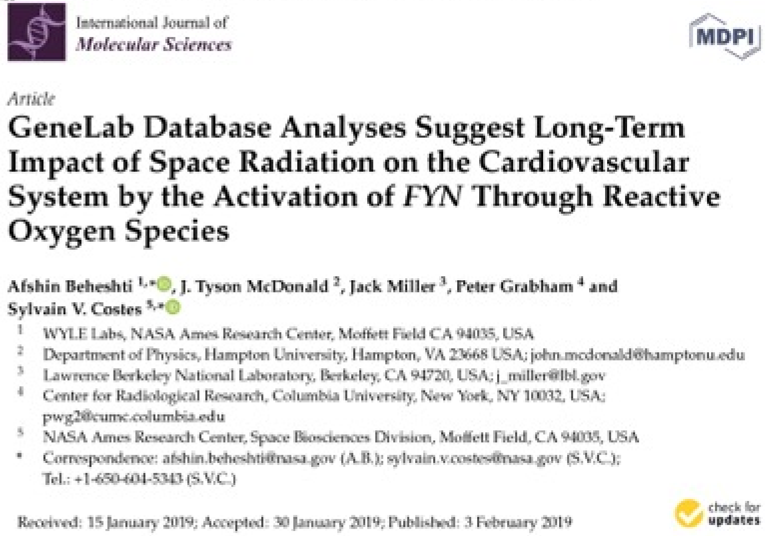

International Journal of *Molecular Sciences*

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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
3 Lawrence Berkeley National Laboratory, Berkeley, CA 94720, USA; j_miller@lbl.gov
4 Center for Radiological Research, Columbia University, New York, NY 10032, USA; pwg2@cumc.columbia.edu
5 NASA Ames Research Center, Space Biosciences Division, Moffett Field, CA 94035, USA
* Correspondence: afshin.beheshti@nasa.gov (A.B.); sylvain.v.costes@nasa.gov (S.V.C.); Tel.: +1-650-604-5343 (S.V.C.)

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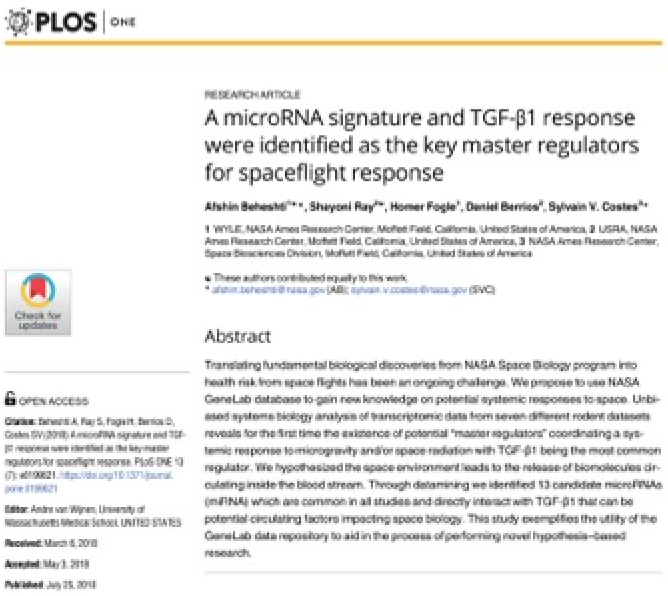
check for updates

miRNA Signature Prediction Associated with Space Flight



PLOS | ONE

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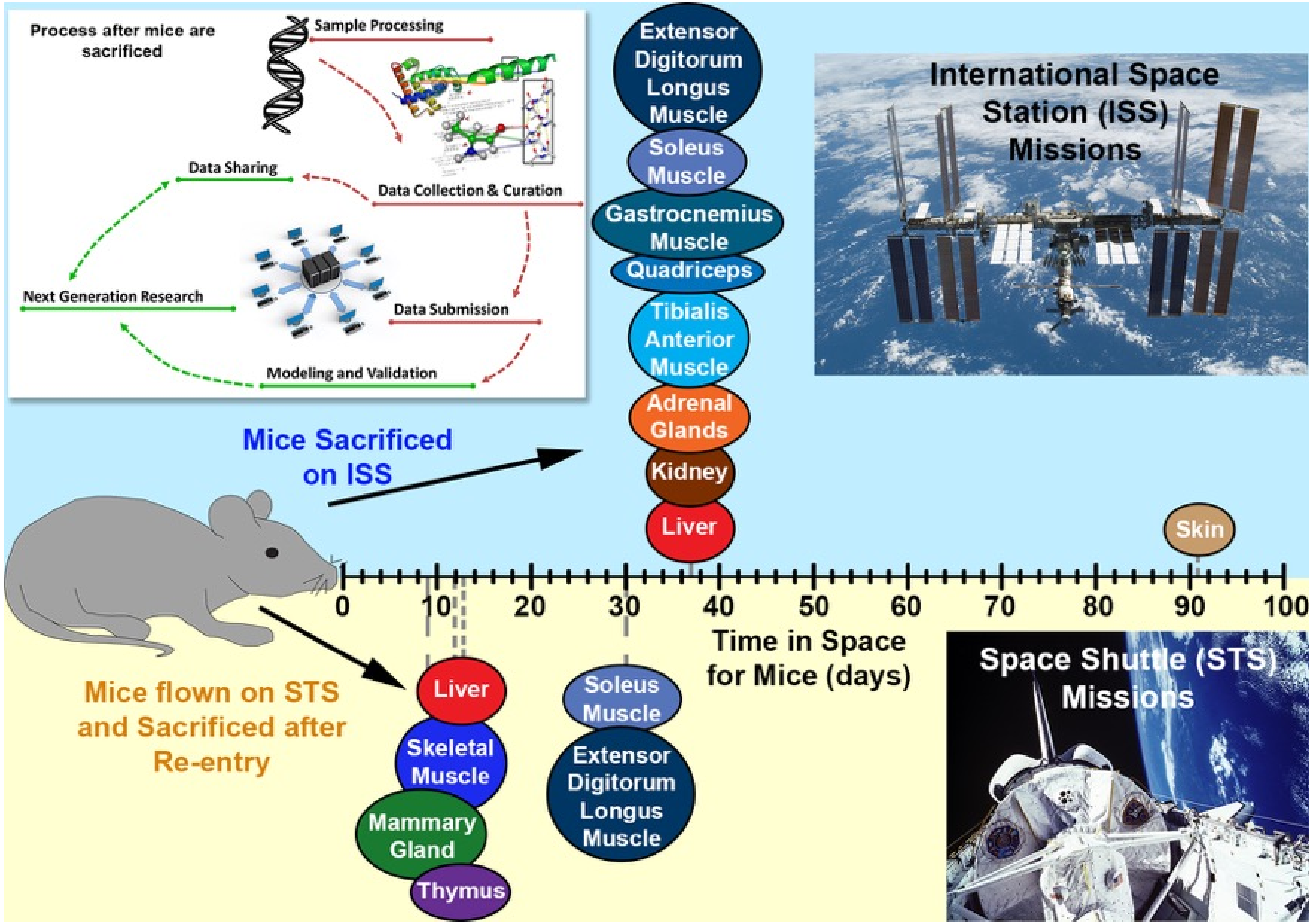
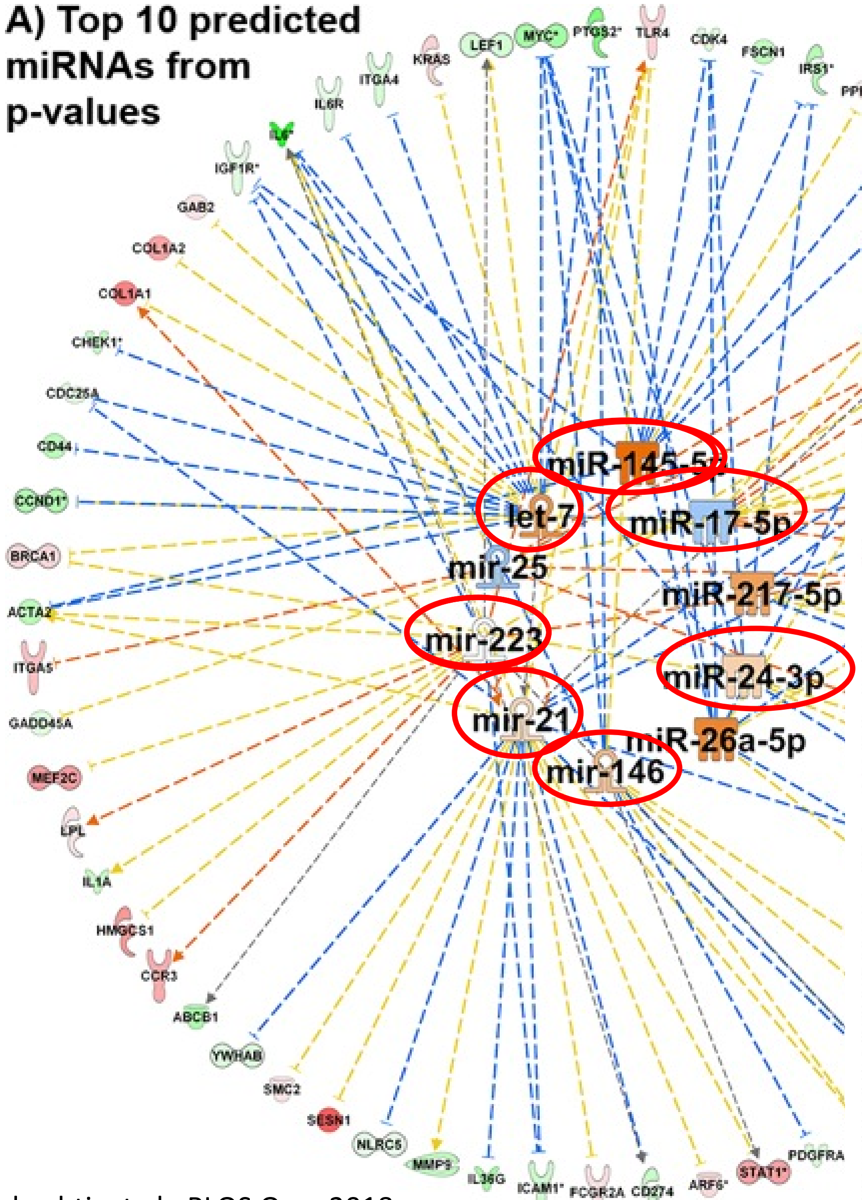


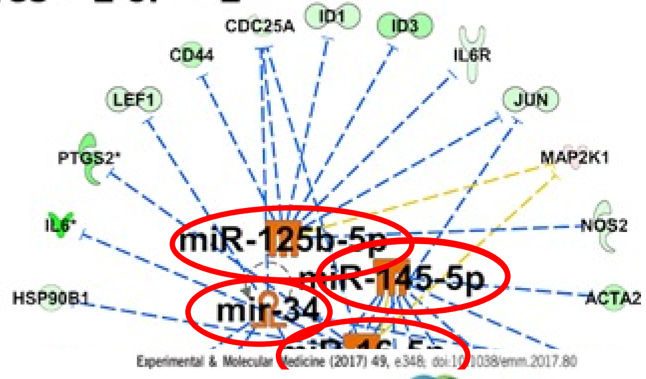
https://genelab.nasa.gov/

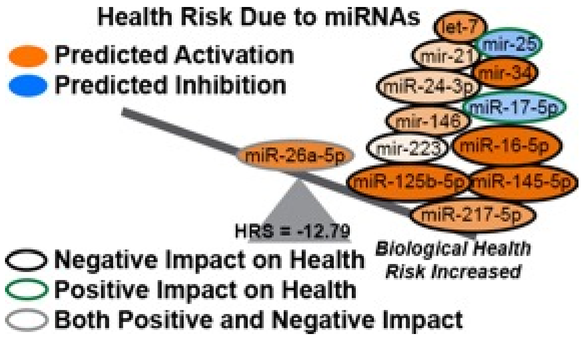
Predicted miRNAs Involved with Spaceflight

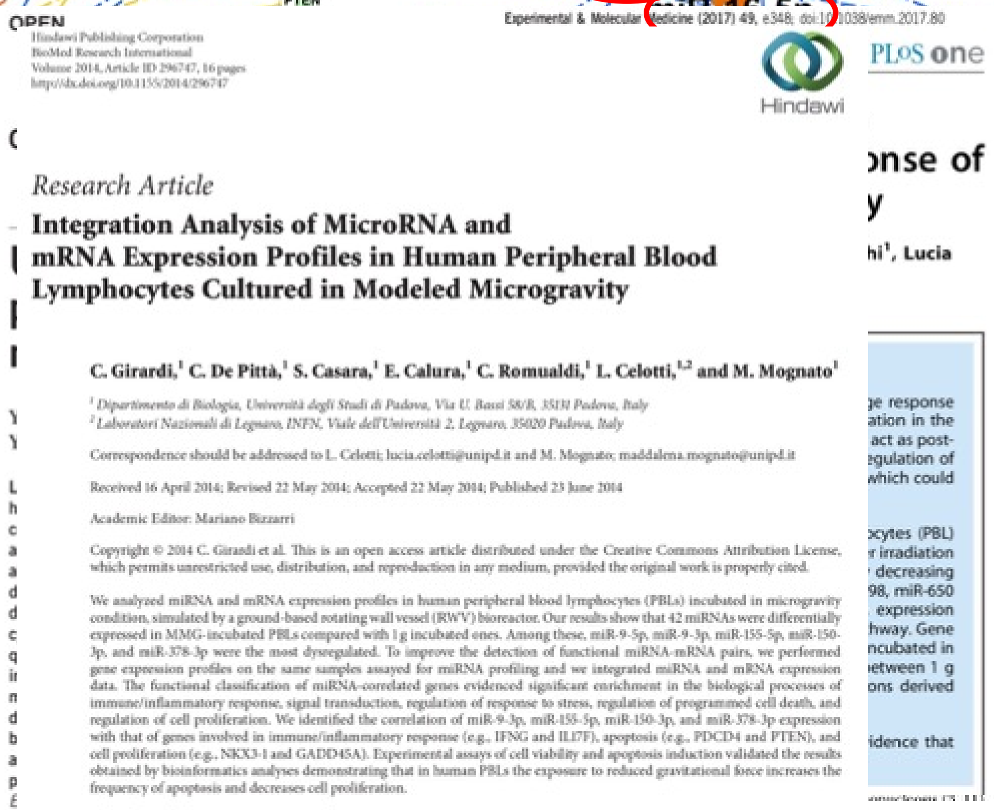
A) Top 10 predicted miRNAs from p-values



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







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Hindawi Publishing Corporation
BioMed Research International
Volume 2014, Article ID 296747, 16 pages
http://dx.doi.org/10.1155/2014/296747

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PLOS one

Research Article

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

C. Girardi,[1] C. De Pittà,[1] S. Casara,[1] E. Calura,[1] C. Romualdi,[1] L. Celotti,[1,2] and M. Mognato[1]

[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

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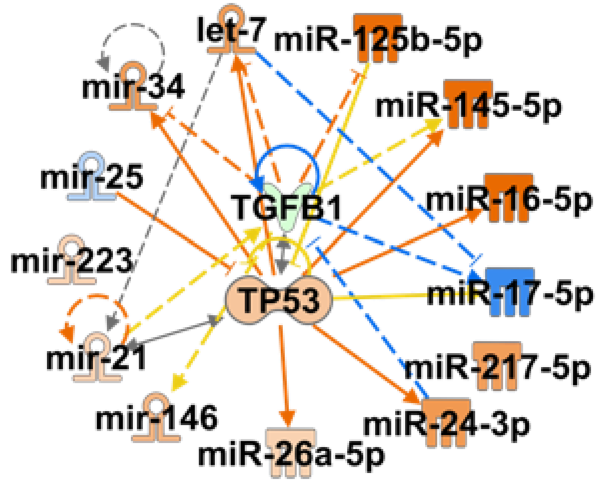
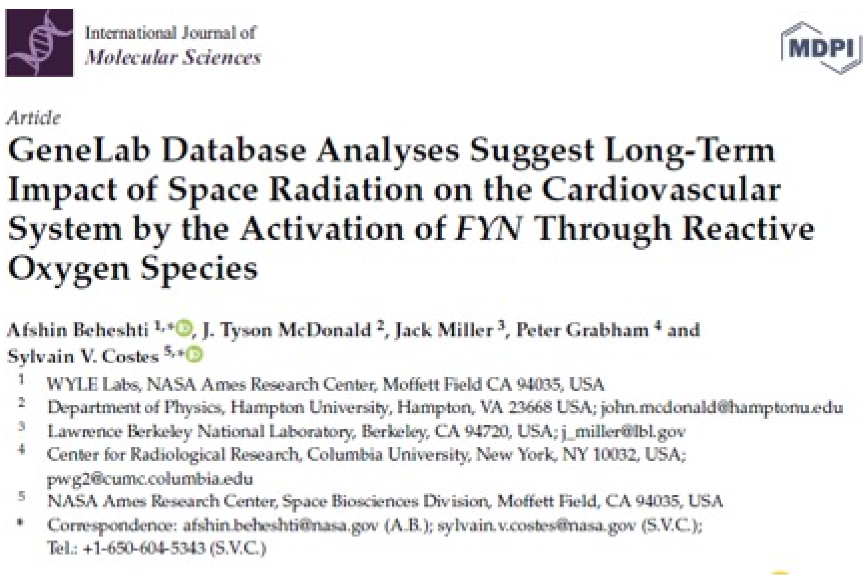
We analyzed miRNA and mRNA expression profiles in human peripheral blood lymphocytes (PBLs) incubated in microgravity condition, simulated by a ground-based rotating wall vessel (RWV) bioreactor. Our results show that 42 miRNAs were differentially expressed in MMG-incubated PBLs compared with 1 g incubated 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.



Beheshti, et al., PLOS One, 2018

Predict miRNAs with Space Radiation Cardiovascular Risk



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4 Center for Radiological Research, Columbia University, New York, NY 10032, USA; pwg2@cumc.columbia.edu
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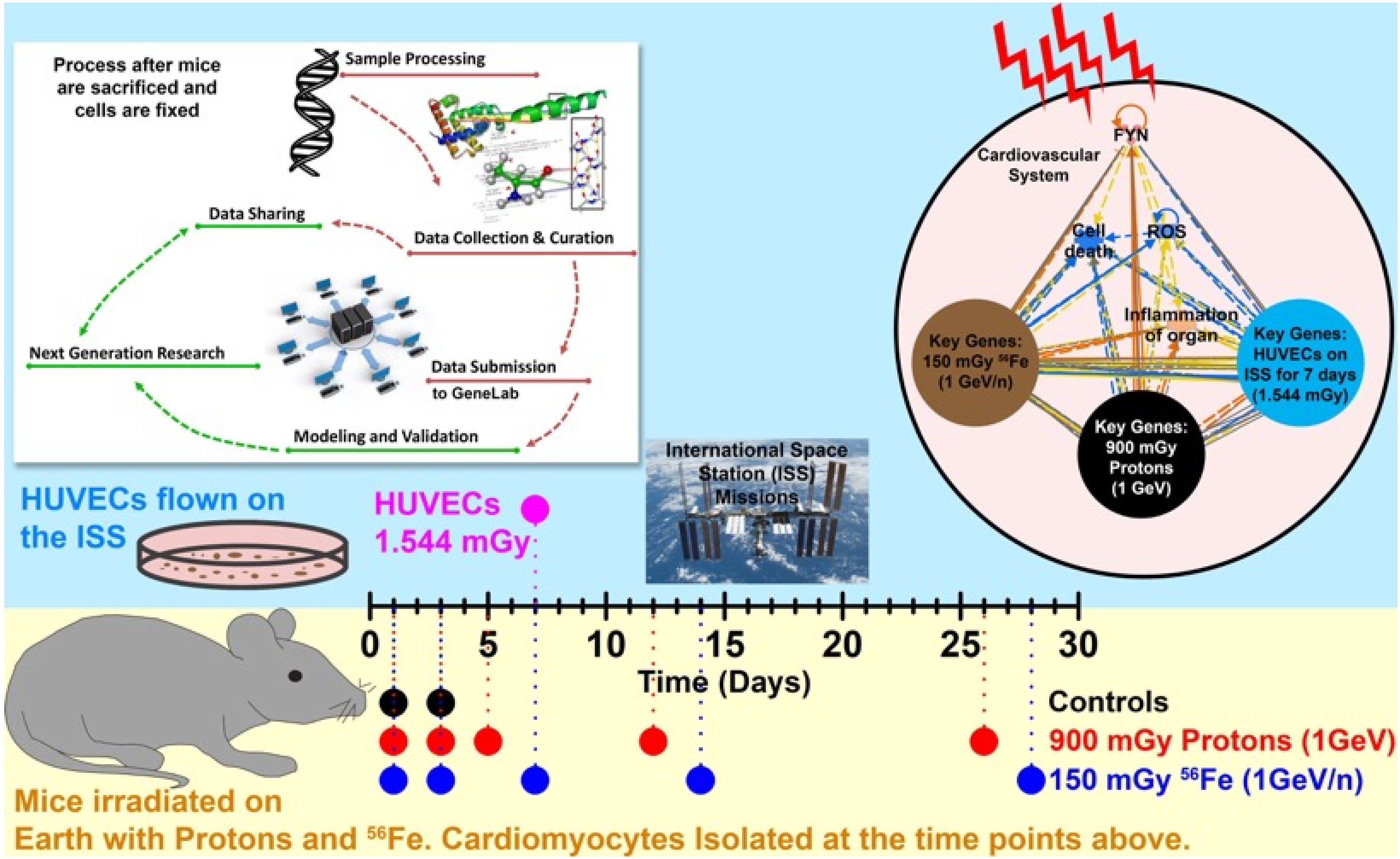
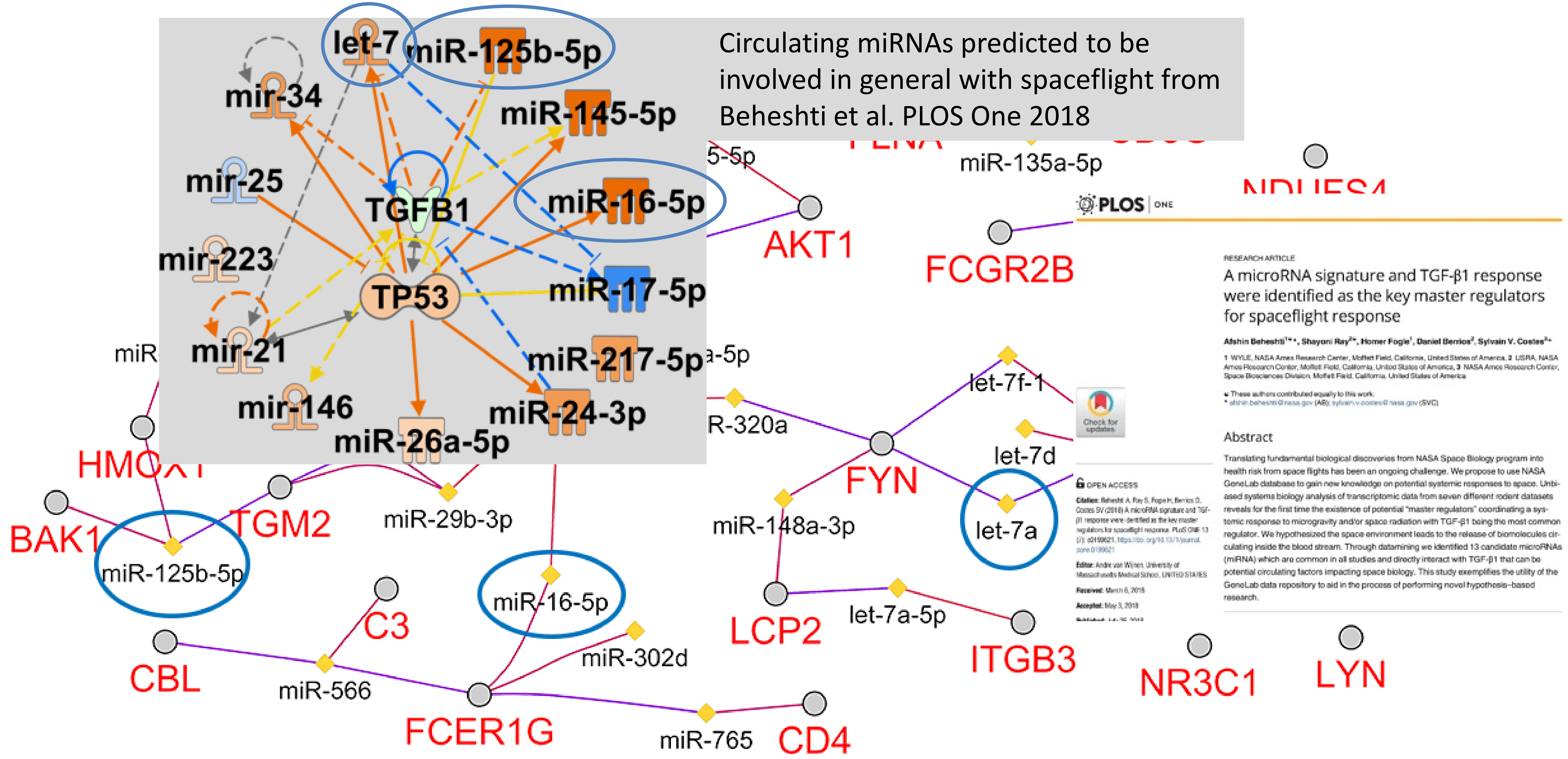
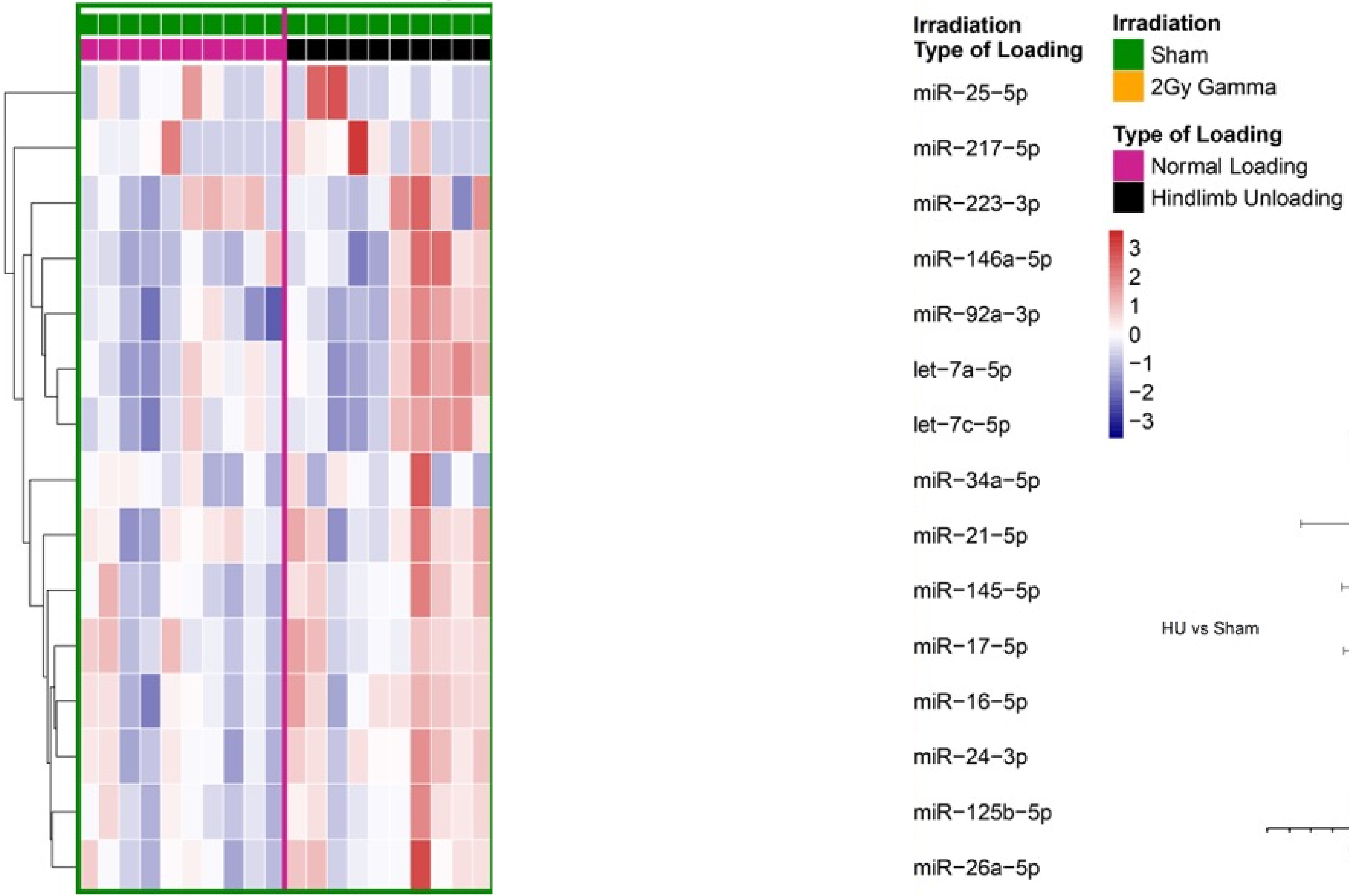


Predict miRNAs with Space Radiation Cardiovascular Risk

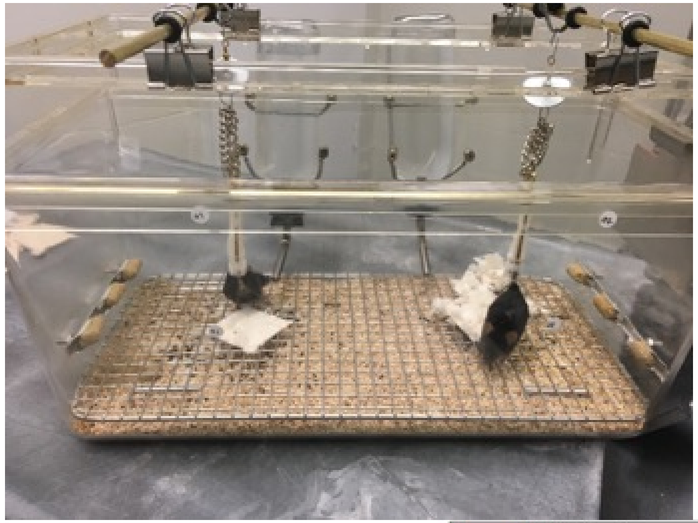


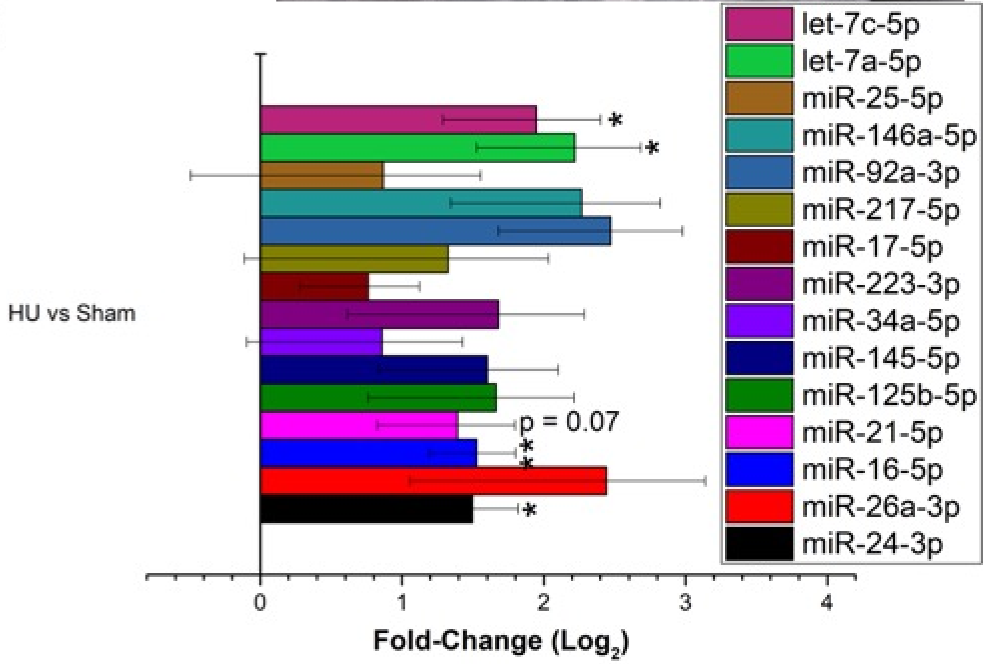
Presence of miRNA signature in Serum of Mice in Simulated Space Environment

miRNA Signature in Serum



Hindlimb Unloading

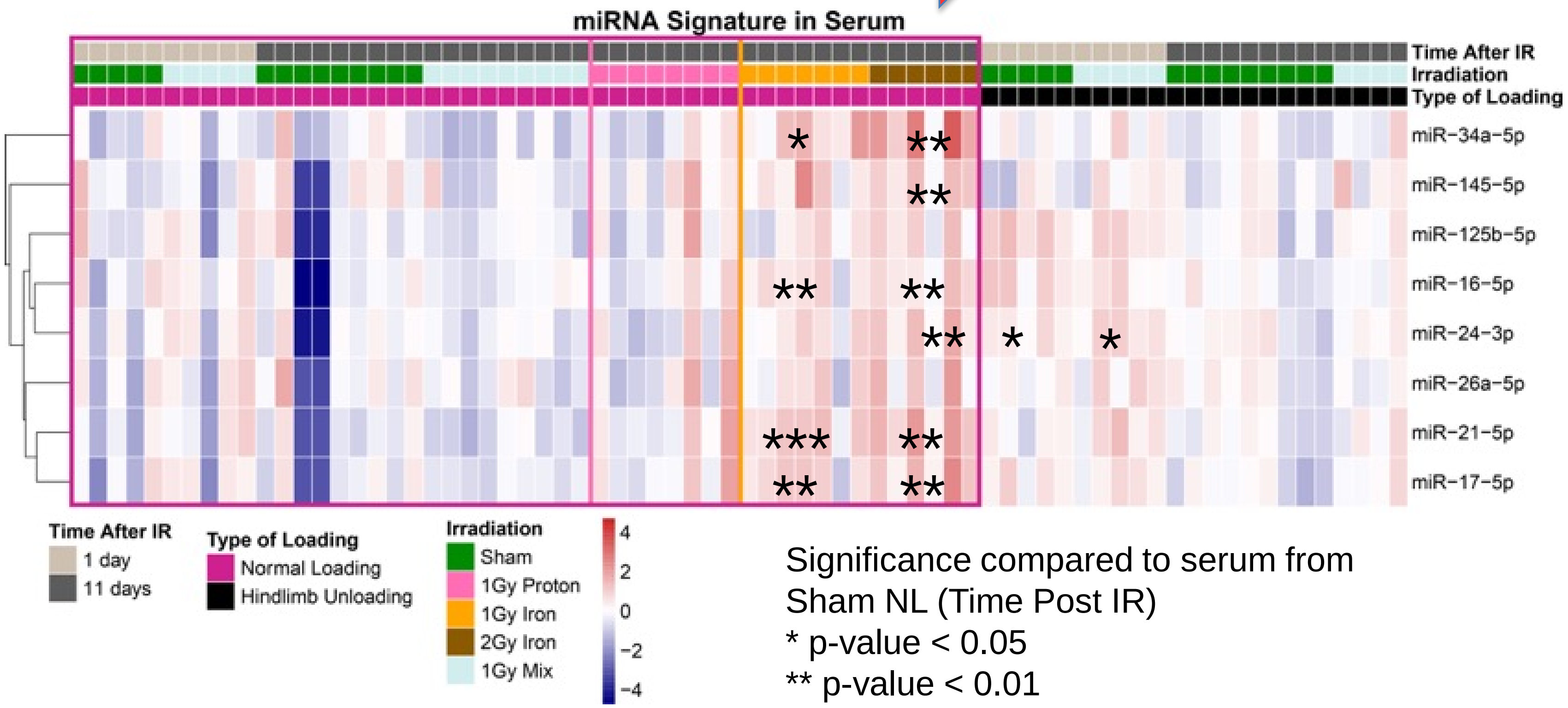




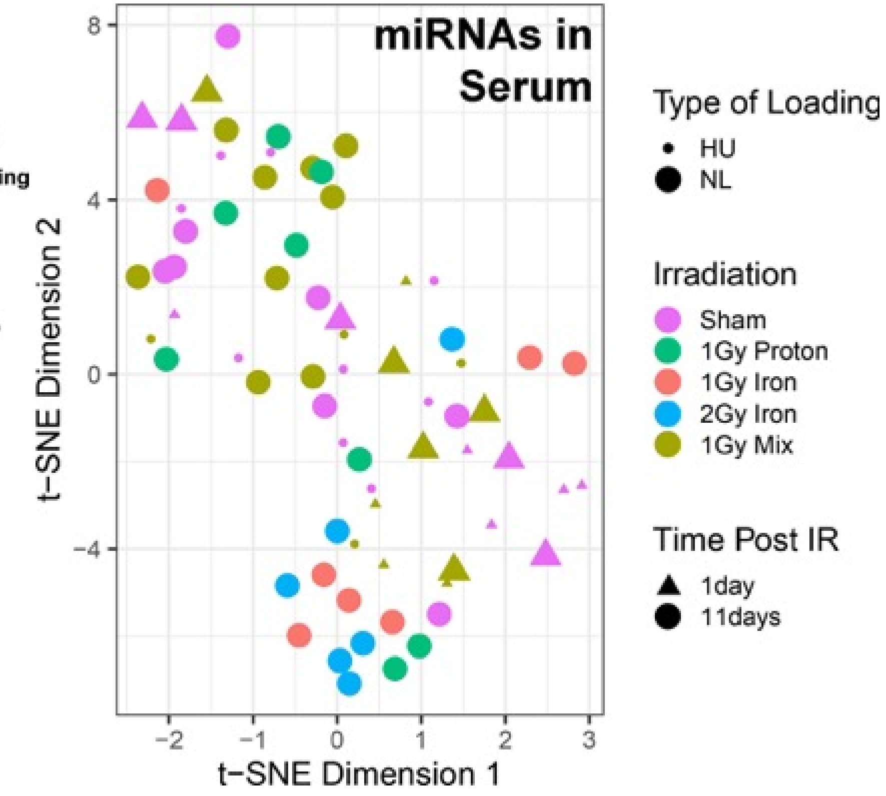
Preliminary data on miRNA signature Presence with Space Radiation

- 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 ^{56}Fe (1 Gy and 2 Gy), 150 MeV Proton (1Gy) or ‘1Gy Mix' (0.5Gy ^{56}Fe and 0.5Gy Proton)

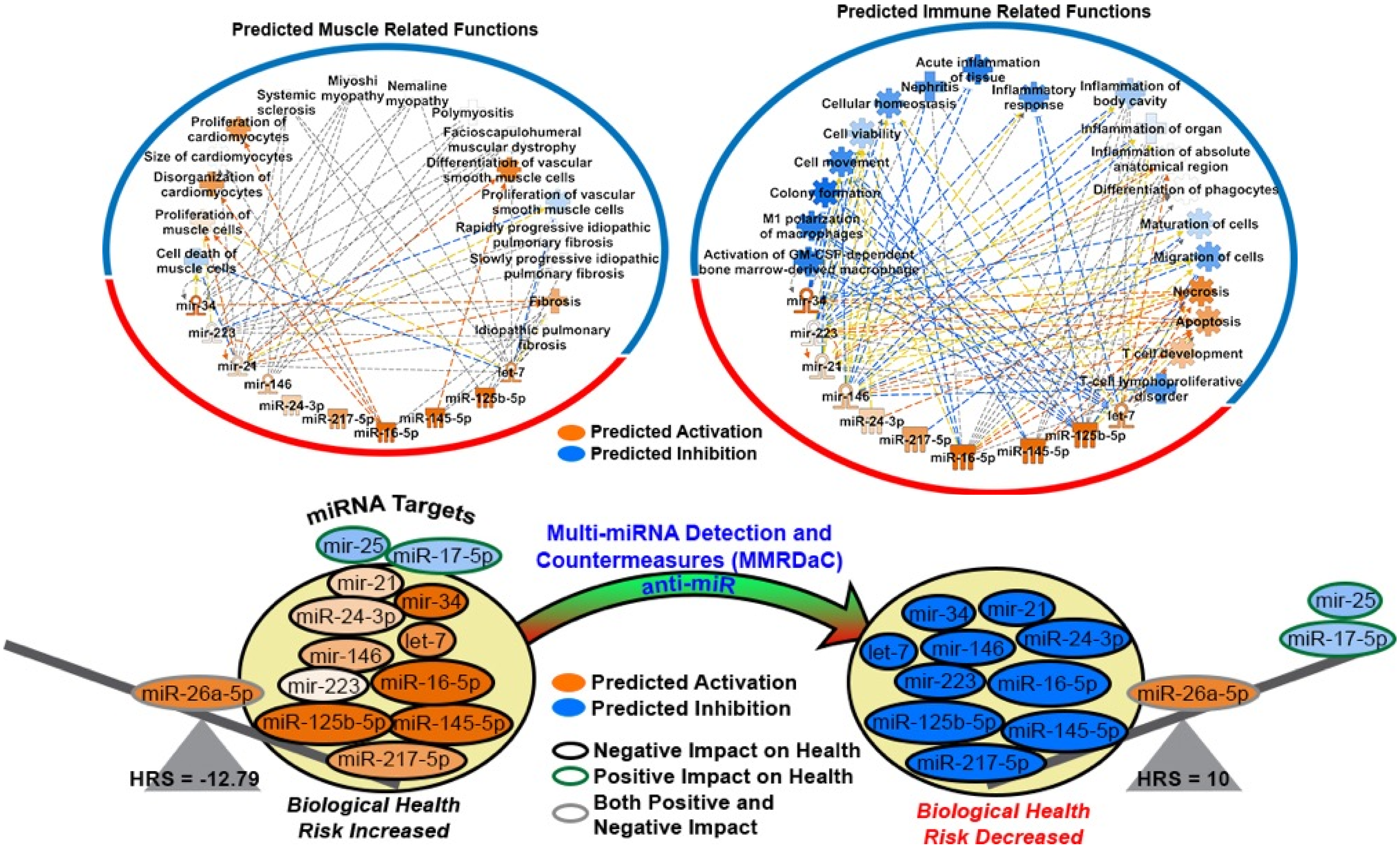
Increasing Dose and Ions causes increase miRNAs in serum



Significance compared to serum from Sham NL (Time Post IR)
* p-value < 0.05
** p-value < 0.01
*** p-value < 0.001



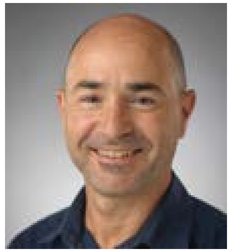
Impact of the Space Biology miRNA Signature on Functions and potential use for a novel Countermeasure



SLPSRA

Acknowledgments for miRNA Studies

NASA

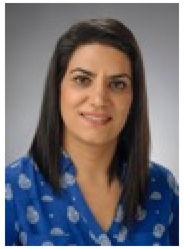

Sylvain Costes
Space Bio miRNAs

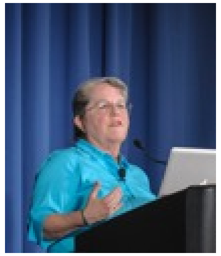

Egle Cekanaviciute
Quantifying miRNAs


Sherina Malkani
Quantifying miRNAs


Ann-Sofie Schreurs
Provided Archived Tissues


Margareth Cheng-Campbell
Quantifying miRNAs

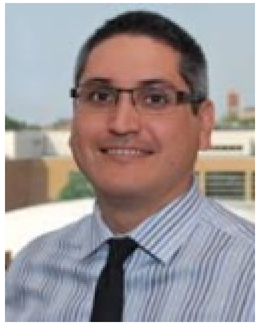

Yasaman Shirazi
Provided Archived Tissues


Ruth Globus
Provided Archived Tissues

NASA
Ames Research Center
Space Biosciences
NASA AMES RESEARCH CENTER


Elizabeth Blaber
Space Bio miRNAs

NASA
Ames Research Center
Rensselaer


J. Tyson McDonald
HAMPTON UNIVERSITY
THE STANDARD OF EXCELLENCE


Charles Vanderburg
BROAD INSTITUTE


Peter Grabham
Columbia University Irving Medical Center

This work is supported by:

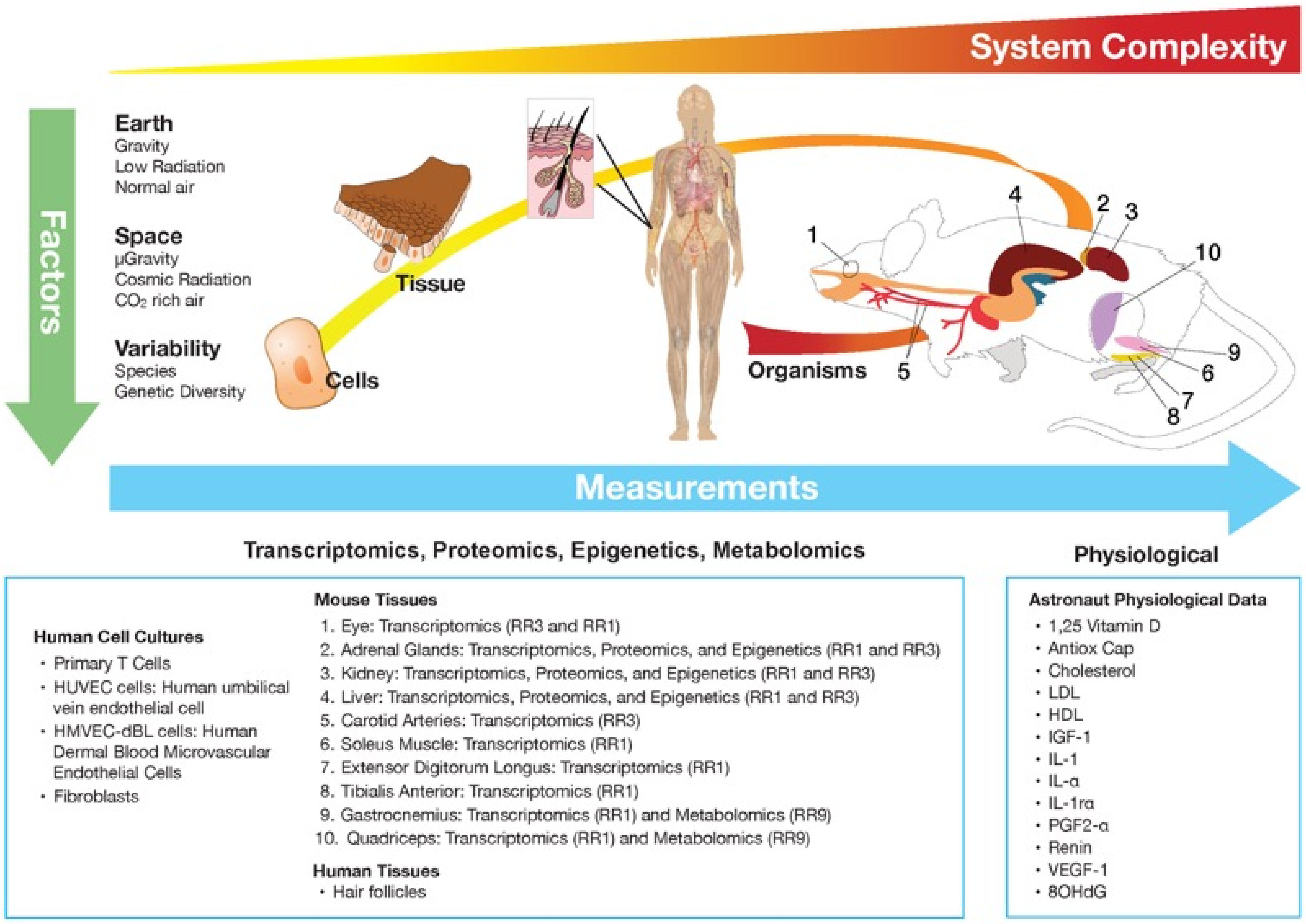
NASA

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)

TRANSLATIONAL RESEARCH INSTITUTE FOR SPACE HEALTH

Multi-Omics Analysis using GeneLab database recognizes Mitochondrial Dysfunction as a mediator of spaceflight health risks



- 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

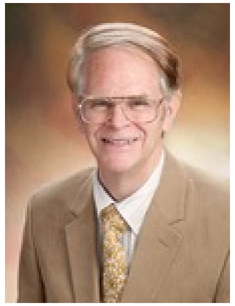

Brin Rosenthal

UNIVERSITY of CALIFORNIA, SAN DIEGO
SCHOOL OF MEDICINE


Deanne Taylor


Hossein Fazelinia


Komal Rathi


Douglas Wallace


Larry Singh

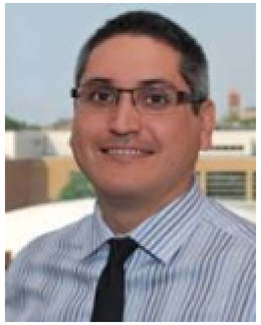
Children's Hospital of Philadelphia

Perelman School of Medicine
UNIVERSITY of PENNSYLVANIA


Helio Costa


Kathryn Grabek

STANFORD UNIVERSITY


J. Tyson McDonald

HAMPTON UNIVERSITY
THE STANDARD OF EXCELLENCE


Gary Hardiman


Willian da Silveira

QUEEN'S UNIVERSITY BELFAST


Jeffrey Scott Willey

WAKE FOREST UNIVERSITY

AWG Members Involved


Chris Mason


Cem Meydan


Jonathan Foox

Flavia Rius

Cornell University


Yared Kidane

Texas Scottish Rite Hospital for Children


Evagelia C. Laiakis

Georgetown University
Georgetown University Medical Center


Robert Meller, D.Phil

Morehouse School of Medicine


Susana Zanello

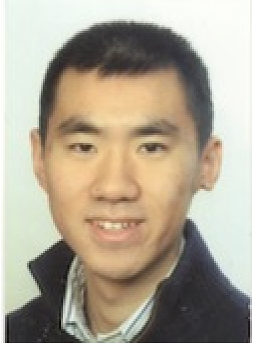

Scott Smith


Sara Zwart

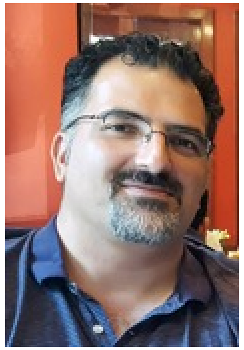
NASA

Space Center Houston
Manned Space Flight Education Foundation


Sonja Schrepfer


Dong Wang

UCSF
University of California
San Francisco

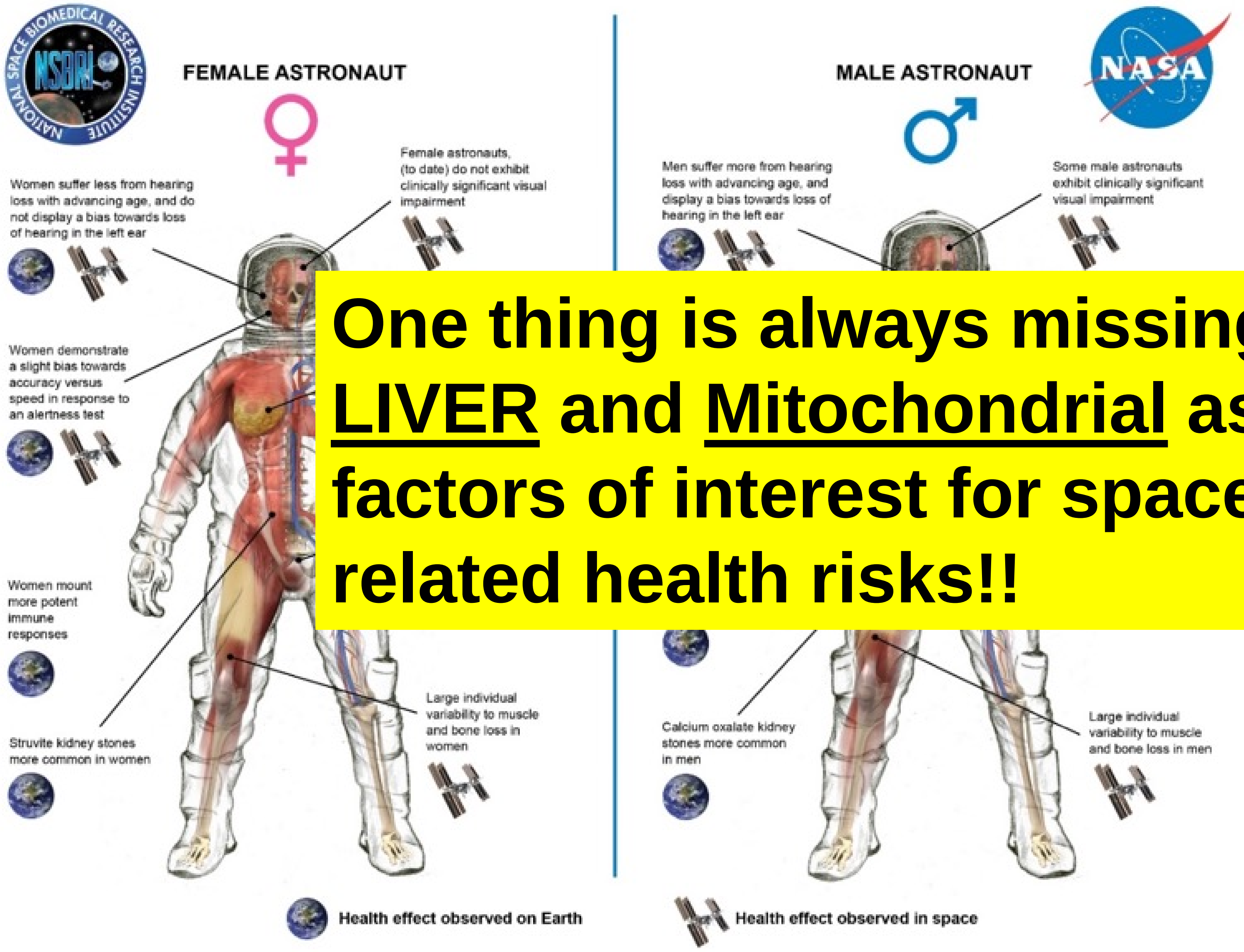

Afshin Beheshti


Sylvain Costes

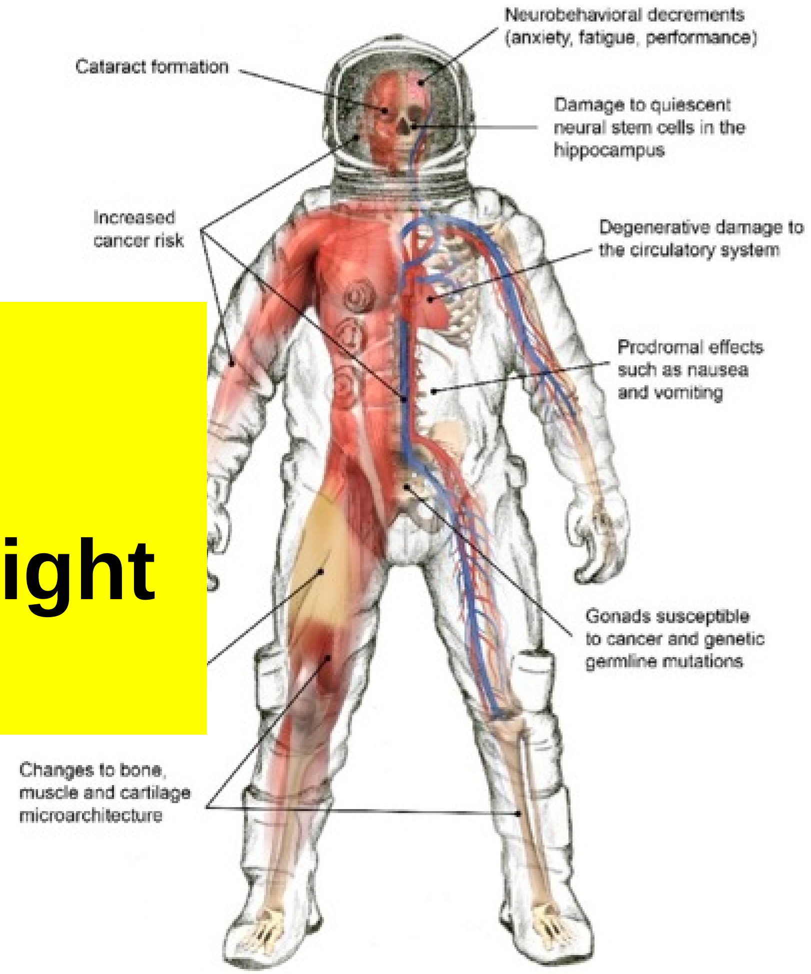
NASA

Ames Research Center

Health Risks On Astronauts in Space



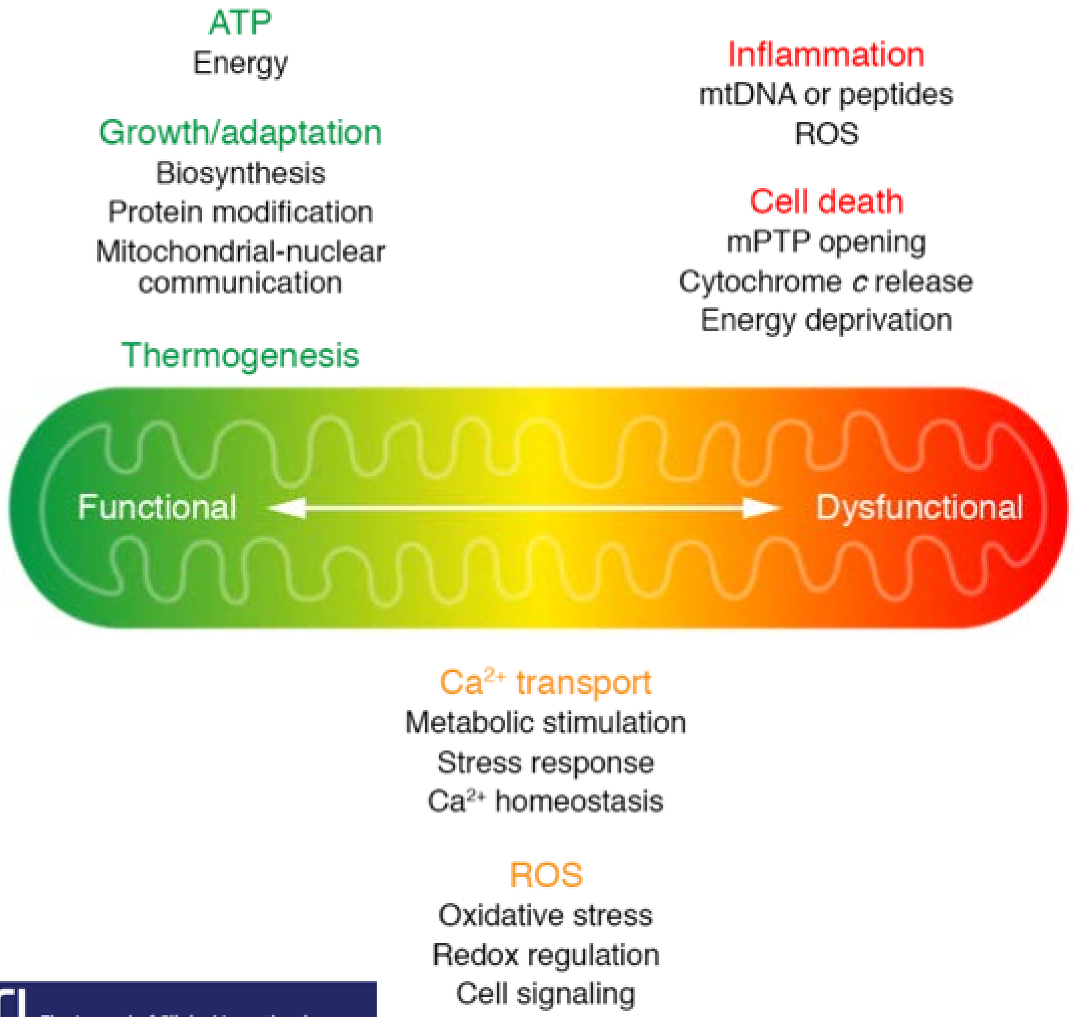
One thing is always missing: <u>LIVER</u> and <u>Mitochondrial</u> as factors of interest for spaceflight related health risks!!

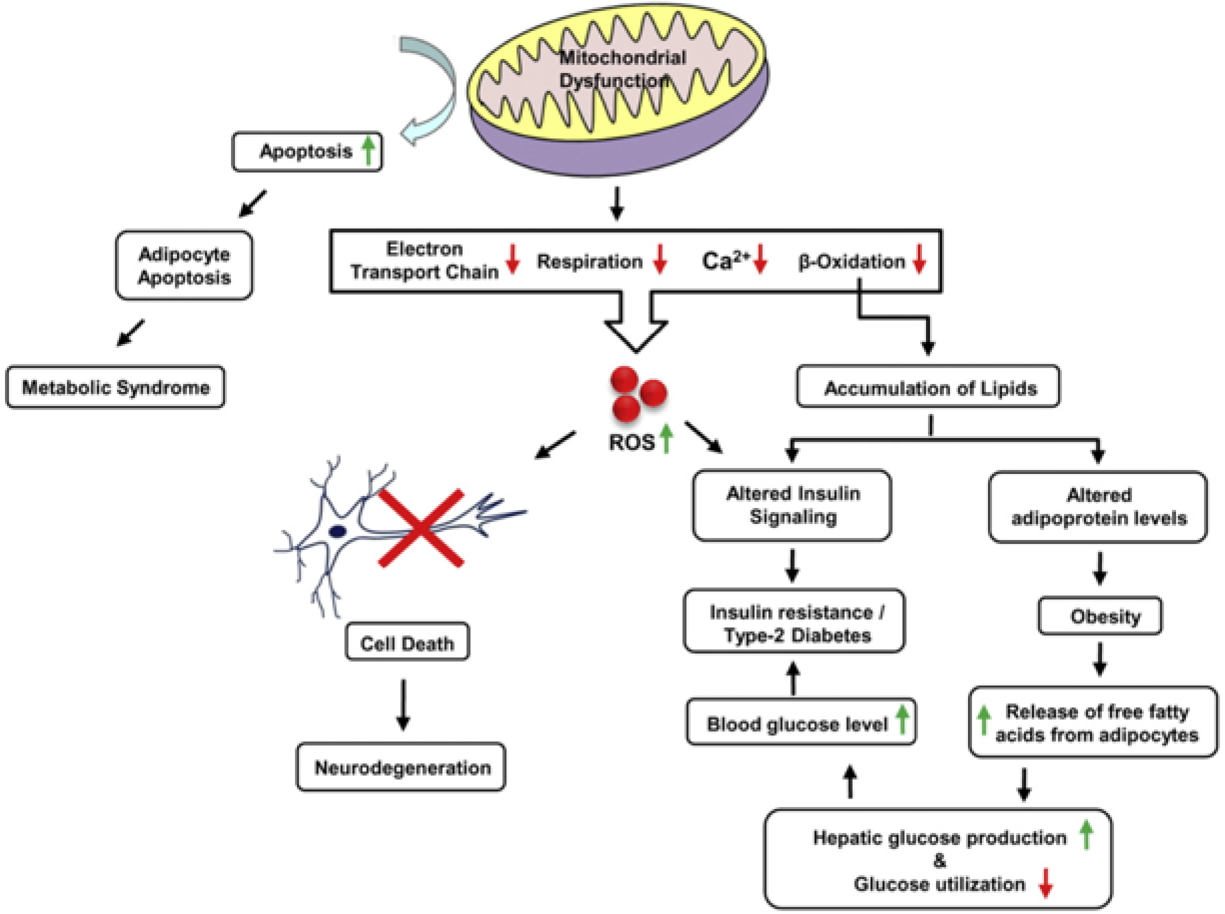


Select health effects due to space radiation exposures.

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

The Mitochondrial Stress Response





JCI The Journal of Clinical Investigation

Mitochondrial dysfunction in pathophysiology of heart failure

Bo Zhou, Rong Tian

J Clin Invest. 2018;128(9):3716-3726. https://doi.org/10.1172/JCI120849.

Review Series

Biochimica et Biophysica Acta 1863 (2017) 1132–1146

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

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

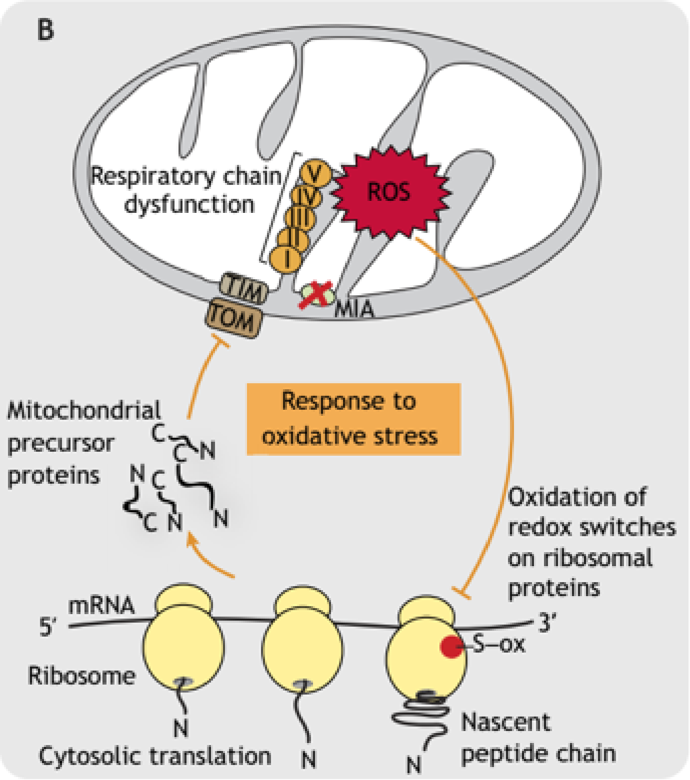
Linking mitochondrial dysfunction, metabolic syndrome and stress signaling in Neurodegeneration☆

Saurabh Kumar Jha [1], Niraj Kumar Jha [1], Dhiraj Kumar, Rashmi K. Ambasta, Pravir Kumar *

Molecular Neuroscience and Functional Genomics Laboratory, Department of Biotechnology, Delhi Technological University (Formerly DCE), Delhi 110042, India

The Mitochondrial Stress Response

Respiratory Chain Dysfunction resulting in halt of translation



Journal of Cell Science
Home Articles About us For authors Journal info Contact
REVIEW
Mitochondrial stress-dependent regulation of cellular protein synthesis
Ulrike Topf, Barbara Uszczynska-Ratajczak, Agnieszka Chacinska
Journal of Cell Science 2019 132: jcs226258 doi: 10.1242/jcs.226258 Published 26 April 2019

Cell arrest in response to oxidative stress

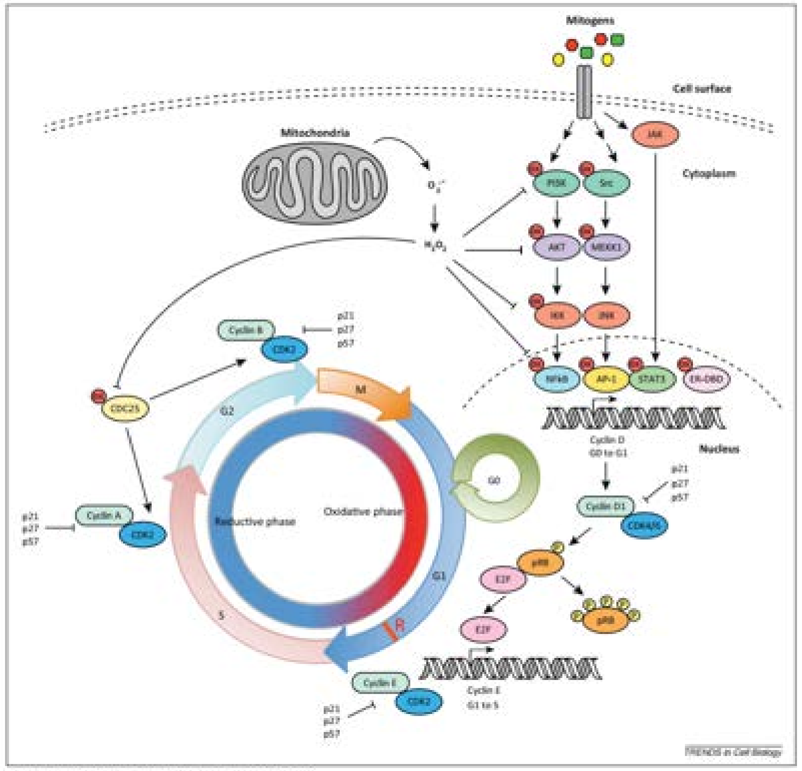
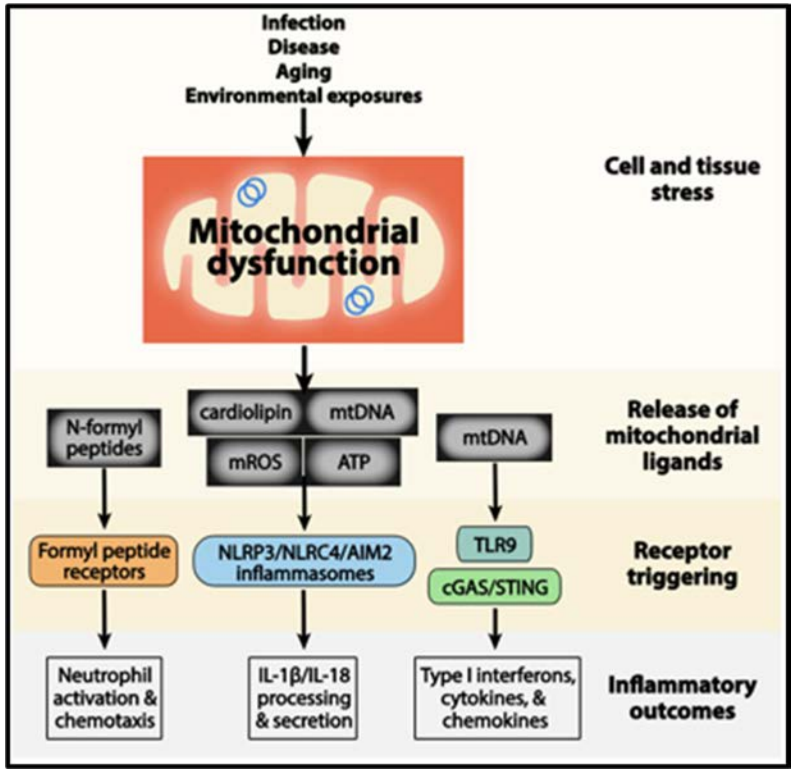


Figure 1. Overview of redox control of the eukaryotic cell-cycle.

Trends in Cell Biology
REVIEW | VOLUME 22, ISSUE 11, P592-601, NOVEMBER 01, 2012
Redox control of cell proliferation
Joyce Chiu • Ian W. Dawes
Published: August 28, 2012 • DOI: https://doi.org/10.1016/j.tcb.2012.08.002

Mitochondrial stress as a trigger innate immune responses



ELSEVIER
Toxicology
Volume 391, 1 November 2017, Pages 54-63
Mitochondrial dysfunction as a trigger of innate immune responses and inflammation
A. Phillip West
Show more
https://doi.org/10.1016/j.tox.2017.07.016

JCI The Journal of Clinical Investigation
Mitochondrial dysfunction in pathophysiology of heart failure
Bo Zhou, Rong Tian
J Clin Invest. 2018;128(9):3716-3726. https://doi.org/10.1172/JCI120849.
Review Series

The Mitochondrial Stress Response

Mitochondrial Dysfunction Impacts Many Organs

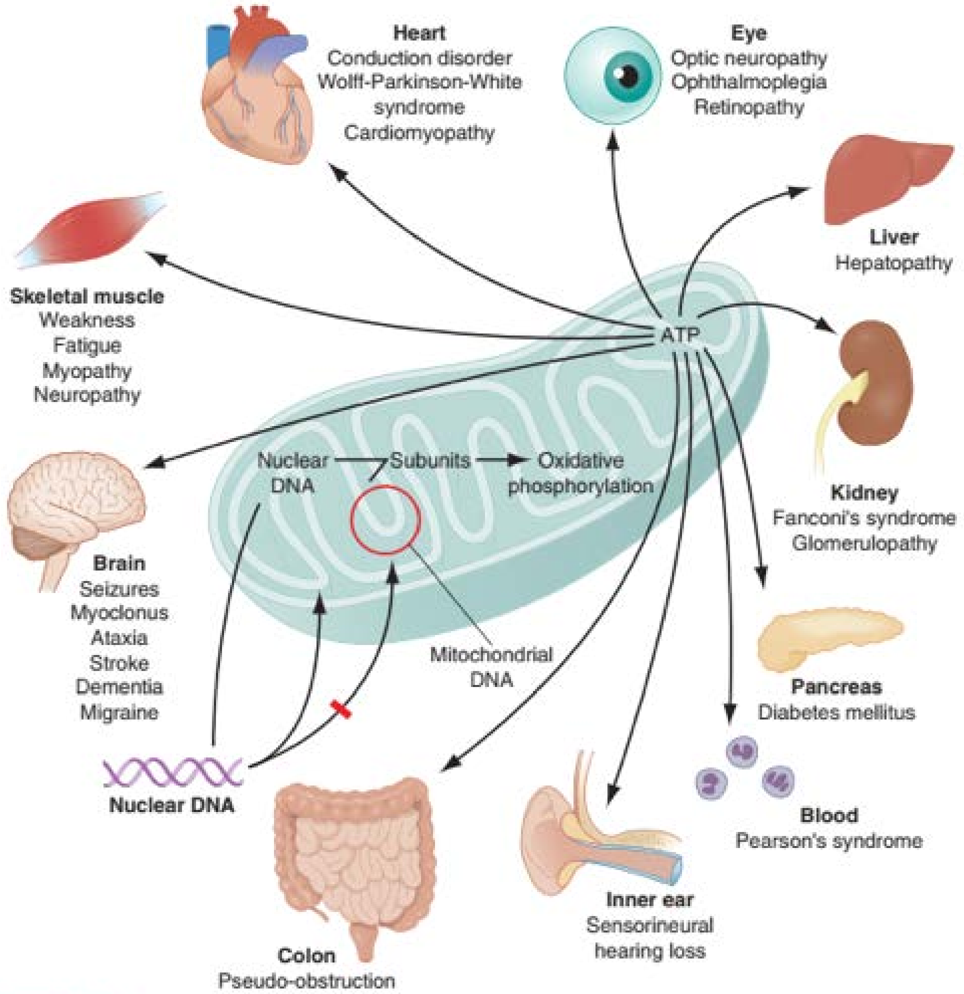


FIGURE 85e-1 Dual genetic control and multiple organ system manifestations of mitochondrial disease. *(Reproduced with permission from DR Johns: Mitochondrial DNA and disease. N Engl J Med 333:638, 1995.)*

Mitochondrial Dysfunction May Differ Between Organs

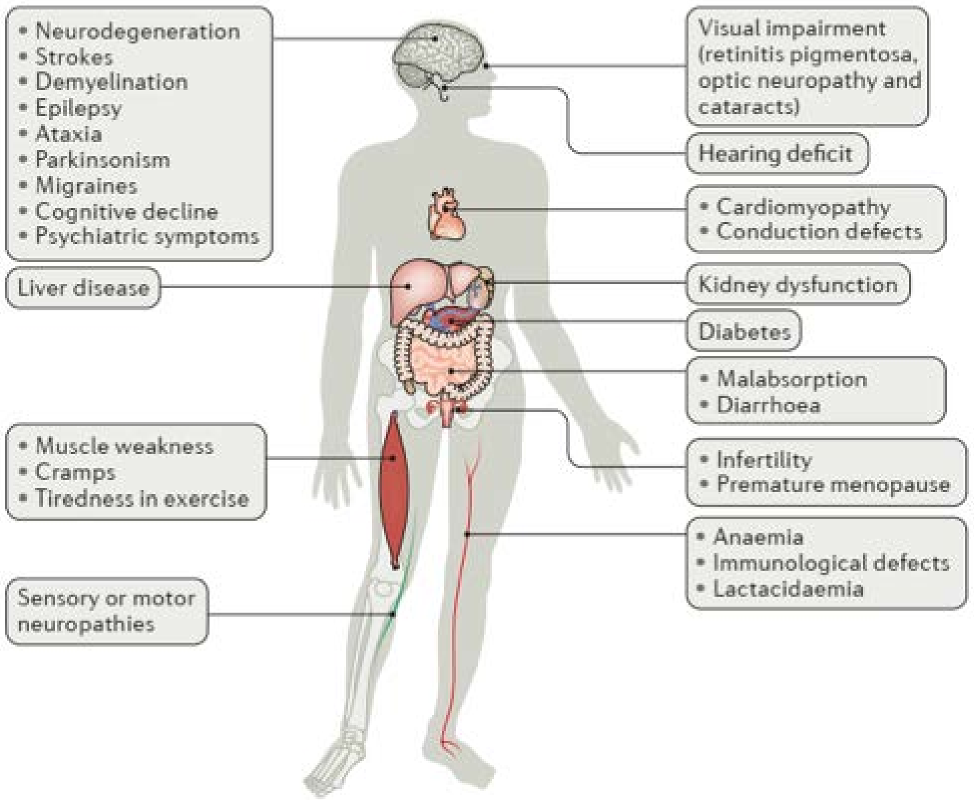
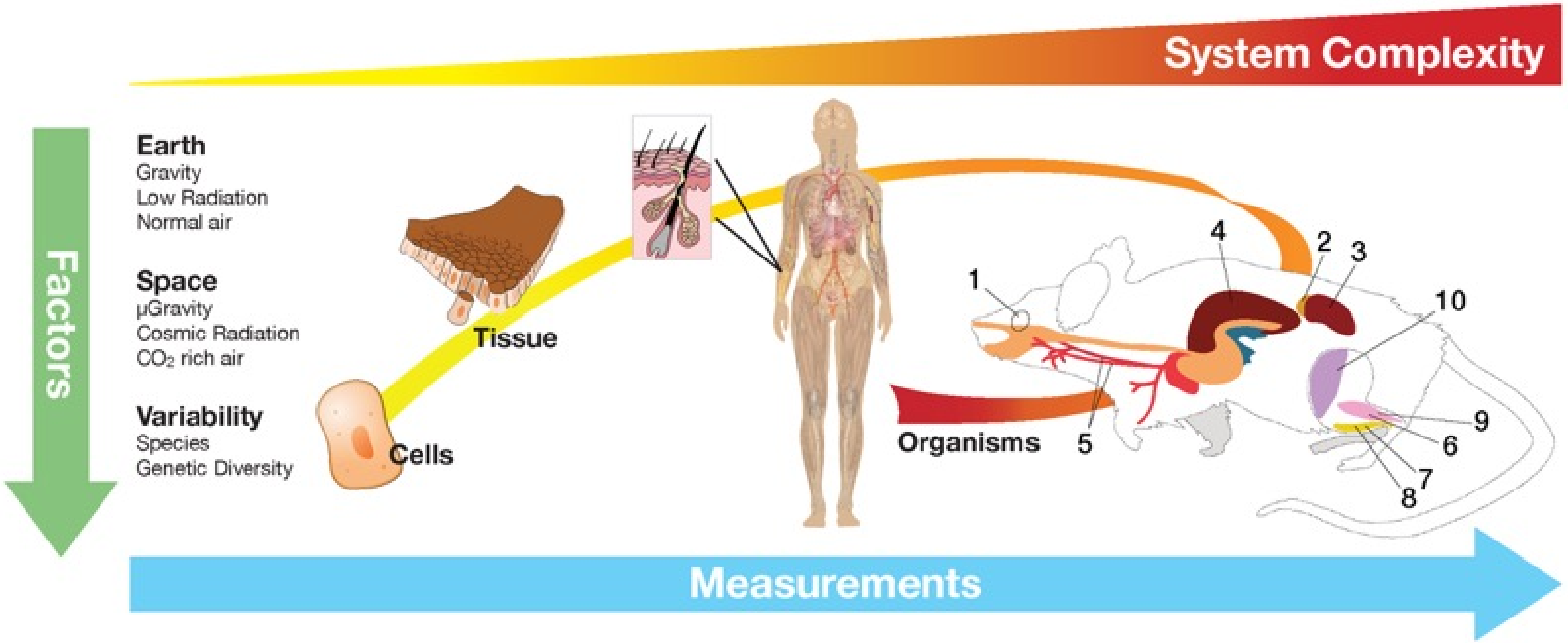


Figure 1 | **The variability of mitochondrial disease manifestations.** Mitochondrial diseases can manifest both in children and in adults, and can present in various organs, including in multiple organs that may have no apparent functional links to each other, such as the brain and liver, or pancreatic 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.

Nat Rev Mol Cell Biol. 2018 Feb;19(2):77-92. doi: 10.1038/nrm.2017.66.

Multi-Omics Analysis using GeneLab database recognizes Mitochondrial Dysfunction as a mediator of spaceflight health risks



Transcriptomics, Proteomics, Epigenetics, Metabolomics

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

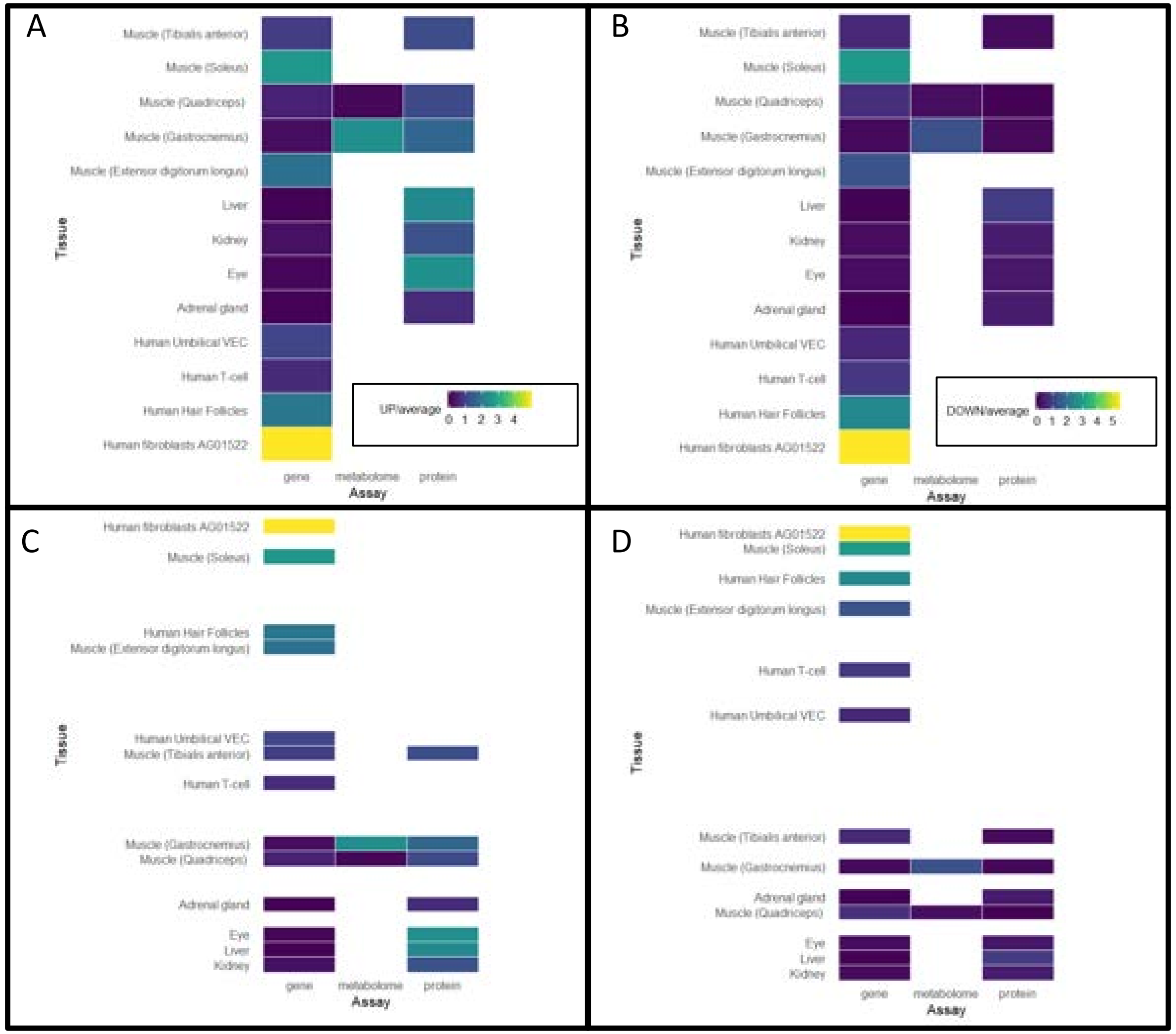
- Hair follicles

Physiological

Astronaut Physiological Data

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

Quantitative Response to Spaceflight Global view of the data



Deanne Taylor Hossein Fazelinia Komal Rathi

Children's Hospital of Philadelphia

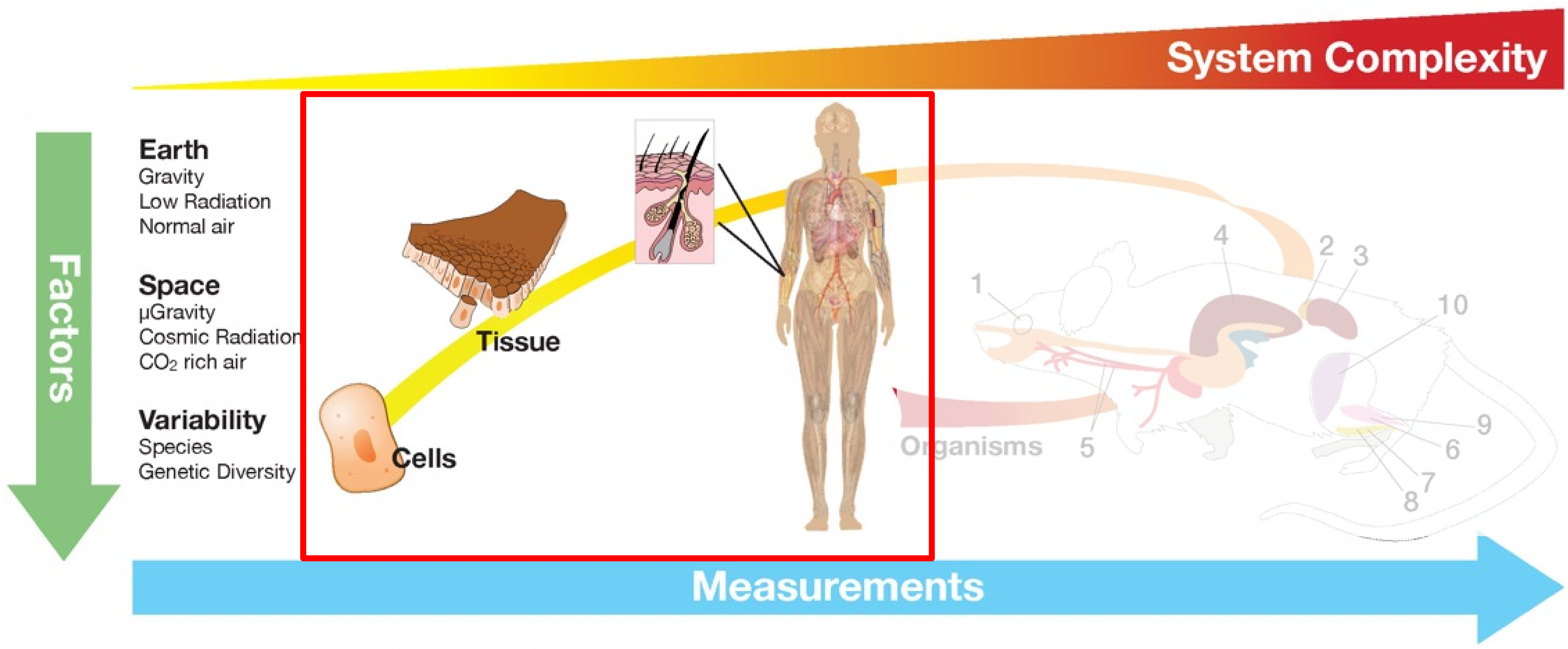
Perelman School of Medicine University of Pennsylvania

Chris Mason Cem Meydan Jonathan Foox

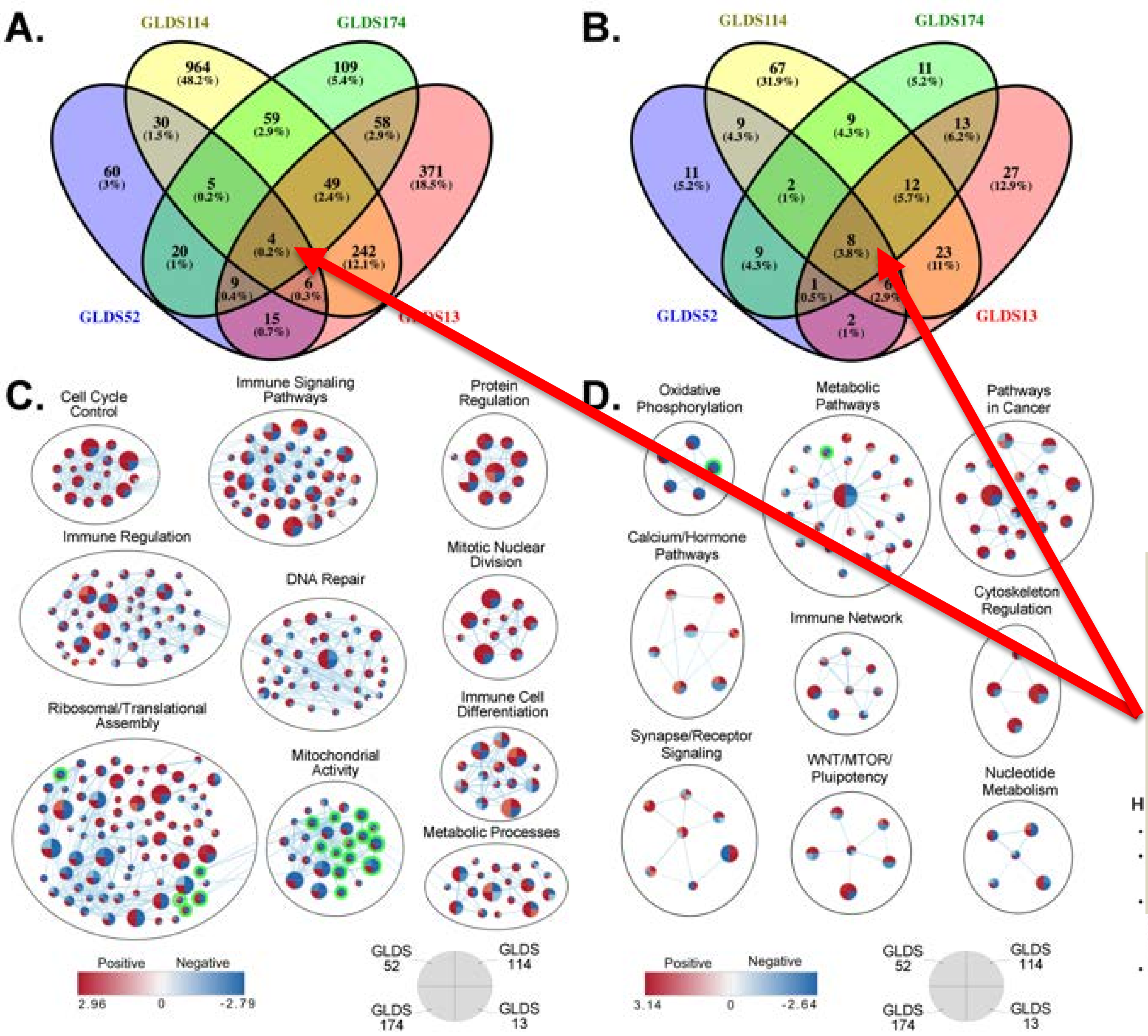
Cornell University

Sylvain Costes

In Vitro Human Dataset Analyses Reveals Conserved Mitochondrial Response to Spaceflight



In Vitro Human Dataset Analyses Reveals Conserved Mitochondrial Response to Spaceflight



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

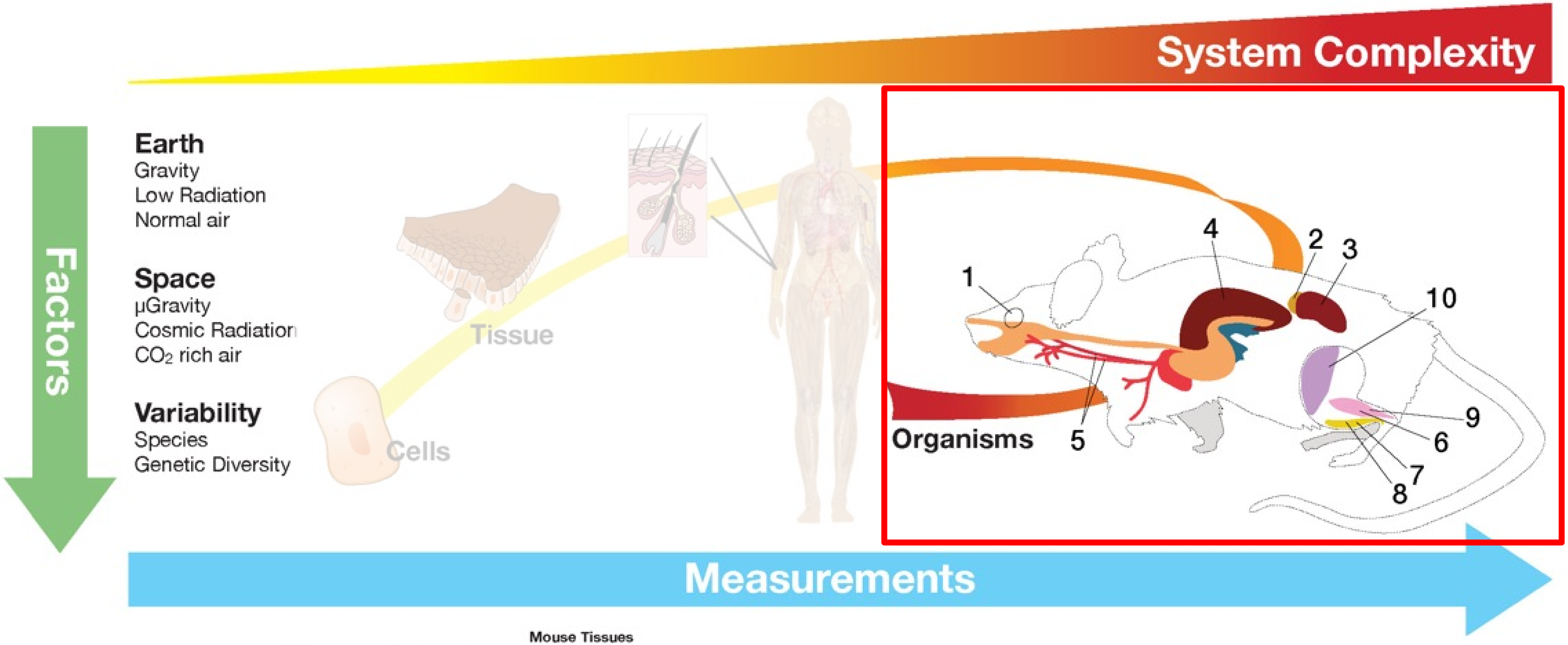
Yared Kidane

SCOTTISH RITE HOSPITAL FOR CHILDREN

HAMPTON UNIVERSITY

THE STANDARD OF EXCELLENCE

Multi-Omics Analysis on mice flown to ISS reveals Mitochondrial driven response stemming from the liver



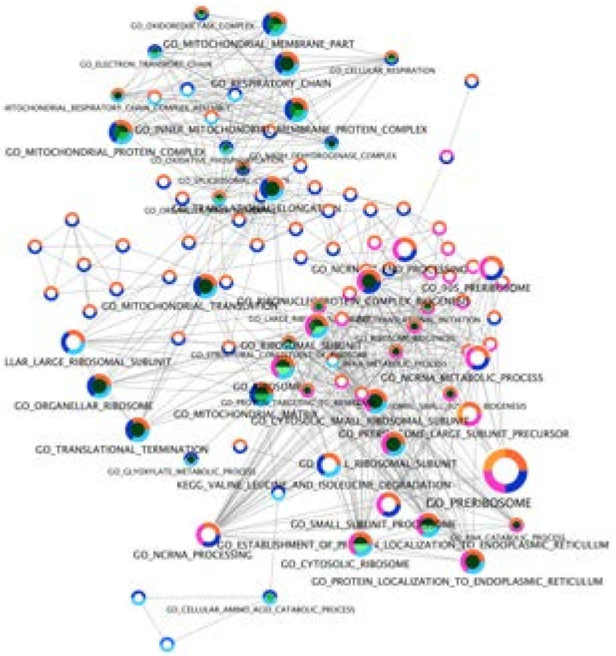
Mouse Tissues

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)

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

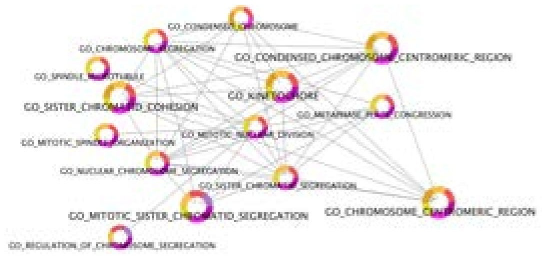
Multi-Omics Analysis on mice flown to ISS reveals Mitochondrial driven response stemming from the liver

A) Mitochondrial Activity

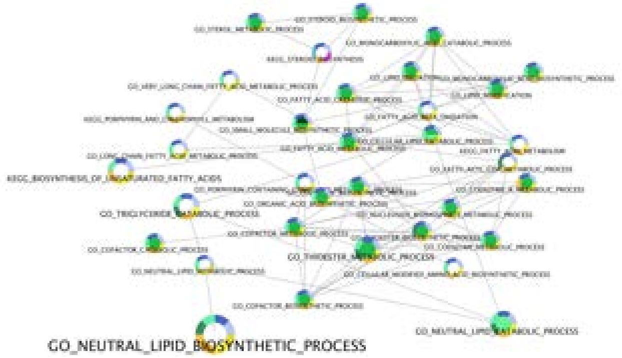


B) Ribosome and Translation

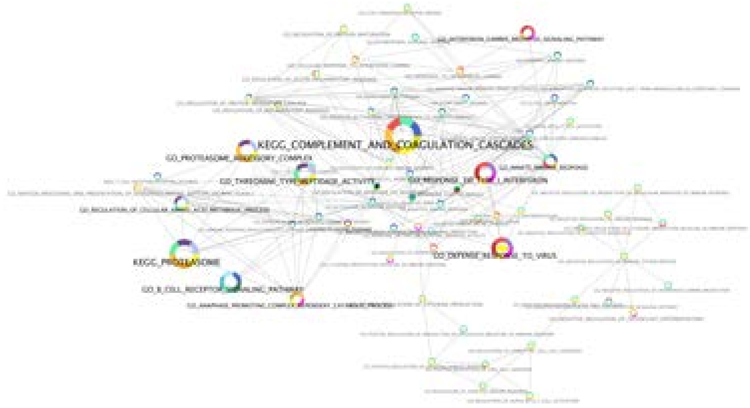
C) Cell Cycle



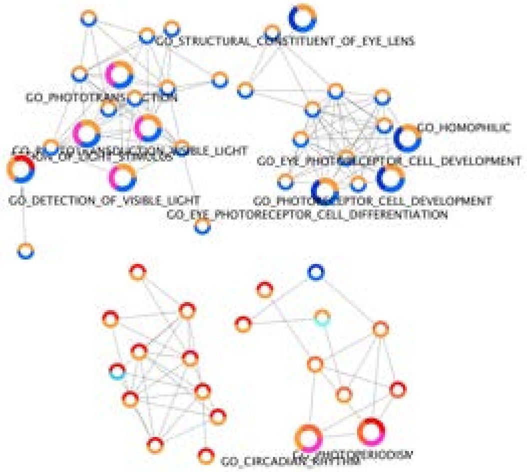
D) Lipid Metabolism



E) Immune Response



F) Photoreceptor Activity / Circadian Rhythm



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

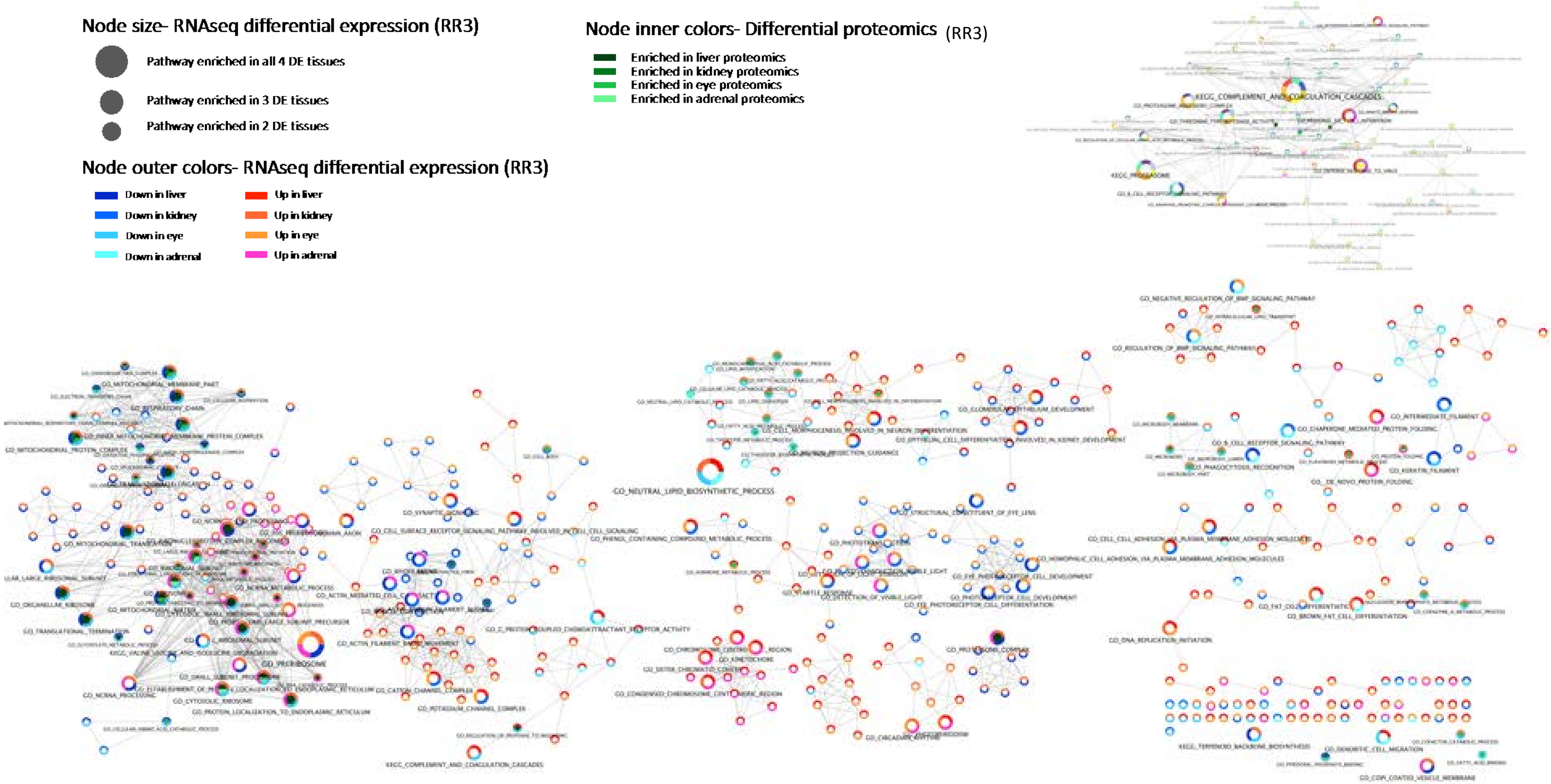
UNIVERSITY of CALIFORNIA, SAN DIEGO
SCHOOL OF MEDICINE


Gary Hardiman


Willian da Silveira

QUEEN'S UNIVERSITY BELFAST

Cross-tissue, cross-omics pathway analysis reveals a convergence on key dysregulated processes



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

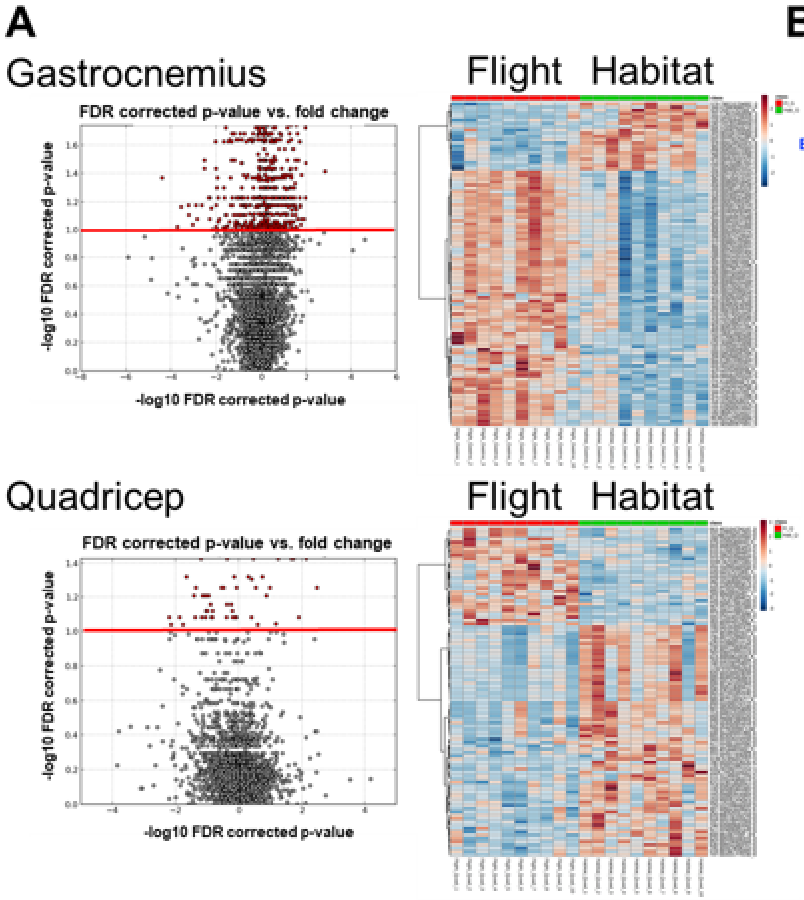

Kathleen Fisch Brin Rosenthal

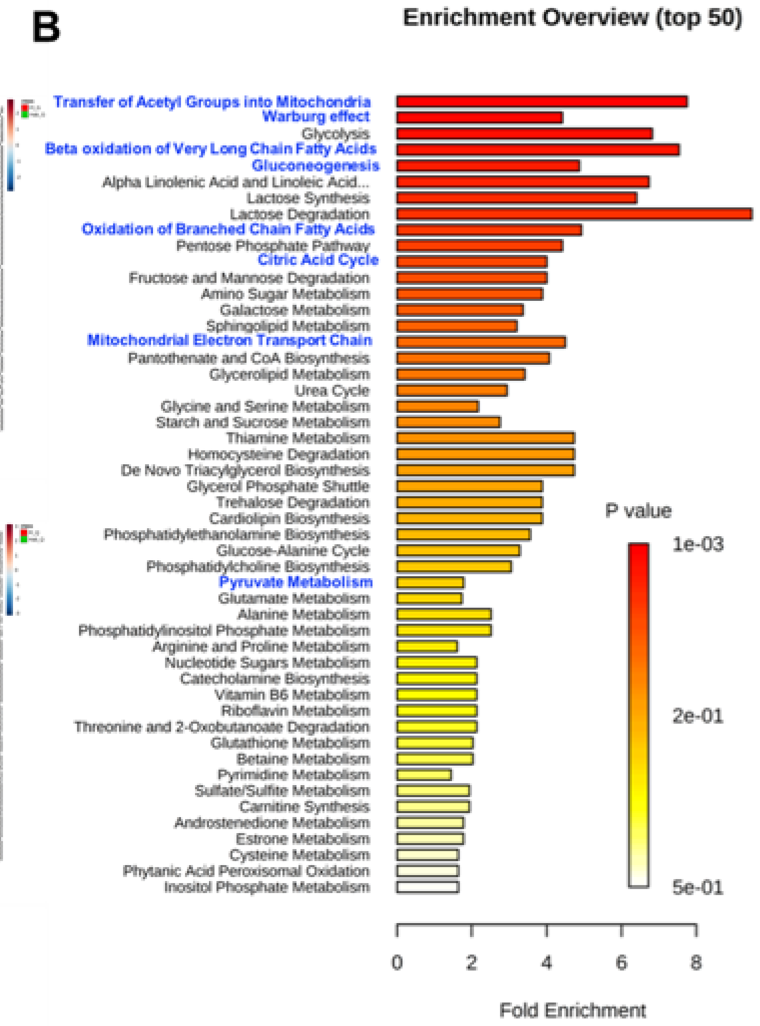
UNIVERSITY of CALIFORNIA, SAN DIEGO
SCHOOL OF MEDICINE


Gary Hardiman Willian da Silveira

QUEEN'S UNIVERSITY BELFAST

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





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.

- 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

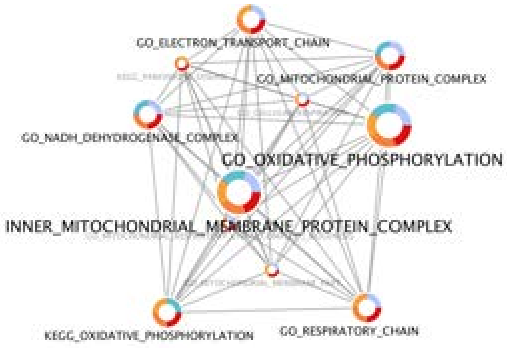
GEORGETOWN UNIVERSITY
Georgetown University Medical Center

Jeffrey Scott Willey

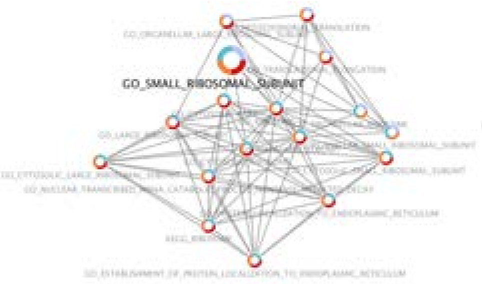
WAKE FOREST UNIVERSITY

Metabolomics Related to Proteomic and Transcriptomic data

C) Mitochondrial Activity

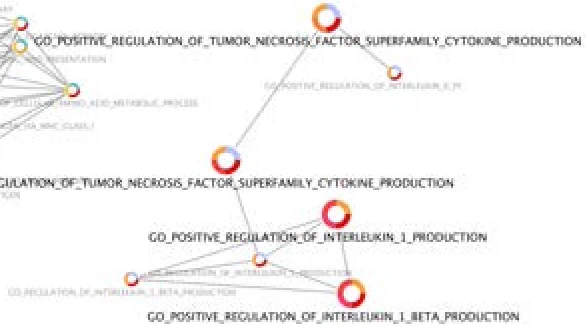


D) Ribosome and Translation



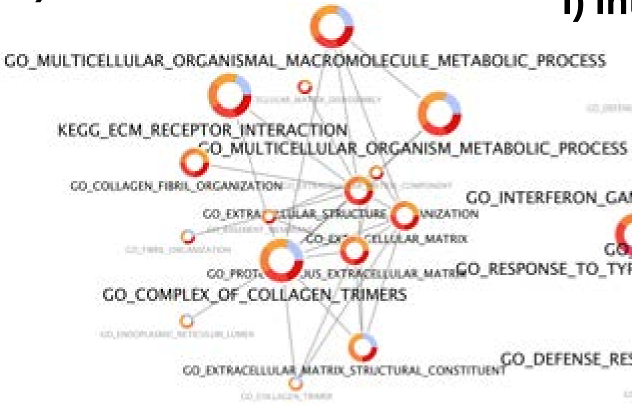
E) Proteasome

F) TNF/IL1 Response



G) Sympathetic and Feeding Behavior

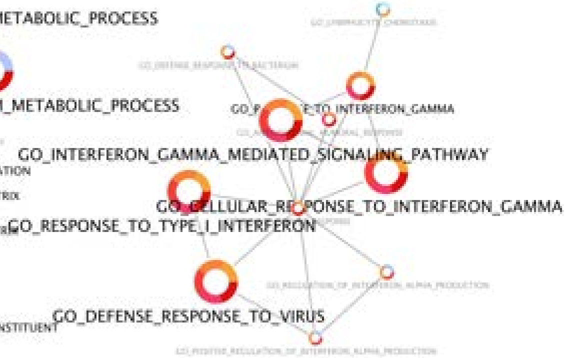
H) Metabolism and ECM



Node outer colors- RNAseq differential expression

- Down in carotid
- Down in EDL
- Down in GST
- Down in Quad
- Down in SLS
- Down in TA
- Up in carotid
- Up in EDL
- Up in GST
- Up in Quad
- Up in SLS
- Up in TA

I) Interferon Response



Node outer colors- RNAseq differential expression

- Down in carotid
- Down in EDL
- Down in GST
- Down in Quad
- Down in SLS
- Down in TA
- Up in carotid
- Up in EDL
- Up in GST
- Up in Quad
- Up in SLS
- Up in TA

Kathleen Fisch

Brin Rosenthal

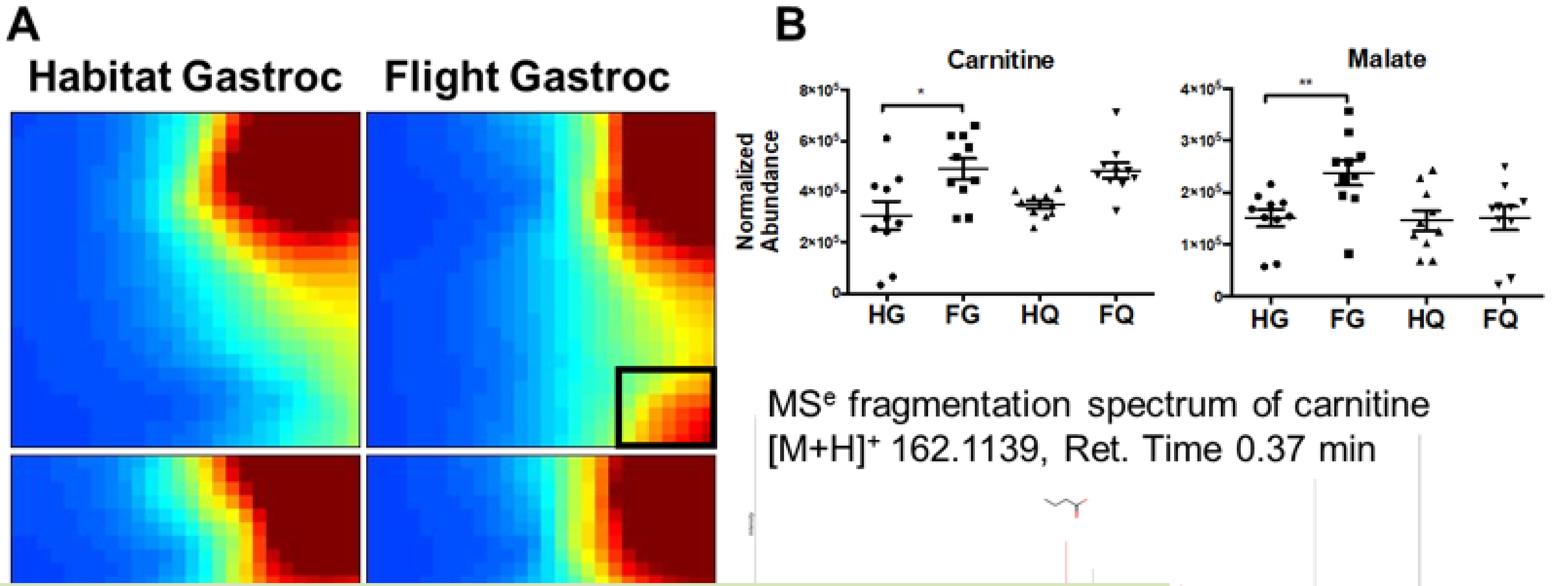
UNIVERSITY of CALIFORNIA, SAN DIEGO
SCHOOL OF MEDICINE

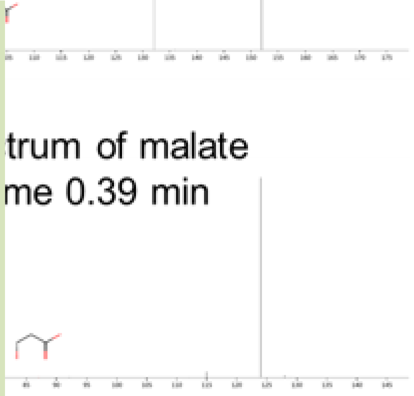
Gary Hardiman

Willian da Silveira

QUEEN'S UNIVERSITY BELFAST

Global Metabolomic Shifts and Specific Mitochondrial related factors





"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

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 QI. Levels are depicted as mean ± standard error of the mean. * $p<0.05$, ** $p<0.01$.

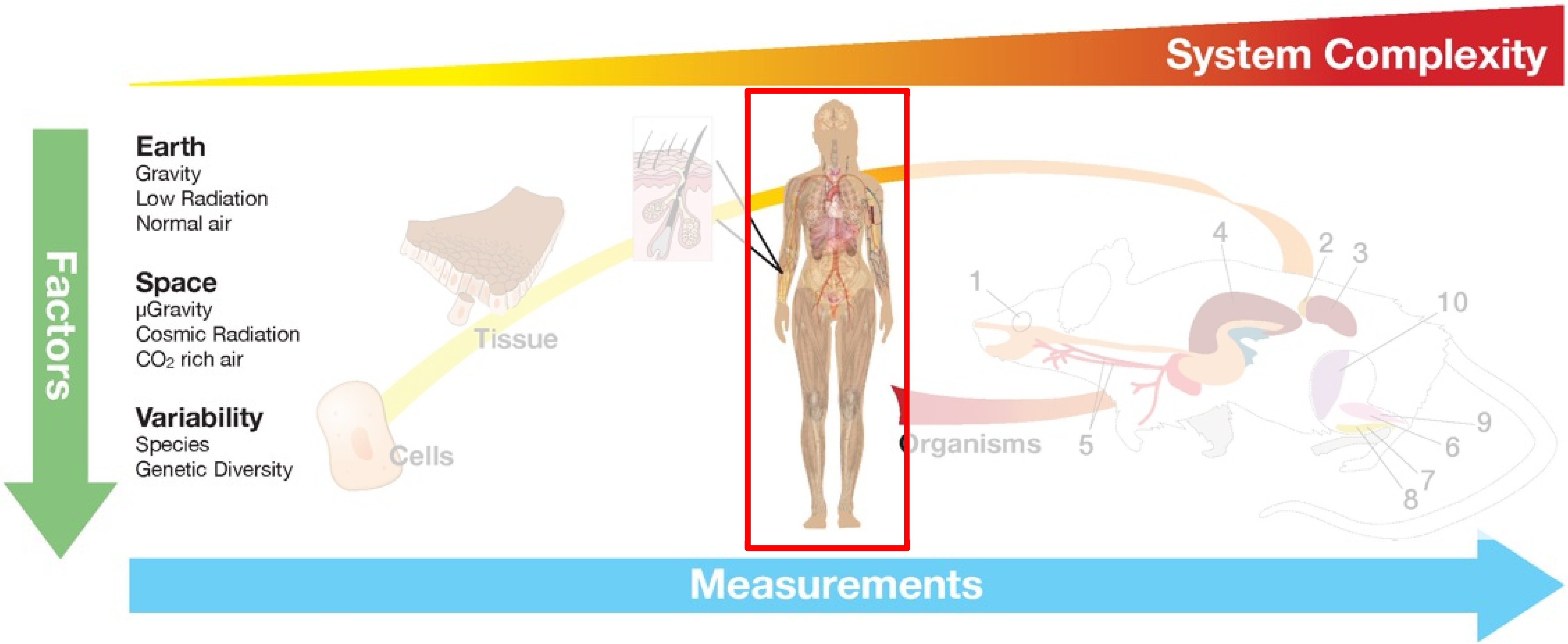
Evagelia C. Laiakis

Georgetown University
Georgetown University Medical Center

Jeffrey Scott Willey

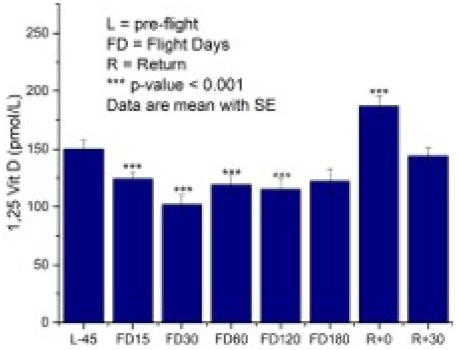
Wake Forest University

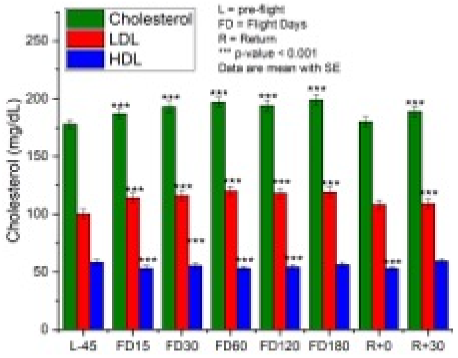
Astronaut Physiological Factors Confirm Omics *in vitro* and *in vivo* analysis!

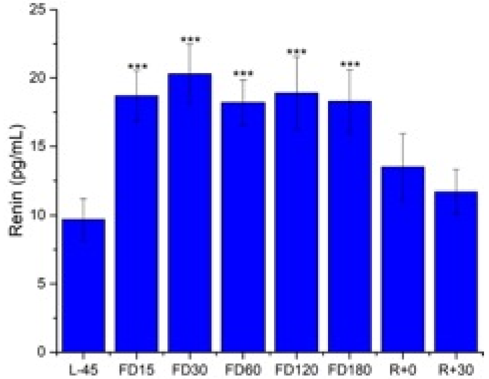


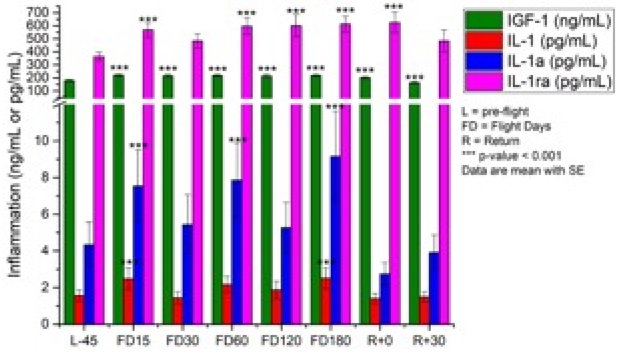
Astronaut Physiological Factors Confirm Omics *in vitro* and *in vivo* analysis!

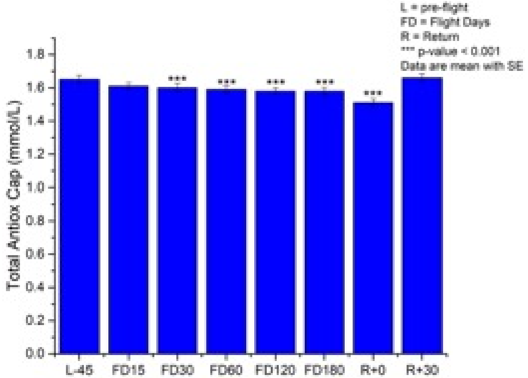
Can cause bone loss

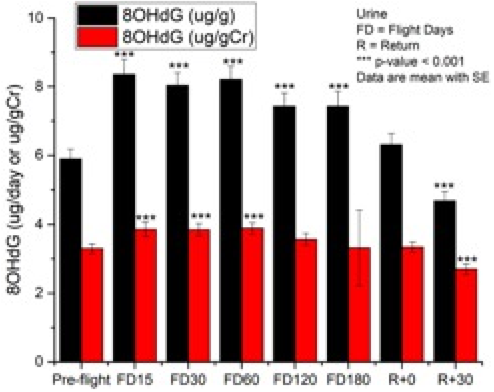


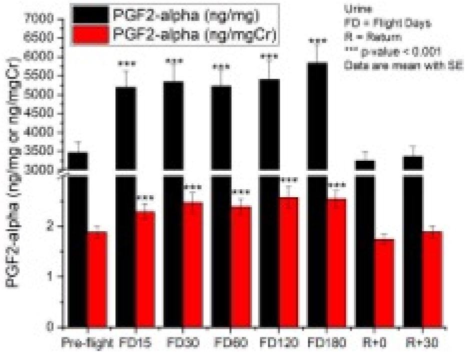


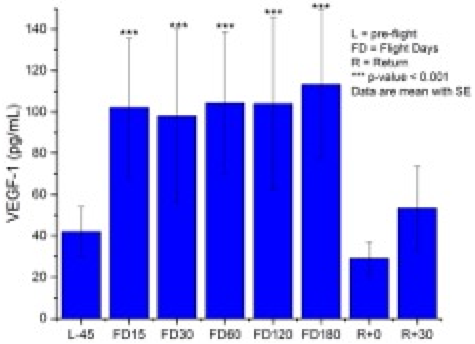








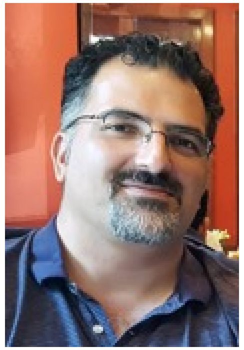




Scott Smith

Sara Zwart

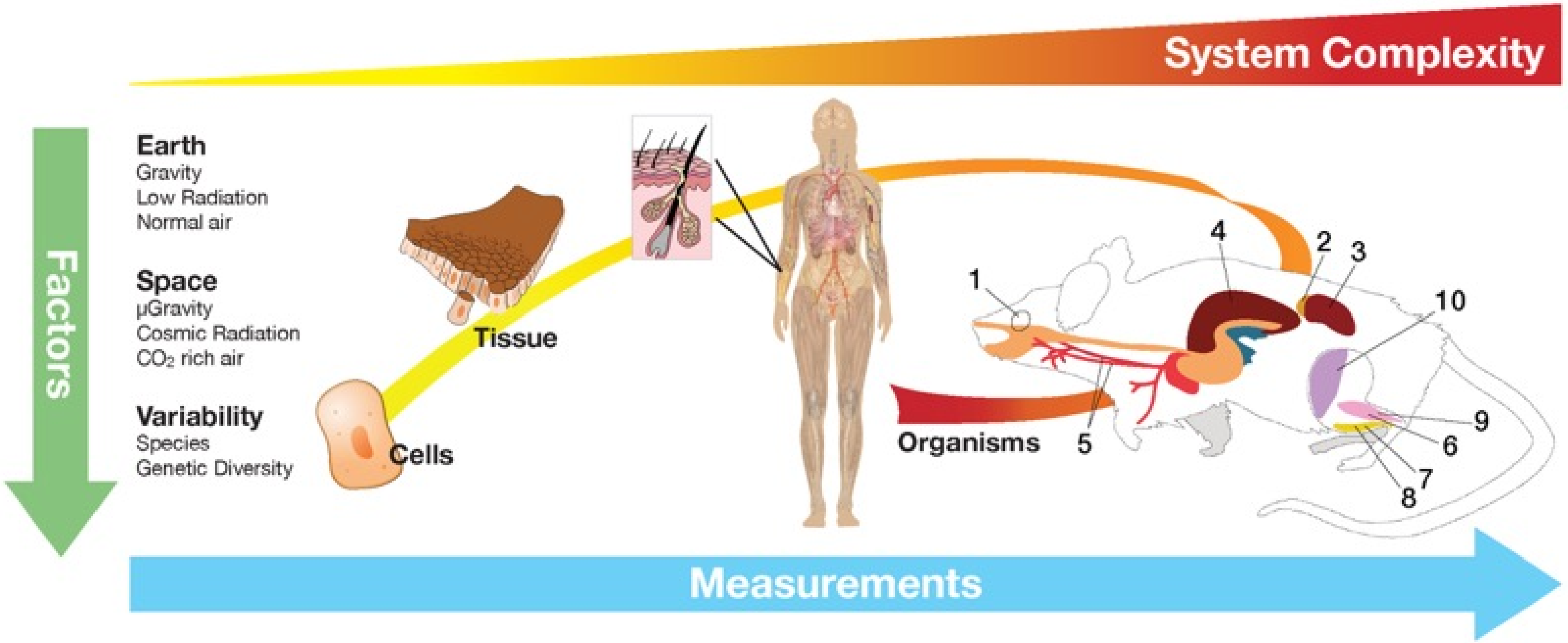
SPACE CENTER HOUSTON
Manned Space Flight Education Foundation



Afshin Beheshti

Ames Research Center

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



Transcriptomics, Proteomics, Epigenetics, Metabolomics

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)

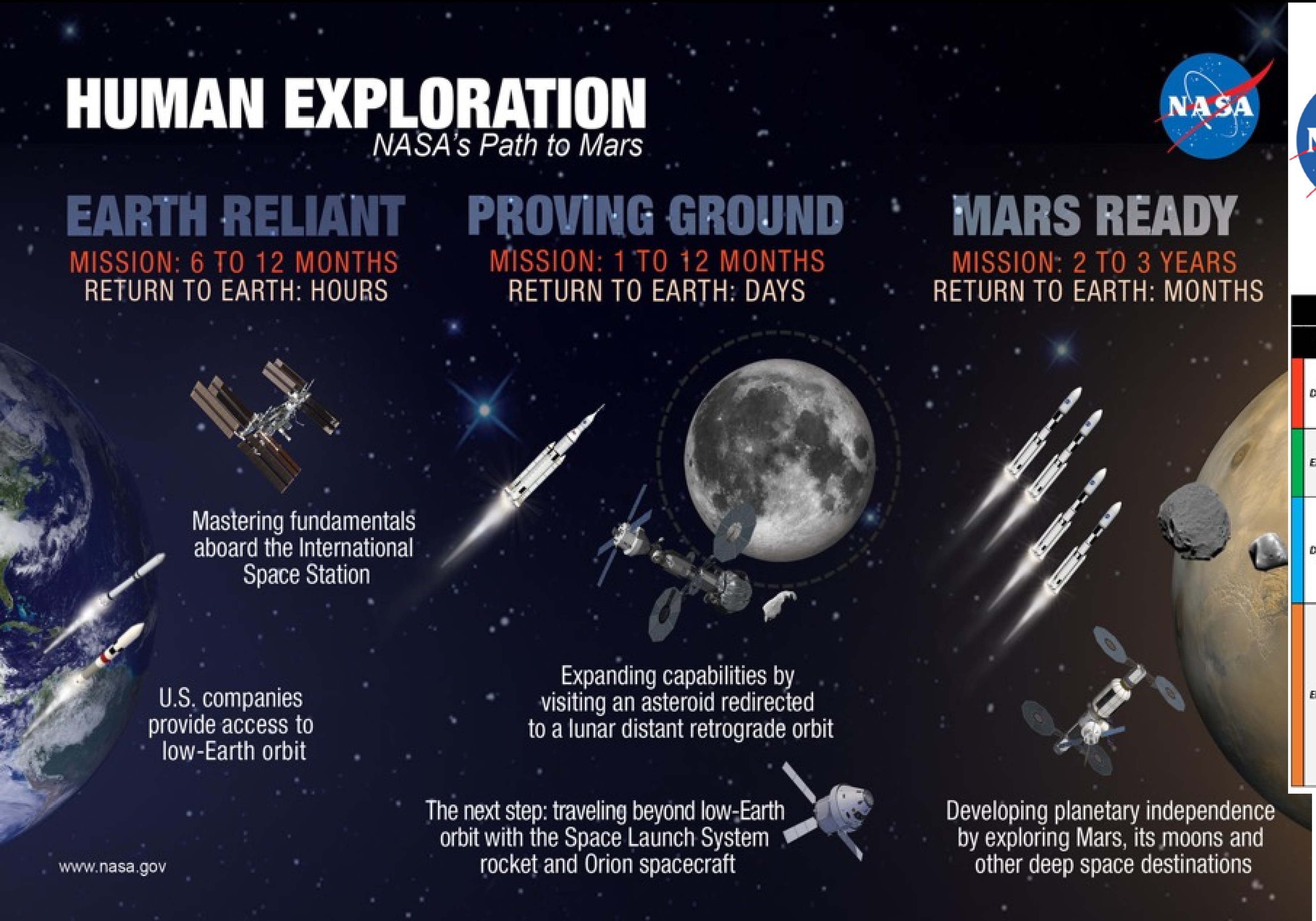
Human Tissues
- Hair follicles

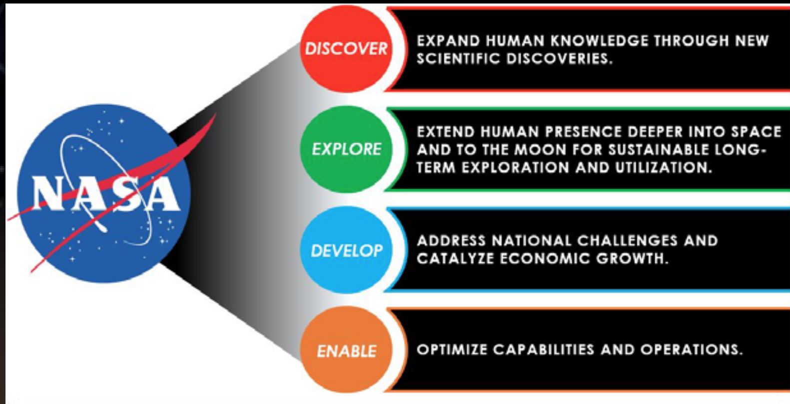
Physiological

Astronaut Physiological Data
- 1,25 Vitamin D
- Antiox Cap
- Cholesterol
- LDL
- HDL
- IGF-1
- IL-1
- IL-α
- IL-1rα
- PGF2-α
- Renin
- VEGF-1
- 8OHdG

- **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!





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.

Acknowledgements

https://genelab.nasa.gov/