National Aeronautics and Space Administration

The NASA GeneLab Project

Sylvain V. Costes, PhD
GeneLab Project Manager

Special Seminar

Genetics, Genomics, & Systems Biology

University of Chicago

September 25, 2018

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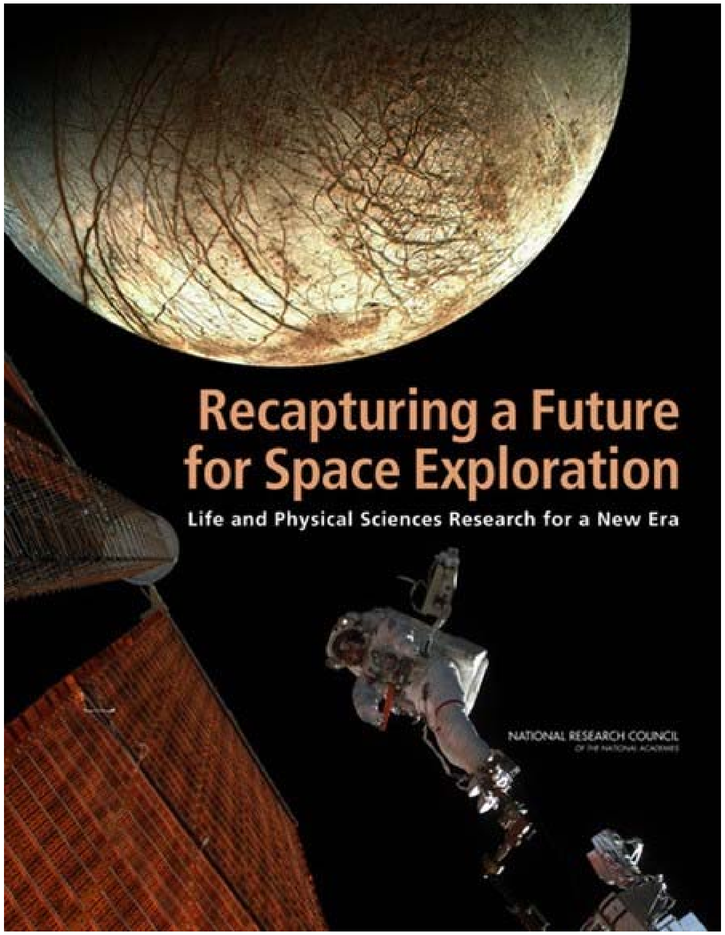
NRC Decadal Survey



"*…**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…*"

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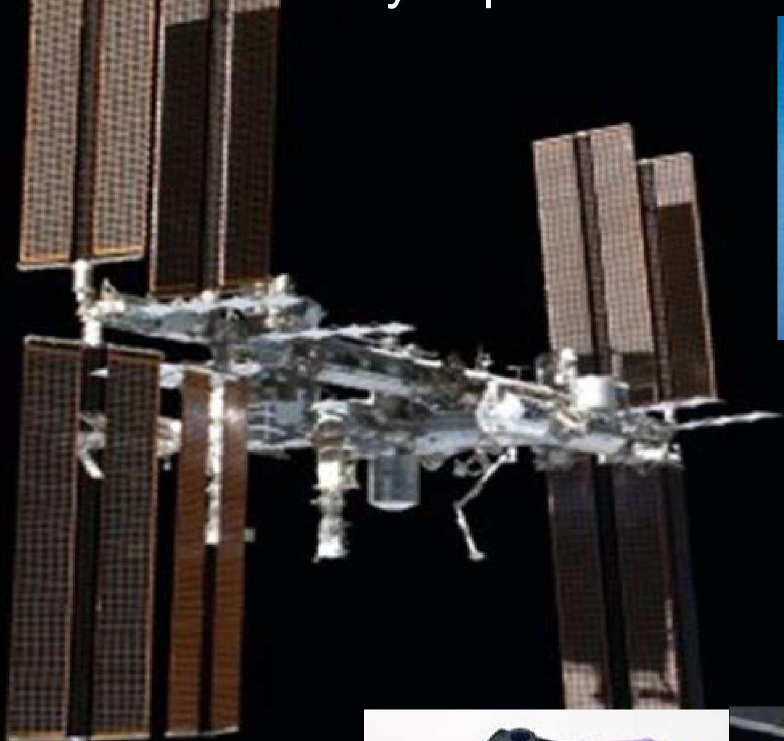
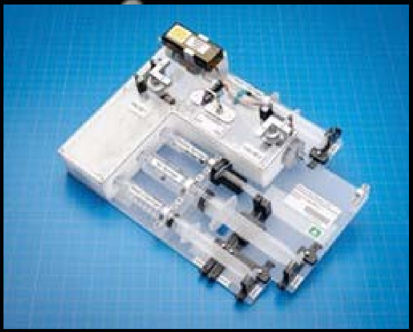
Omics Acquisition in Space is Now a Reality

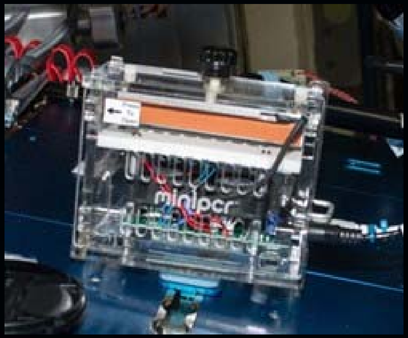
This is truly an exciting time for cellular and molecular biology, omics and biomedicine research on ISS with these amazing additions to the suite of ISS Laboratory capabilities.





Sample Preparation Module

Oxford Nanopore MinION Gene Sequencer



Mini-PCR

Cepheid Smart Cycler qRT-PCR

Reaction tube containing lyophilized chemical assay bead (proprietary)

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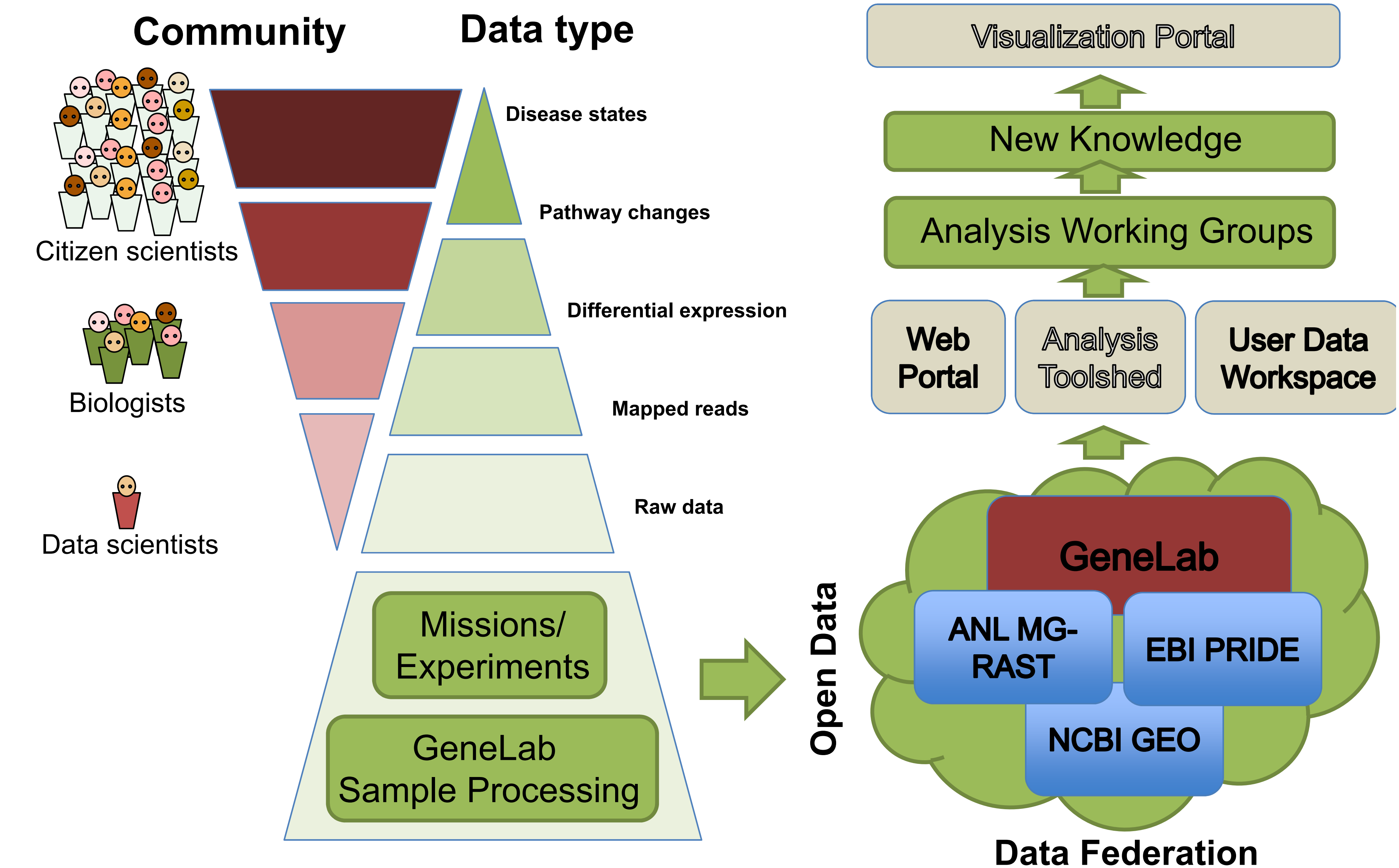
GeneLab Team

GeneLab Data Democratization



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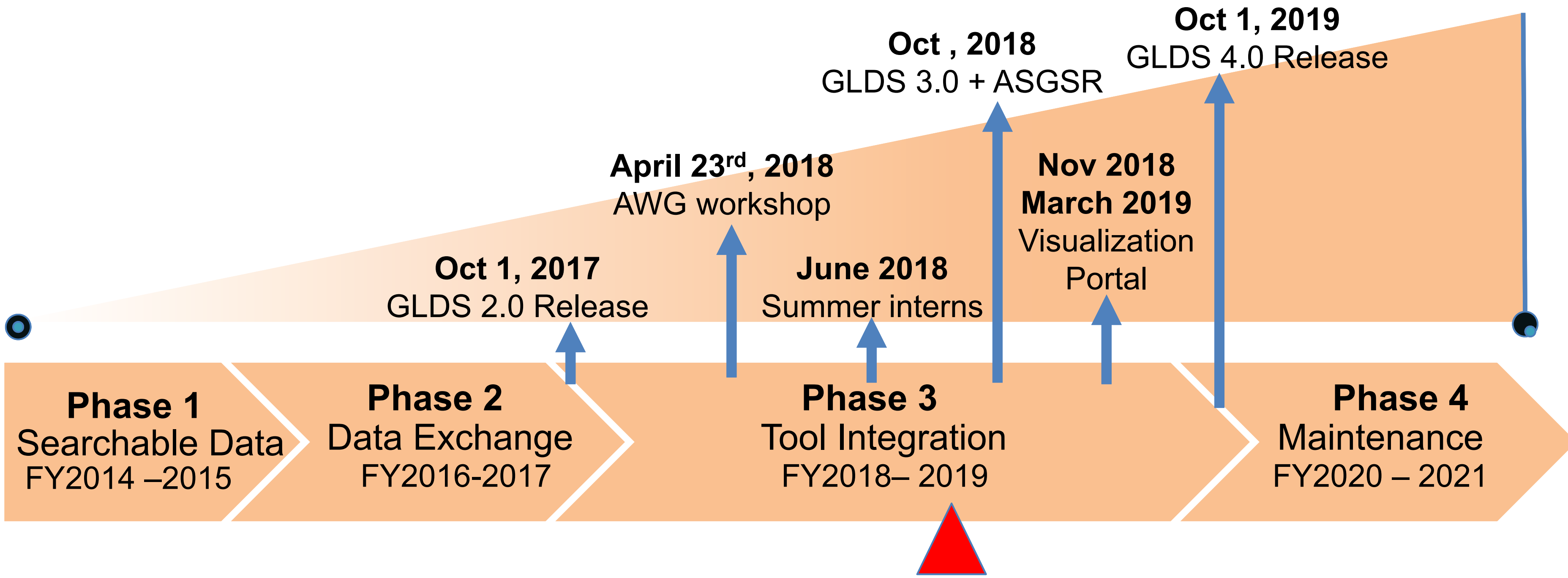
Phased Implementation



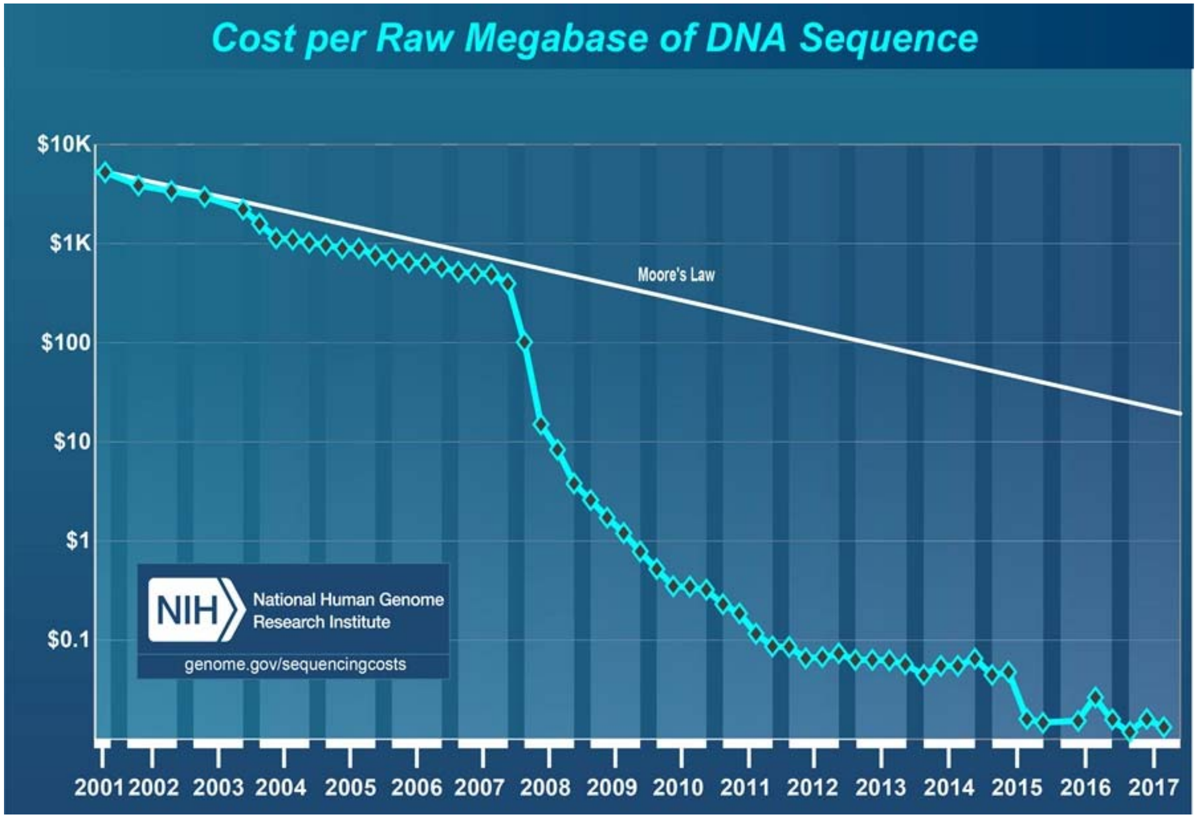
Data System
- ✓ Public Website
- ✓ Searchable Data Repository
- ✓ Top Level Requirements
- ✓ New Data and Legacy Data

Data System
- ✓ Link to Public Databases via Data Federation
- ✓ Integrated Search (e.g., data mashup)

Data System
- Integrated Platform across model organisms
- Build Community via AWG
- Provide access to biocomputational tools for omics analysis
- Provide collaboration framework and tools

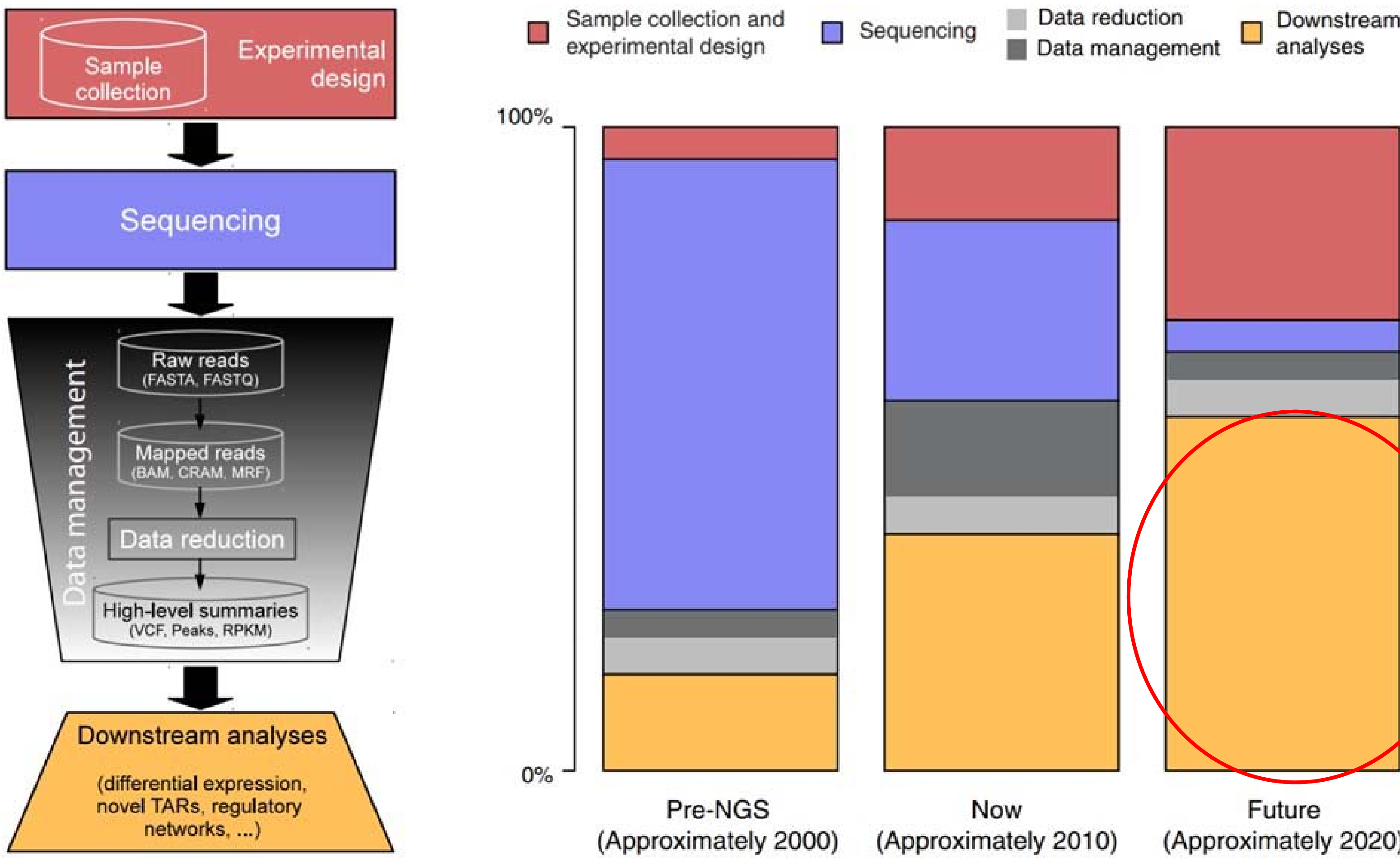
Open Source Maintenance
- User community becomes primary provider of new tools/knowledge
- Maintain integrity of data, and data system

Sequencing cost in 2017



- Labor, administration, management, utilities, reagents, and consumables
- Sequencing instruments and other large equipment (amortized over three years)
- Informatics activities directly related to sequence production (e.g., laboratory information management systems and initial data processing)
- Submission of data to a public database
- Indirect Costs (http://oamp.od.nih.gov/dfas/faq/indirect-costs#difference) as they relate to the above items

The real cost of OMICS



Sboner et al. Genome Biology 2011 12:125 doi:10.1186/gb-2011-12-8-125

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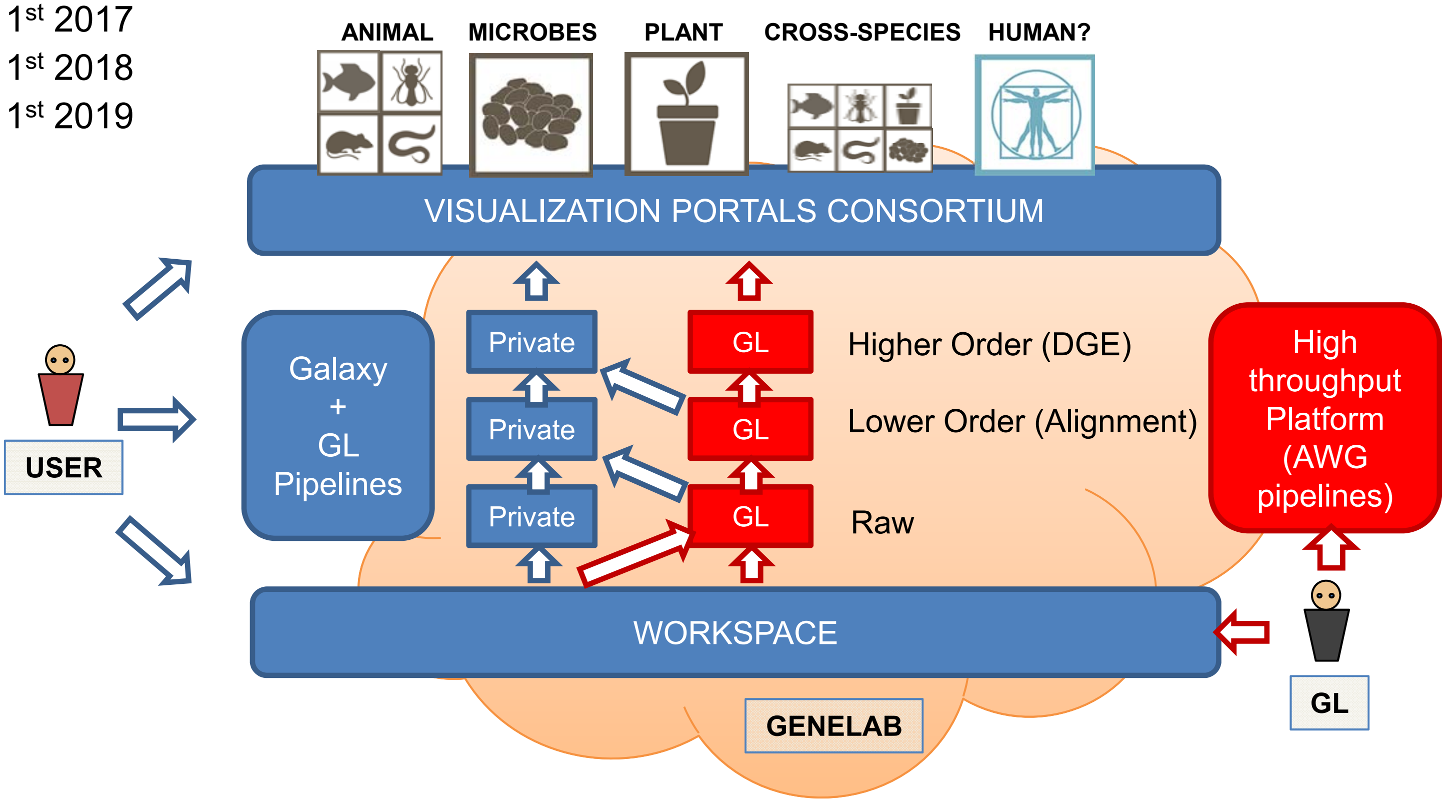
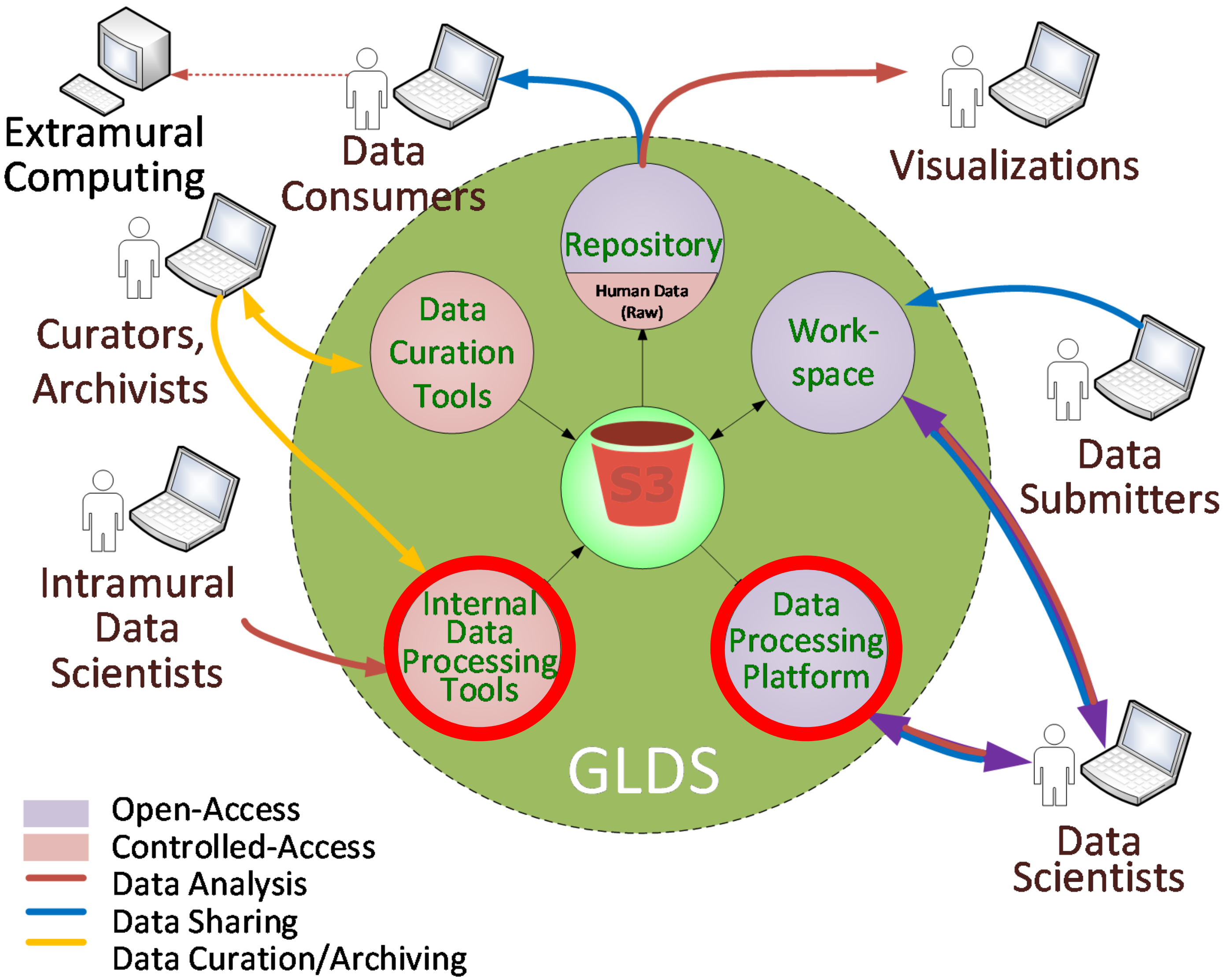
From GLDS 2.0 to GLDS 4.0

GLDS 2.0 – Oct 1st 2017
GLDS 3.0 – Oct 1st 2018
GLDS 4.0 – Oct 1st 2019



GLDS Systems Architecture Phase III



Guiding principles to look at GeneLab data

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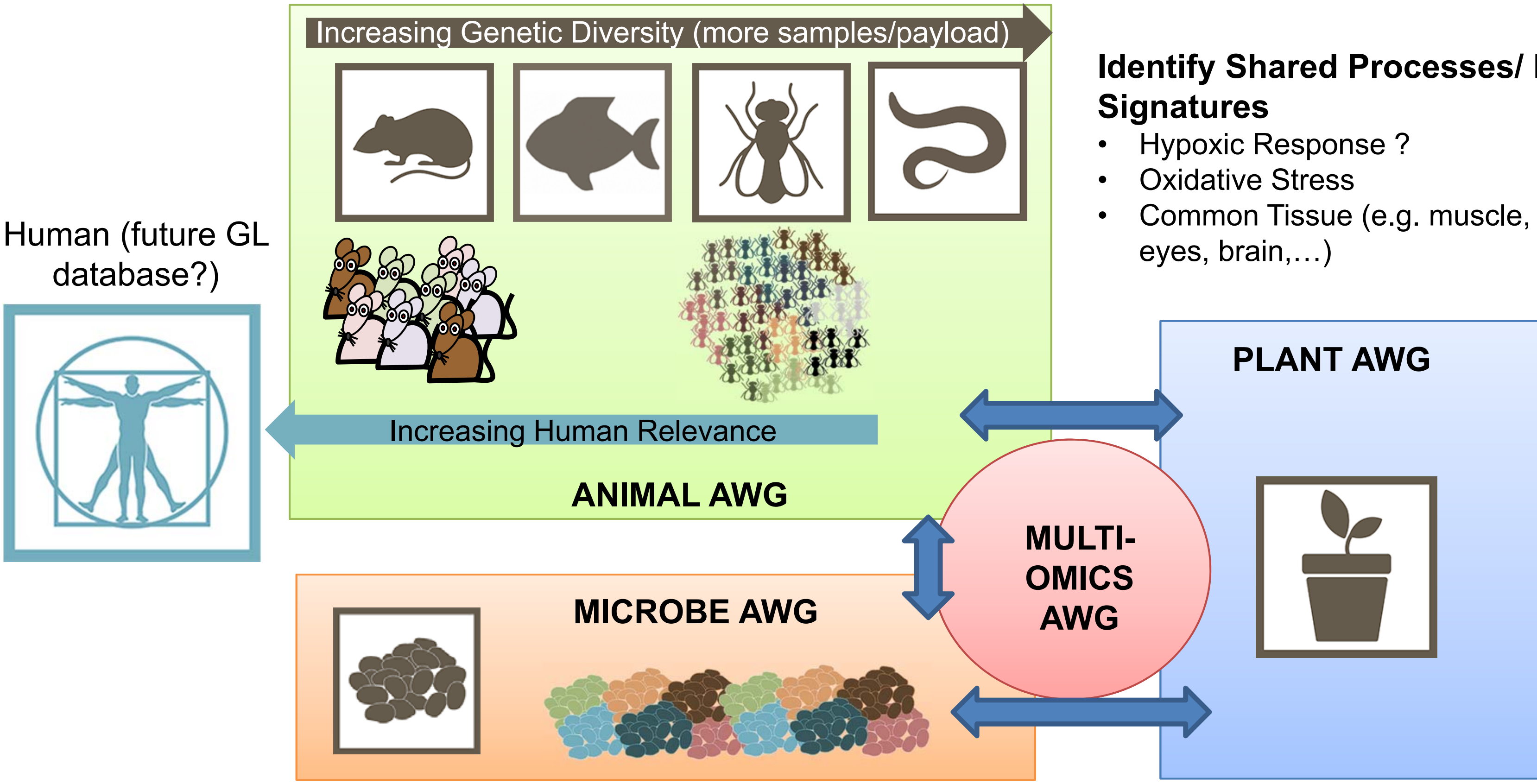

Identify Shared Processes/ Molecular Signatures

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

Overview: Database content

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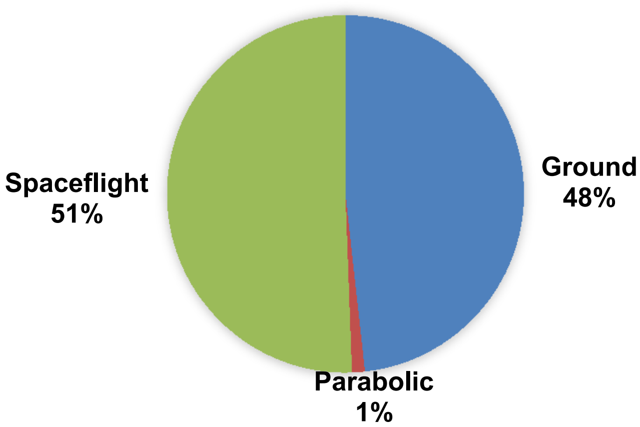
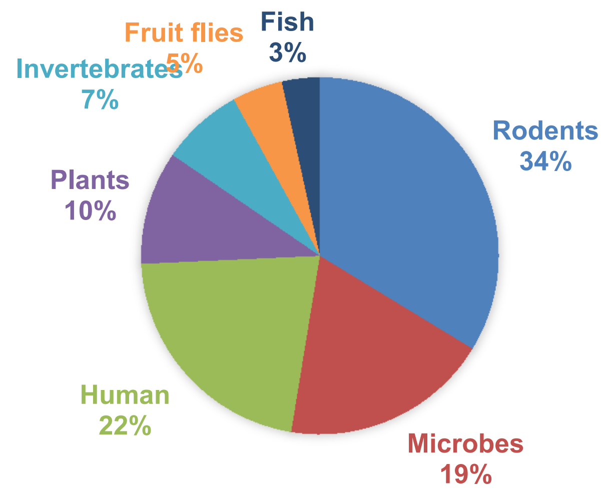
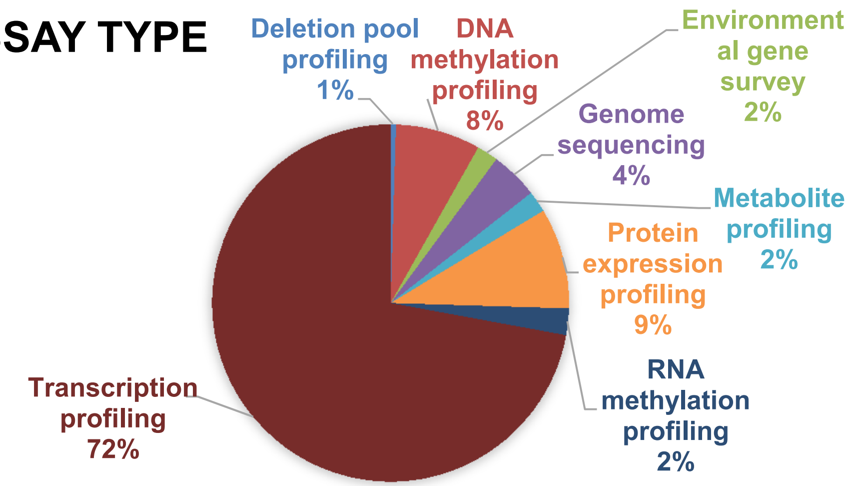
STUDY TYPE



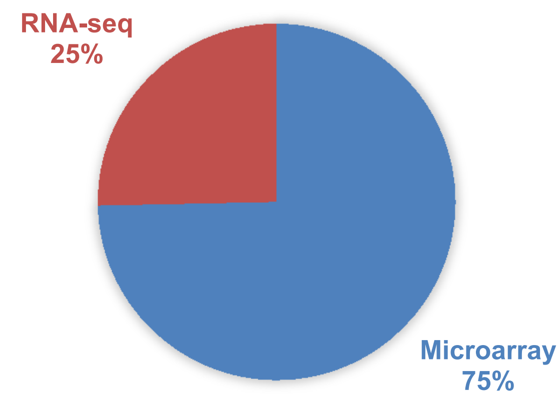
ORGANISM



ASSAY TYPE



TRANSCRIPTION PROFILING



Total # of studies: 172

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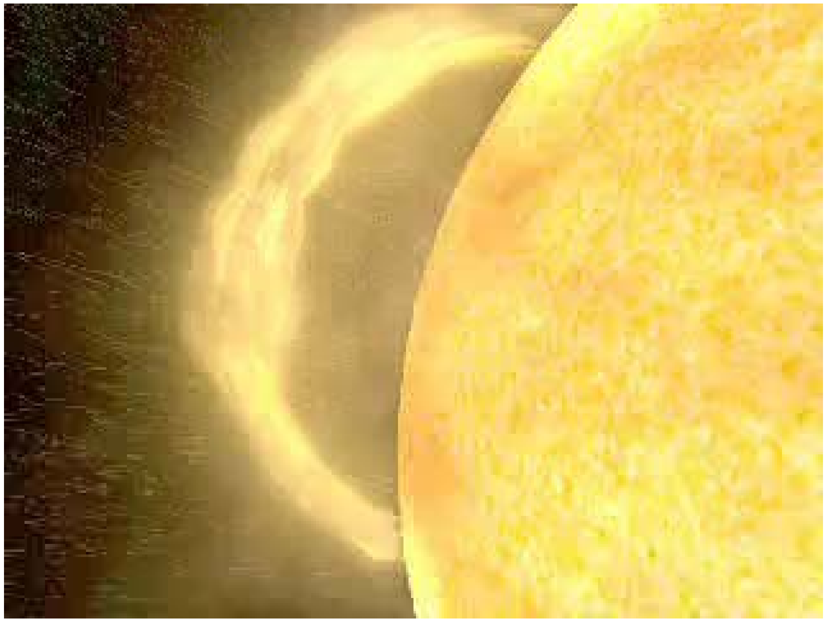
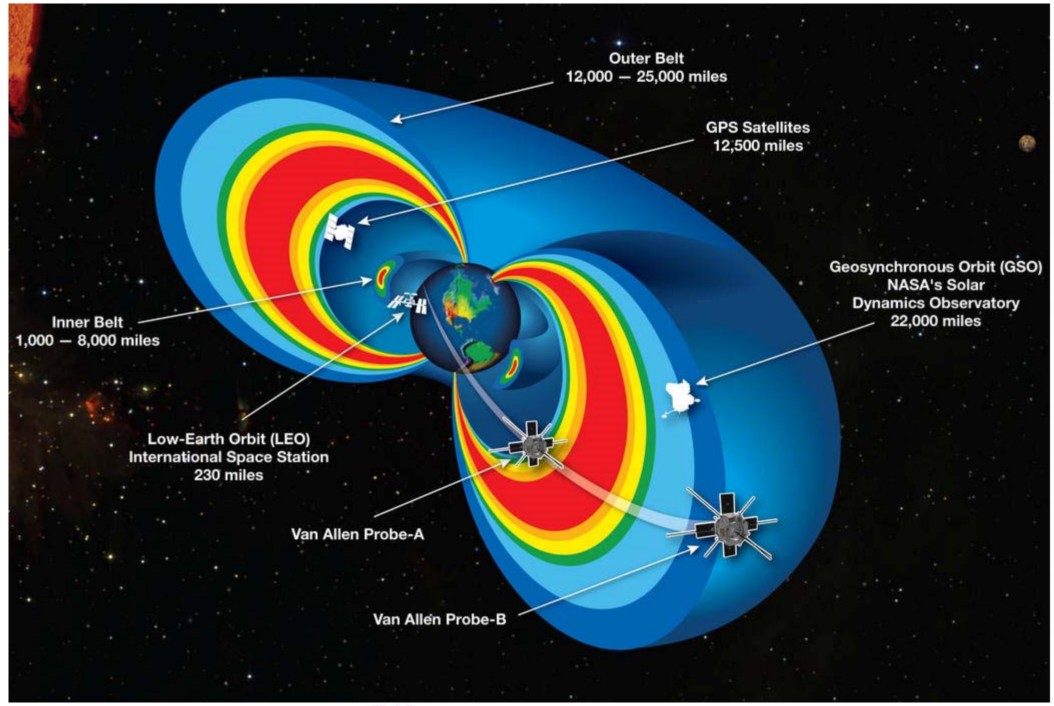
The Radiation Factor

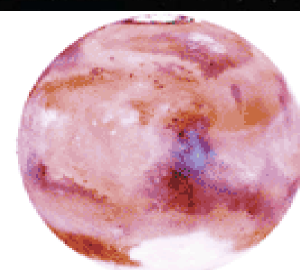




2½ Years, 2,600 X-Rays

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.



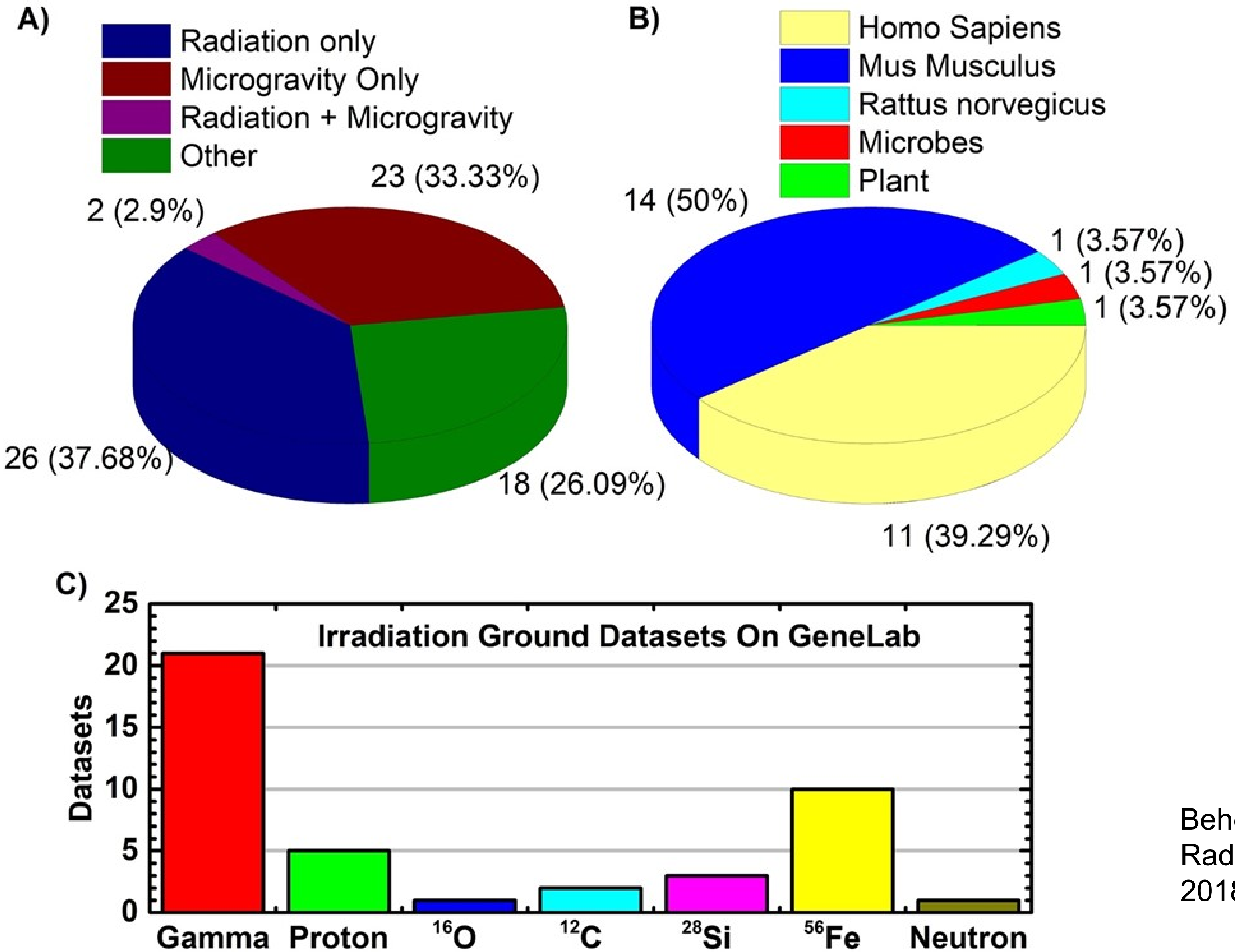
NASA

	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

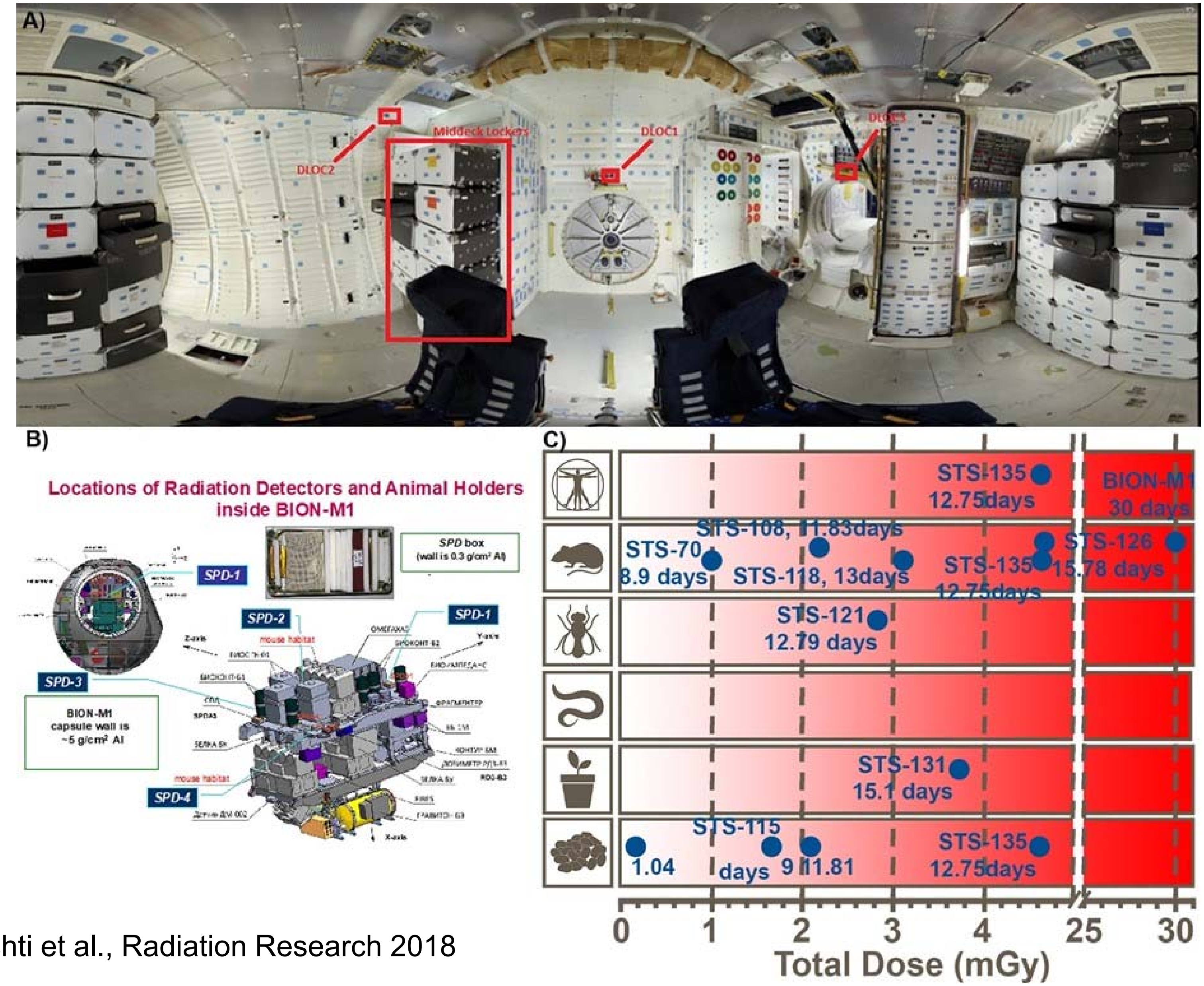
Source: Brookhaven National Laboratory, U.S. Department of Energy

69 Ground Data Sets: Radiation and simulated microgravity



Beheshti et al., Radiation Research 2018

ion Dosimetry for STS samples (ISS to follow)



Beheshti et al., Radiation Research 2018

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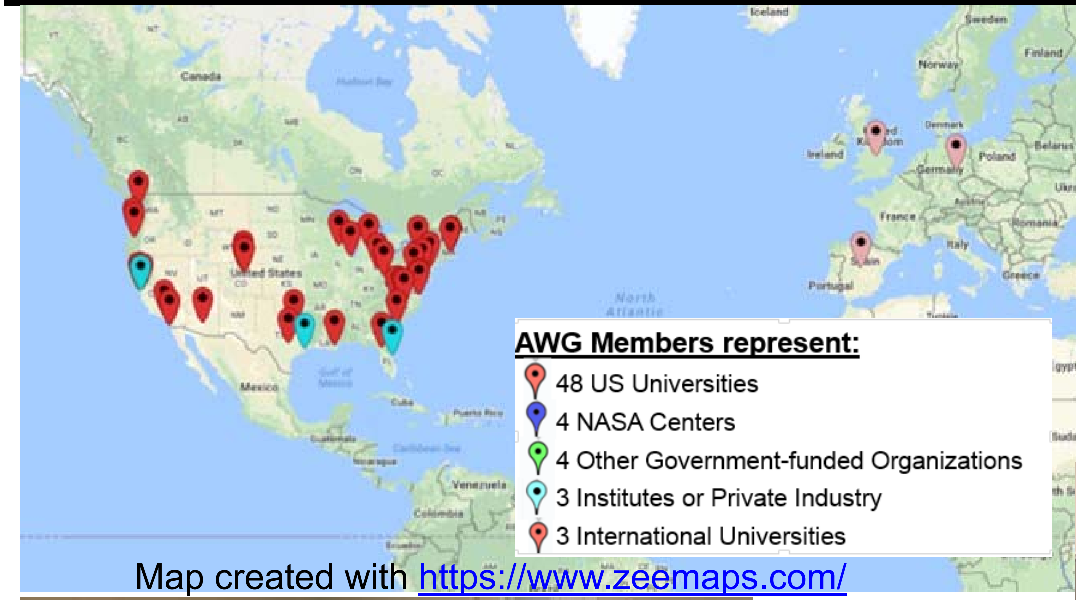
GeneLab Analysis Working Groups: Letting the scientific community take the lead



Map created with https://www.zeemaps.com/

Total AWG Members: 114

AWG Members Per Group:

Animal	47
Multi-Omics/System Biology	33
Plants	24
Microbes	21

**Some members are in multiple groups*



Annual Workshop (April 2018)

2018 Summer Internship: Generate all higher order data

- **Monthly meetings + "Homework"**
- **Deliverables:**
  - Consensus pipelines for primary analysis of data (Microarray, RNASeq, Bisulfite sequencing, Proteomics, 16S metagenomics, Whole genome metagenomics)
  - Recommendations for visualization of data

Publications using GeneLab

Year	Title	Journal	Authors	Status
2017	Validation of Methods to Assess the Immunoglobulin Gene Repertoire in Tissues Obtained from Mice on the International Space Station.	Gravit Space Res.	Rettig TA, Ward C, Pecaut MJ, Chapes SK	Published
2018	A microRNA signature and TGF-β1 response were identified as the key master regulators for spaceflight response	PLoS One	Beheshti A, Ray S, Fogle H, Berrios D, Costes SV	Published
2018	NASA GeneLab Project: Bridging Space Radiation Omics with Ground Studies Project: Bridging Space Radiation Omics with Ground Studies	Radiation Research	Beheshti A, Miller J, Kidane Y, Berrios D, Gebre SG, Costes SV	Published
2018	Global transcriptomic analysis suggests carbon dioxide as an environmental stressor in spaceflight: A GeneLab case study	Scientific Reports	Beheshti A, Cekanaviciute E, Smith DJ, Costes SV	Published
2018	Exploring the Effects of Spaceflight on Mouse Physiology using the Open Access NASA GeneLab Platform	JoVE	A Beheshti, Y Shirazi-Fard, S Choi, D Berrios, SG Gebre, JM Galazka, SV Costes	Undergoing revision
2018	GeneLab: Omics database for spaceflight experiments	Bioinformatics	S Ray, S Gebre, H Fogle, D Berrios, PB Tran , JM Galazka, S V Costes	Submitted

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Cage Effects with rodent experiments: Carbon Dioxide as an Environmental Stressor in Spaceflight

Beheshti A, Cekanaviciute E, Smith DJ, Costes SV. Global transcriptomic analysis suggests carbon dioxide as an environmental stressor in spaceflight: A systems biology GeneLab case study. Sci Rep. 2018;8(1):4191. doi: 10.1038/s41598-018-22613-1. PubMed PMID: 29520055; PMCID: PMC5843582.

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Carbon Dioxide as an Environmental Stressor in Spaceflight

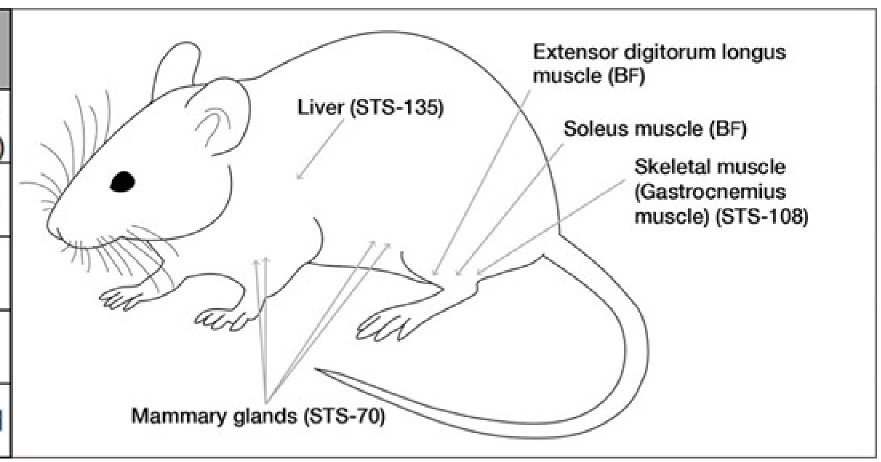
A) Cage Types

Animal Enclosure Module (AEM)

Sample vivarium cage

B)

GeneLab Study	Mission	Species	CO_2 (ppm)	Duration (days)	Tissue Type
GLDS-21	STS-108	mouse	~3000	11.8	skeletal muscle (gastrocnemius)
GLDS-111	BF	mouse	~600	30	soleus muscle
GLDS-111	BF	mouse	~600	30	extensor digitorum
GLDS-25	STS-135	mouse	~3000	13	liver
GLDS-63	STS-70	rat	~3000 (est)	9	mammary gland



Beheshti, et al., Scientific Reports, 2018

PCA Plots Suggest Strong Cage Effect

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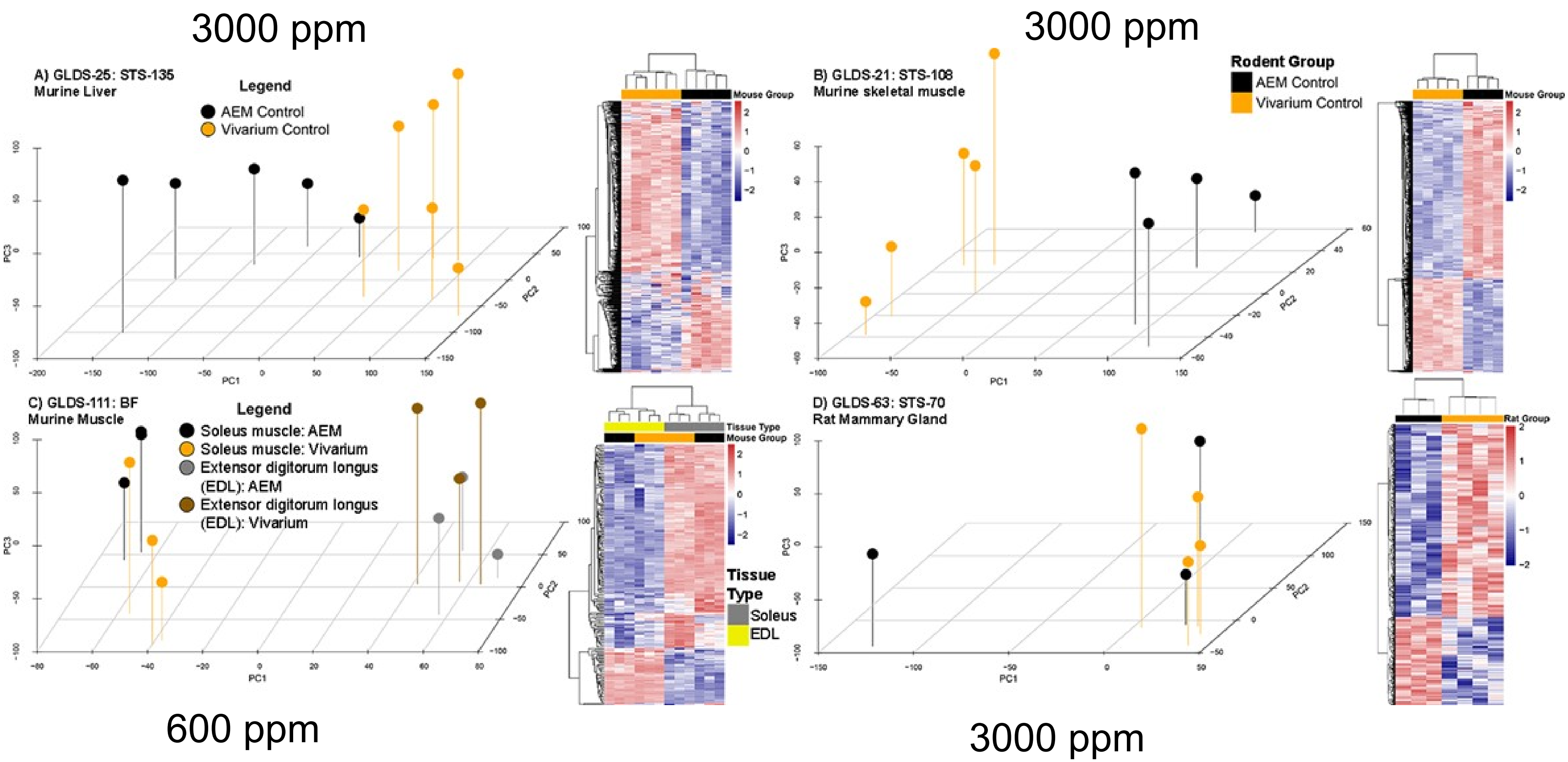
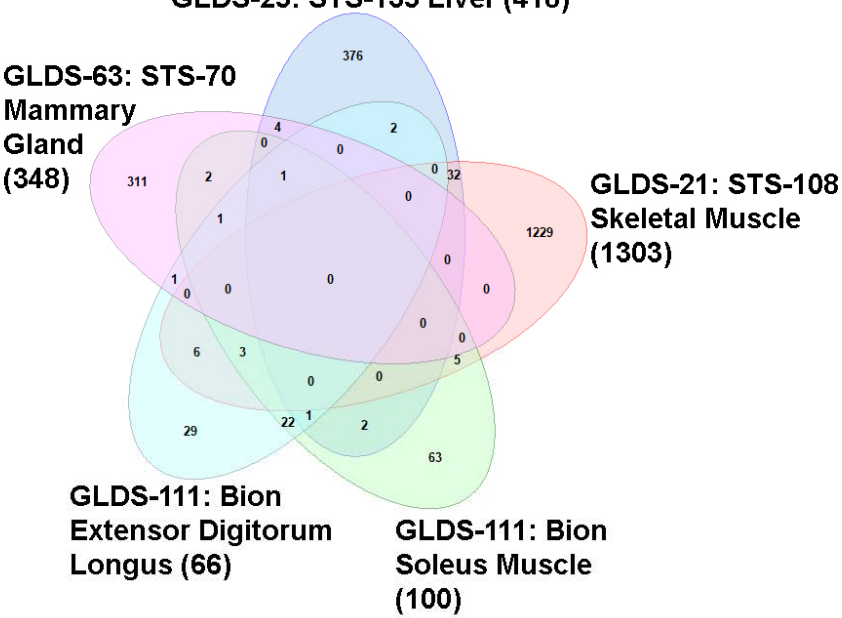


AEM = Animal Enclosure Modules (now referred to as Rodent Habitats)
Vivarium = normal ground based rodent cages

Beheshti, et al., Scientific Reports, 2018

Differential Gene Expression: Cage or CO2 Effect?

A) Venn Diagram of all significant genes



An increase in aldosterone is associated with metabolic syndrome, which is characterized by chronic inflammation; aldosterone secretion can be triggered by hypoxia.

Beheshti, et al., Scientific Reports, 2018

Systems Biology analysis reveals biological spaceflight master regulators

Beheshti, et al., PLOS One, 2018

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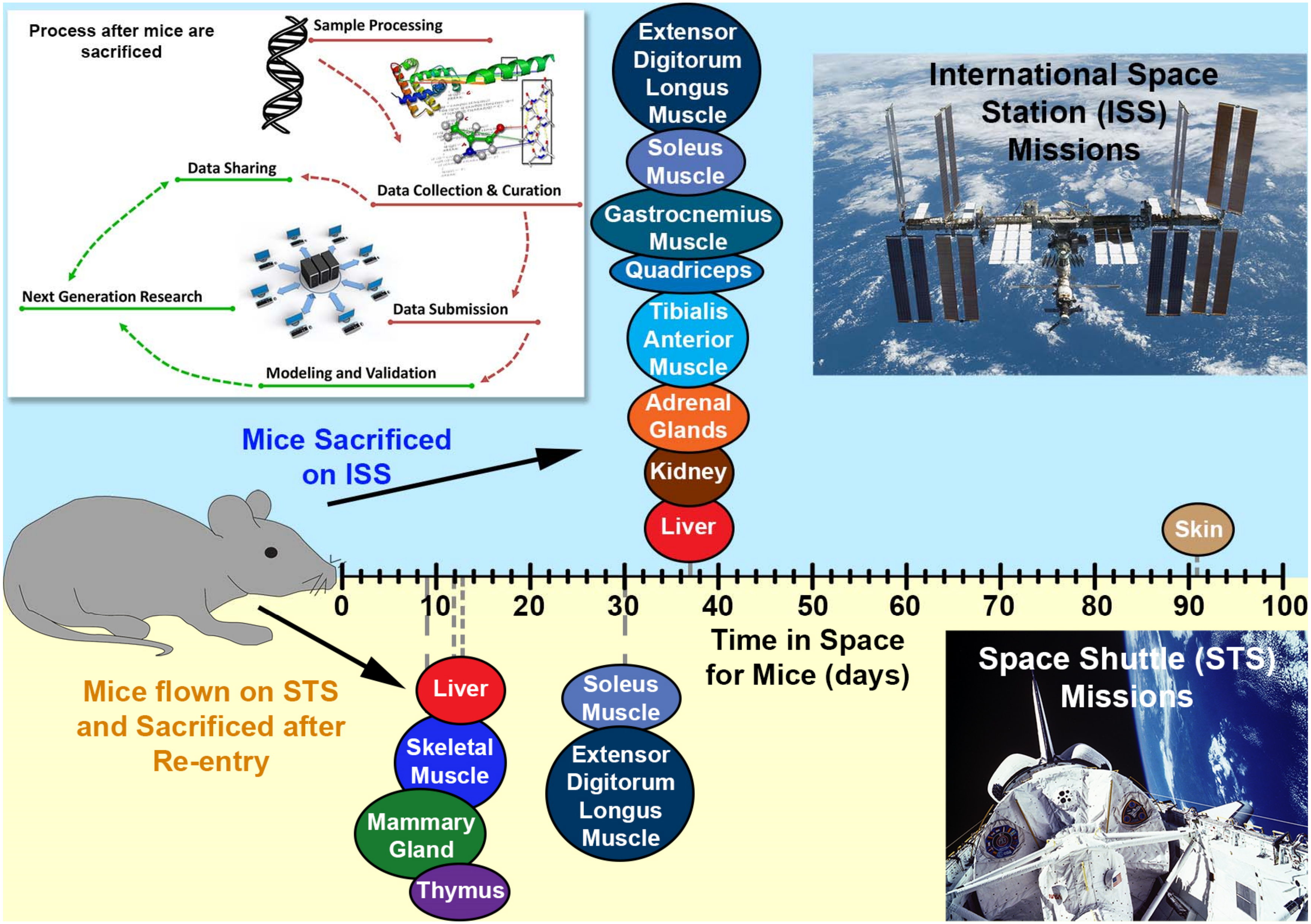
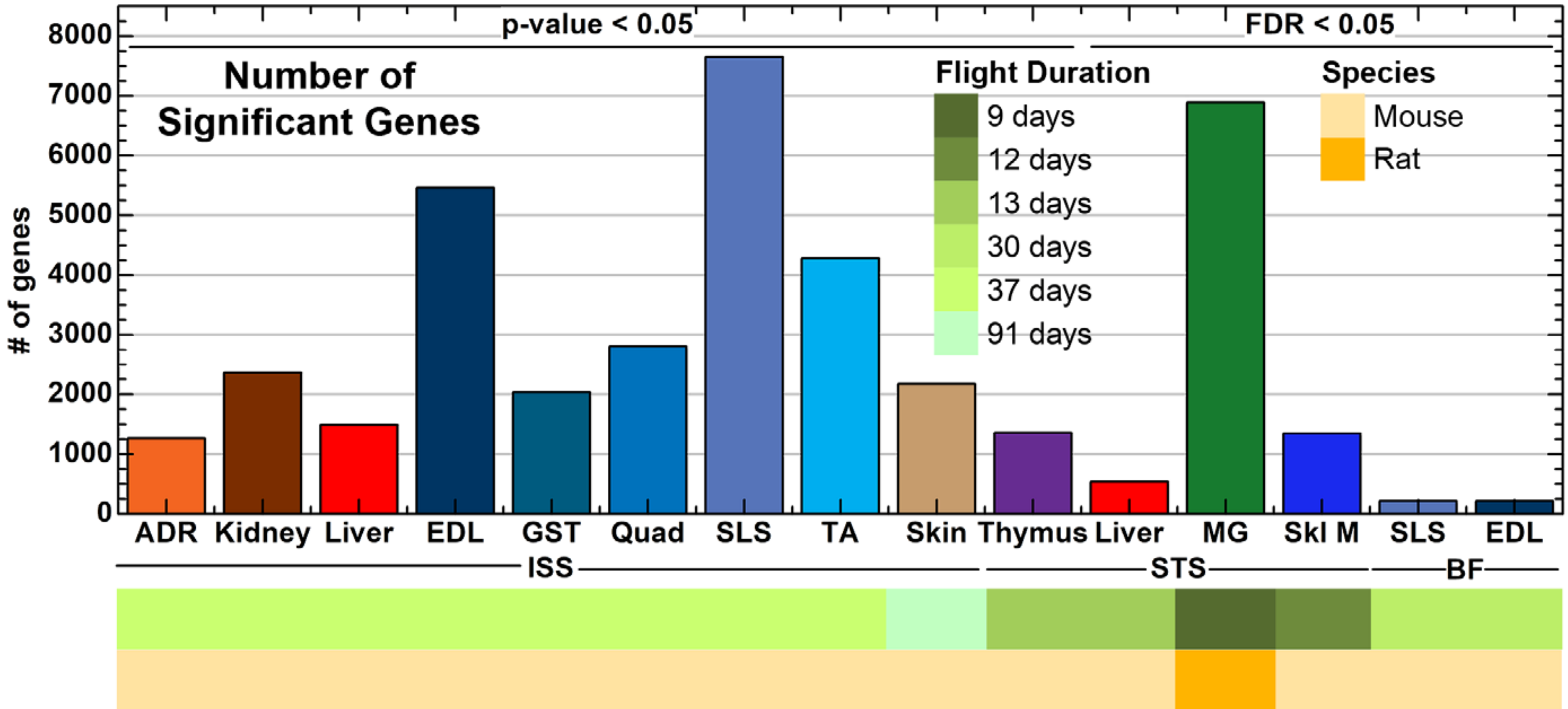
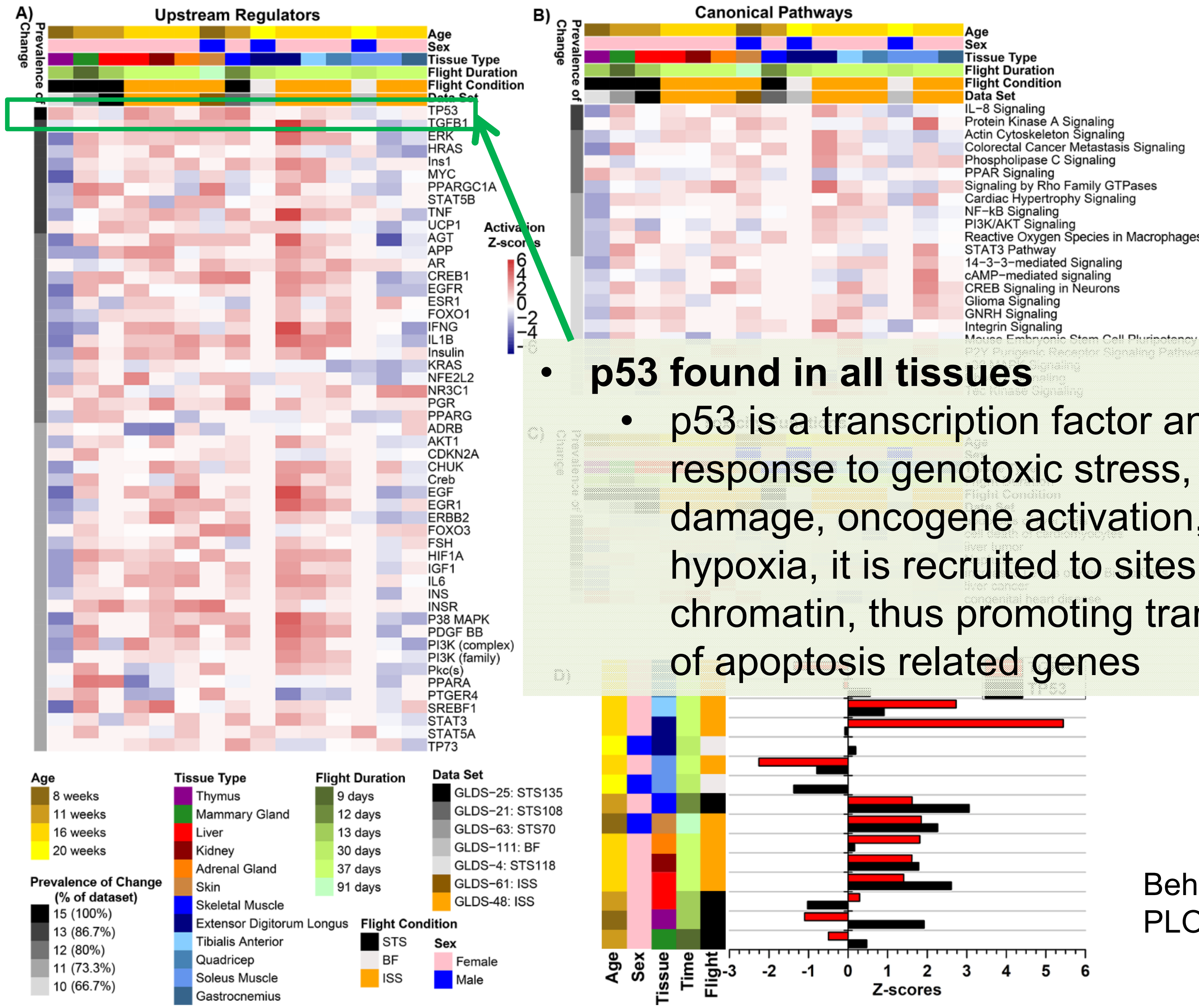
neLab Data Used to Generate Results



Number of Significant Genes from Each Dataset



icted Master Regulators

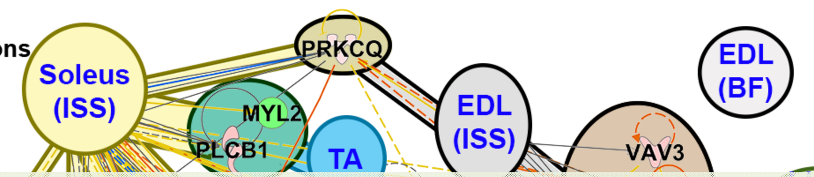


- **p53 found in all tissues**
  - p53 is a transcription factor and in response to genotoxic stress, DNA damage, oncogene activation, and hypoxia, it is recruited to sites in chromatin, thus promoting transcription of apoptosis related genes

Beheshti, et al., PLOS One, 2018

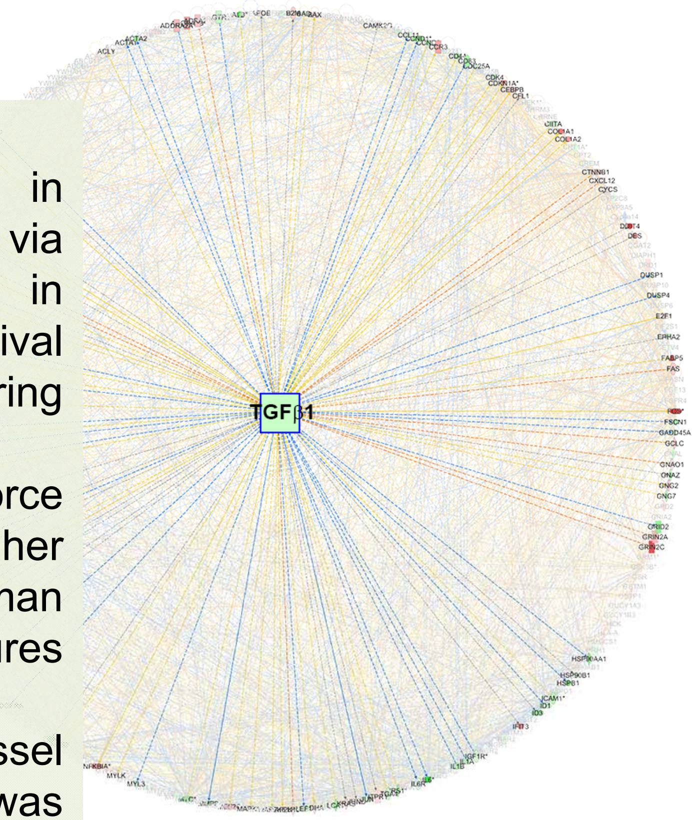
Genes and the Connections

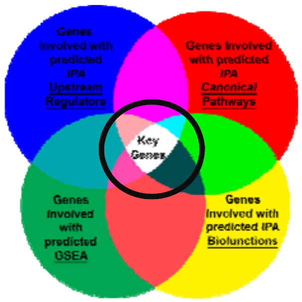
A) Direct Connections for Key Genes for Flight vs AEM



- **TGFβ1 found to be central regulator of key genes**
  - TGFβ is known to play a context specific role in sustaining tissue homeostasis predominantly via transcriptional regulation of genes involved in differentiation, cell motility, proliferation, cell survival along with regulating immune responses during homeostasis and infection.
  - Previous Studies found reduction in gravitational force to diminish TGF-β expression and apoptosis with higher carcinoembryonic antigen expression in 3D human colorectal carcinoma cells, as compared to 3D cultures in unit gravity.
  - In another study, differential regulation of blood vessel growth using basic fibroblast growth factor was identified in modeled microgravity with induction early and late apoptosis, extracellular matrix proteins, endothelin-1 and TGFb1 expression

B) Connections Between all Key Genes for all Datasets (Flight vs AEM): Radial Plot with the most Connected Gene in the Middle

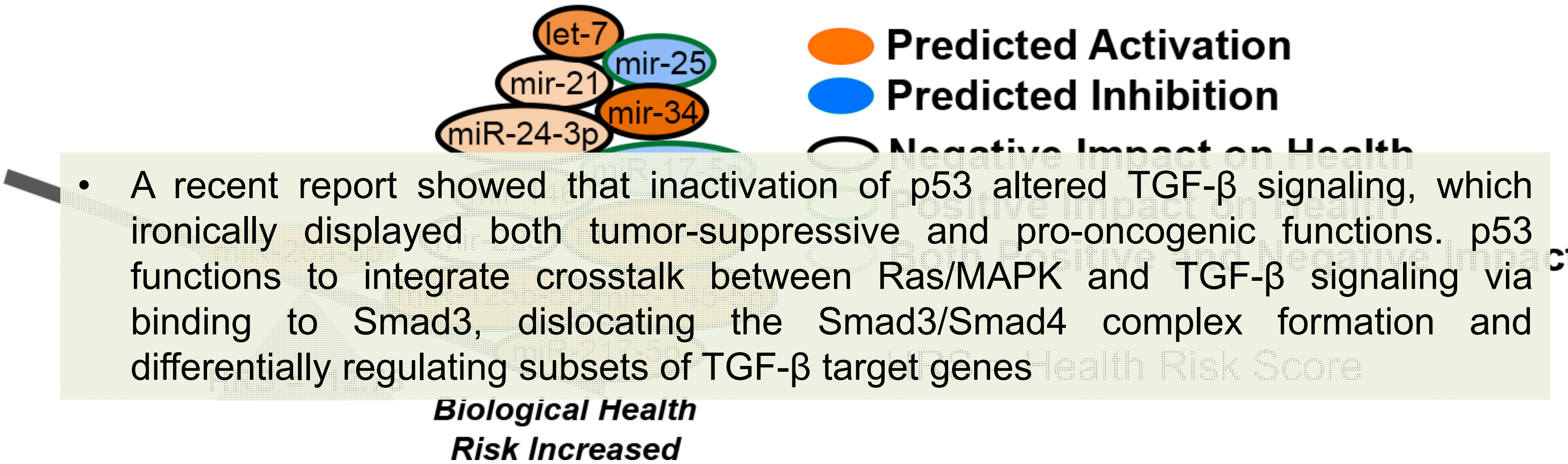




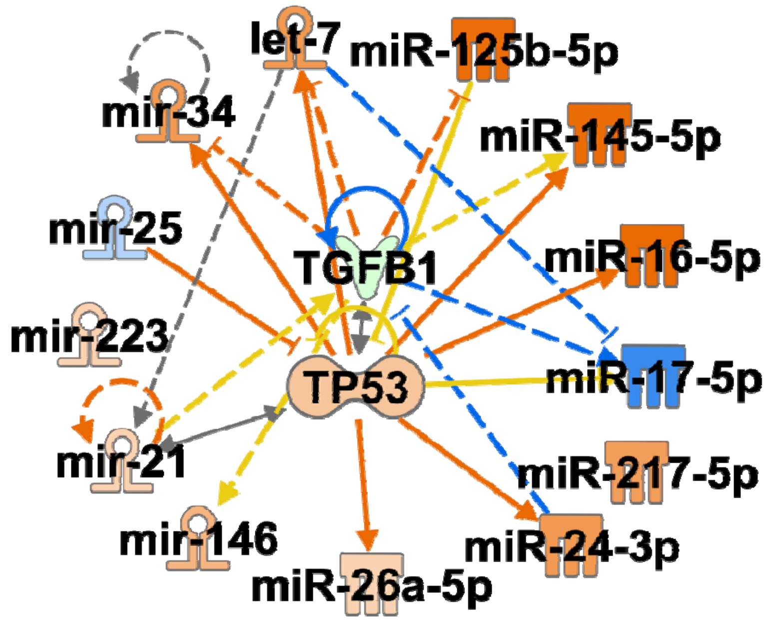
Beheshti, et al., PLOS One, 2018

Predicted miRNAs Involved with Microgravity Effects

Health Risk Due to miRNAs



- A recent report showed that inactivation of p53 altered TGF-β signaling, which ironically displayed both tumor-suppressive and pro-oncogenic functions. p53 functions to integrate crosstalk between Ras/MAPK and TGF-β signaling via binding to Smad3, dislocating the Smad3/Smad4 complex formation and differentially regulating subsets of TGF-β target genes



Beheshti, et al., PLOS One, 2018

Analysis Working Group (AWG) Member related work determines novel systemic biological factors causing damage due to spaceflight

Work in progress

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Goals of Multi-Omics/Sytstems Biology AWG

- **<u>Primary Goal:</u>** To determine the best pipelines, workflow, and tools to analyze relationships between multiple omics platforms (including: transcriptomic, proteomic, genomics, epigenetic, methylation, miRnome, and metabolomics).
  - Develop pipelines/workflows
  - Develop the optimal visualization tools to implement on GeneLab
- **<u>Secondary Goal:</u>** To provide the most biological significant data impacting space biology based on the existing GeneLab data from multiple platforms and species. This will be done through an unbiased Systems Biology approach with the optimal tools decided from the Primary Goal to determine the “master switch or regulator” that is affected due to space flight.

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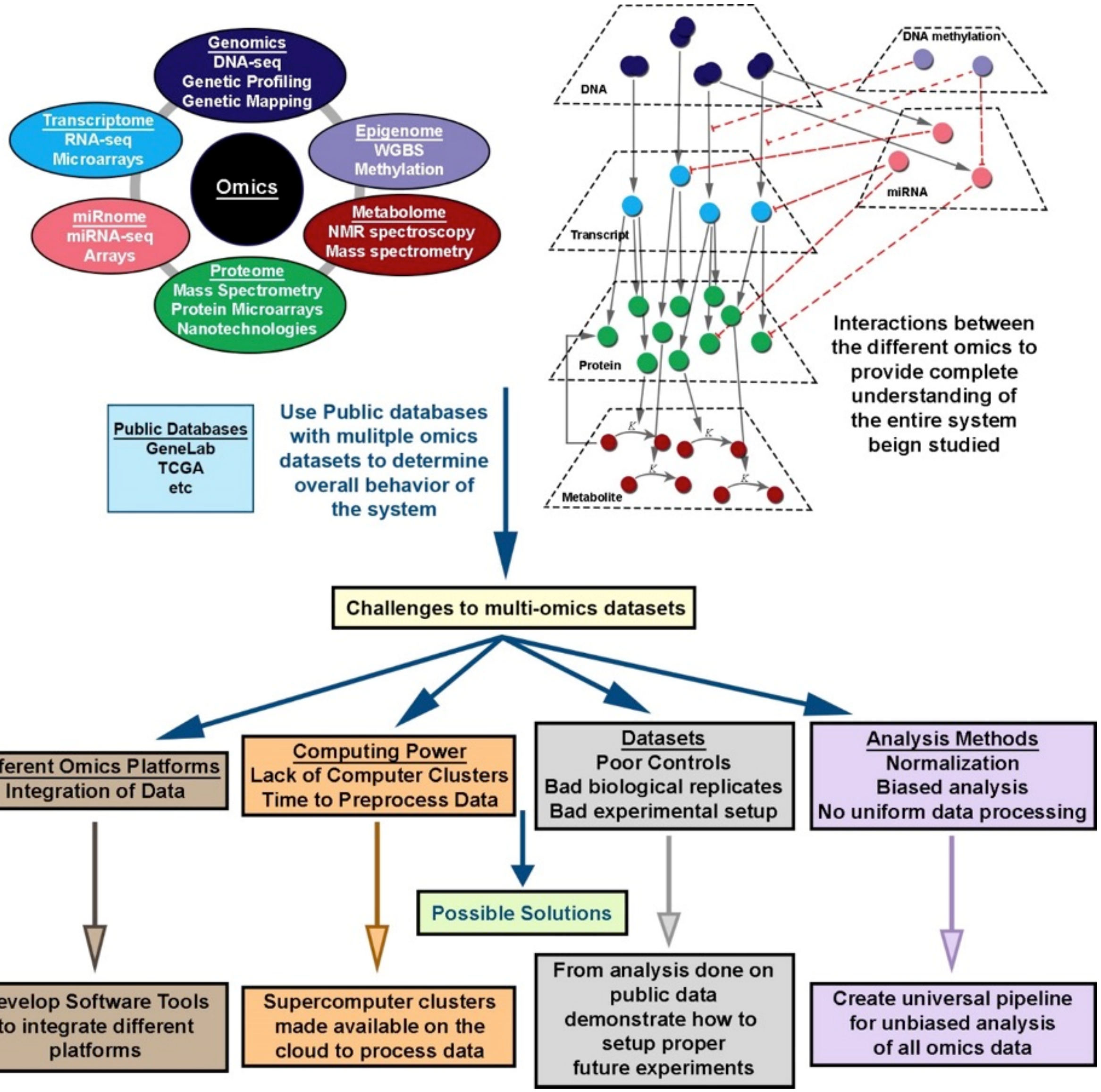
Omics Available on GeneLab and Challenges to Overcome



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Steps to Achieve Goals for Multi-Omics / Systems Biology AWG

1) **Determine, and get consensus for best tools to use for each type of omics and species.**
   a) Specific R and python packages
   b) Other platforms (i.e. GenePattern, Galaxy, homemade, etc)
2) **Determine best approach to correlate cross-platform/omics comparisons.**
   a) Use tools available
   b) Create own possible tools between collaborations from the AWG members labs and people
3) **Use newly created pipeline and tools to analyze existing GeneLab data and develop optimal visualization tools**
   a) Create an unbiased Systems Biology analysis pipeline with the determined tools to determine overall master regulator being affected by space flight for each organism on GeneLab (rodents, plants, microbes, invertebrates, and humans)
      I. First determine individual master regulators for each omic (i.e. Transcriptome, proteins, miRNAs, metabolites, methylated factors, and DNA mutations).
      II. Then determine through the tools created through cross platform/omics the overall master regulators.
   b) Create an unbiased cross-species analysis to determine overall master regulators that commonly impact all organisms.
4) **The final tools that were used for the analysis in 3 will be compiled in one group and assessed by the rest of GeneLab**
   a) These tools will include both existing and homemade analysis tools from the people included in the AWG
   b) The most optimal Visualization tools (both existing and homemade from the AWG members) will be included in our final assessment
   c) Best Systems Biology approach will be assessed and packaged into an easy to use tool for the community
5) **Each step will produce at least one to two papers for publication headed by various members of the AWG**

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AWG Members Involved

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Kathleen Fisch


Brin Rosenthal

UNIVERSITY of CALIFORNIA, SAN DIEGO
SCHOOL OF MEDICINE


Deanne Taylor


Hossein Fazelinia


Komal Rathi

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

MUSC Health
MEDICAL UNIVERSITY of SOUTH CAROLINA

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AWG Members Involved


Chris Mason


Cem Meydan


Jonathan Foox

Flavia Rius

Cornell University


Yared Kidane

NASA
Texas Scottish Rite Hospital for Children


Susana Zanello


Scott Smith


Sara Zwart

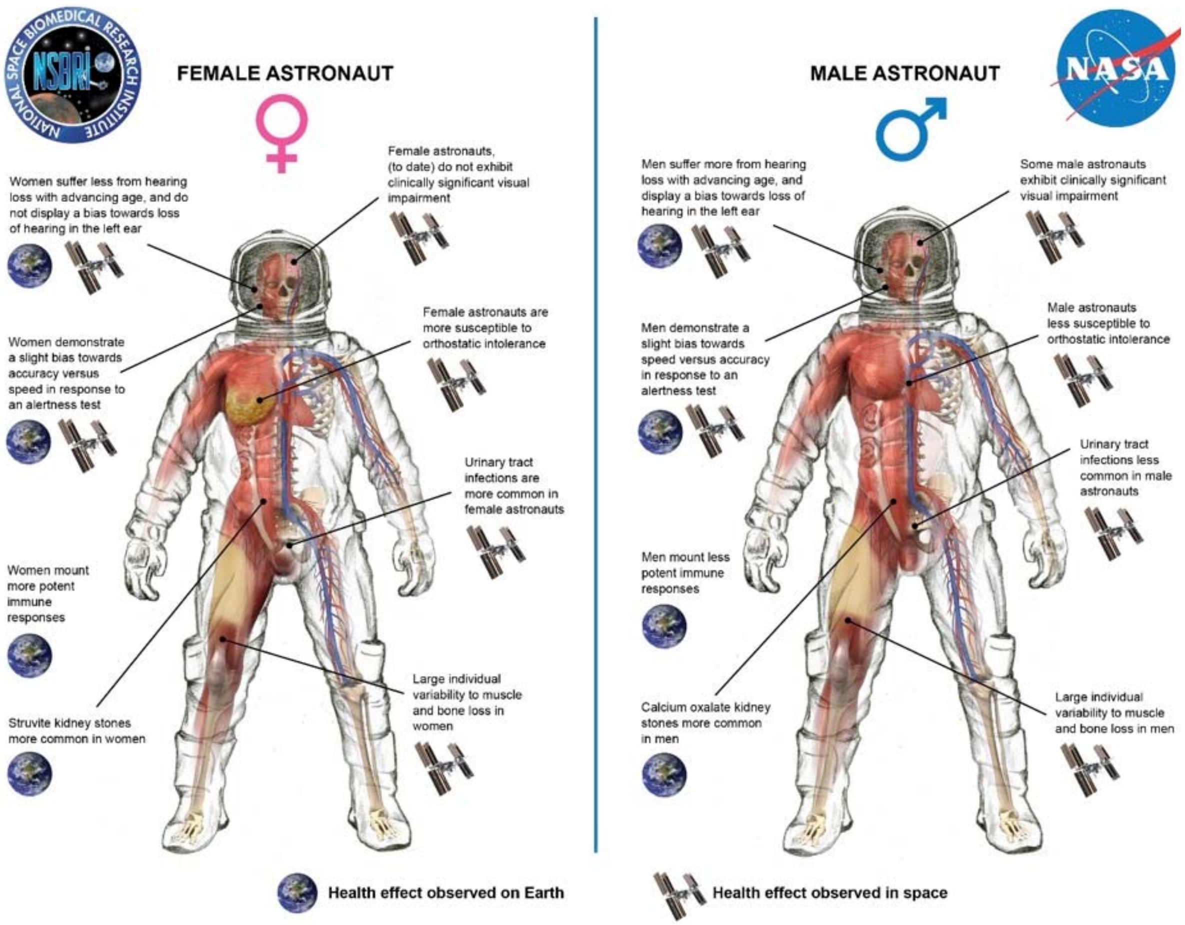
NASA
Space Center Houston
Manned Space Flight Education Foundation

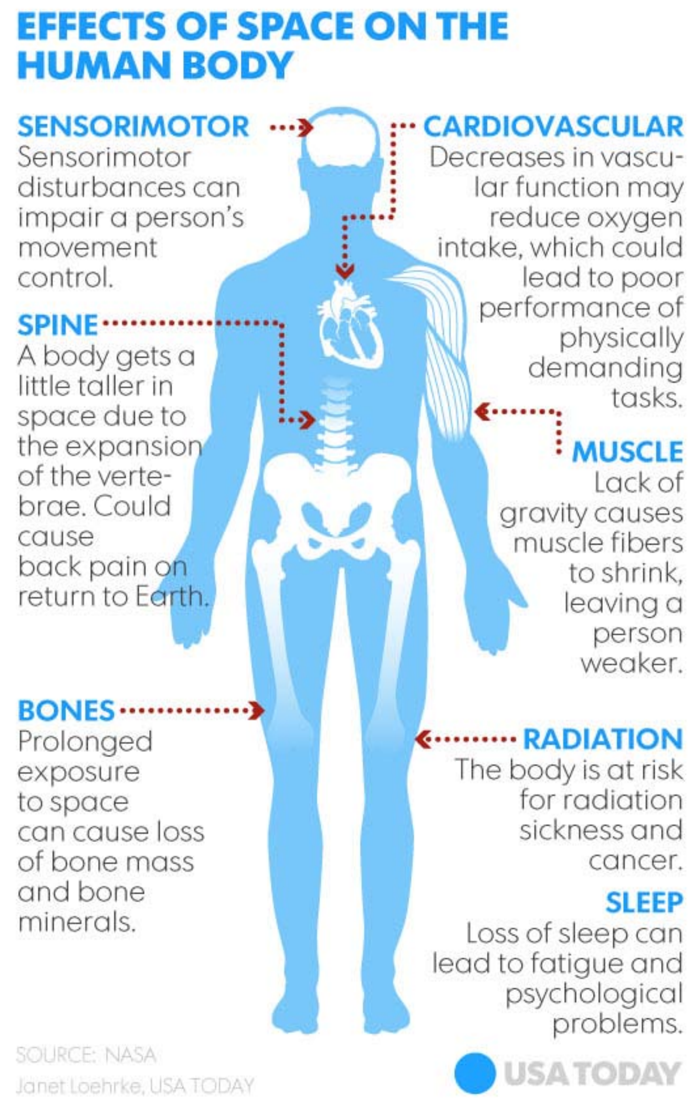

Afshin Beheshti


Sylvain Costes

NASA
Ames Research Center

Health Risks On Astronauts in Space





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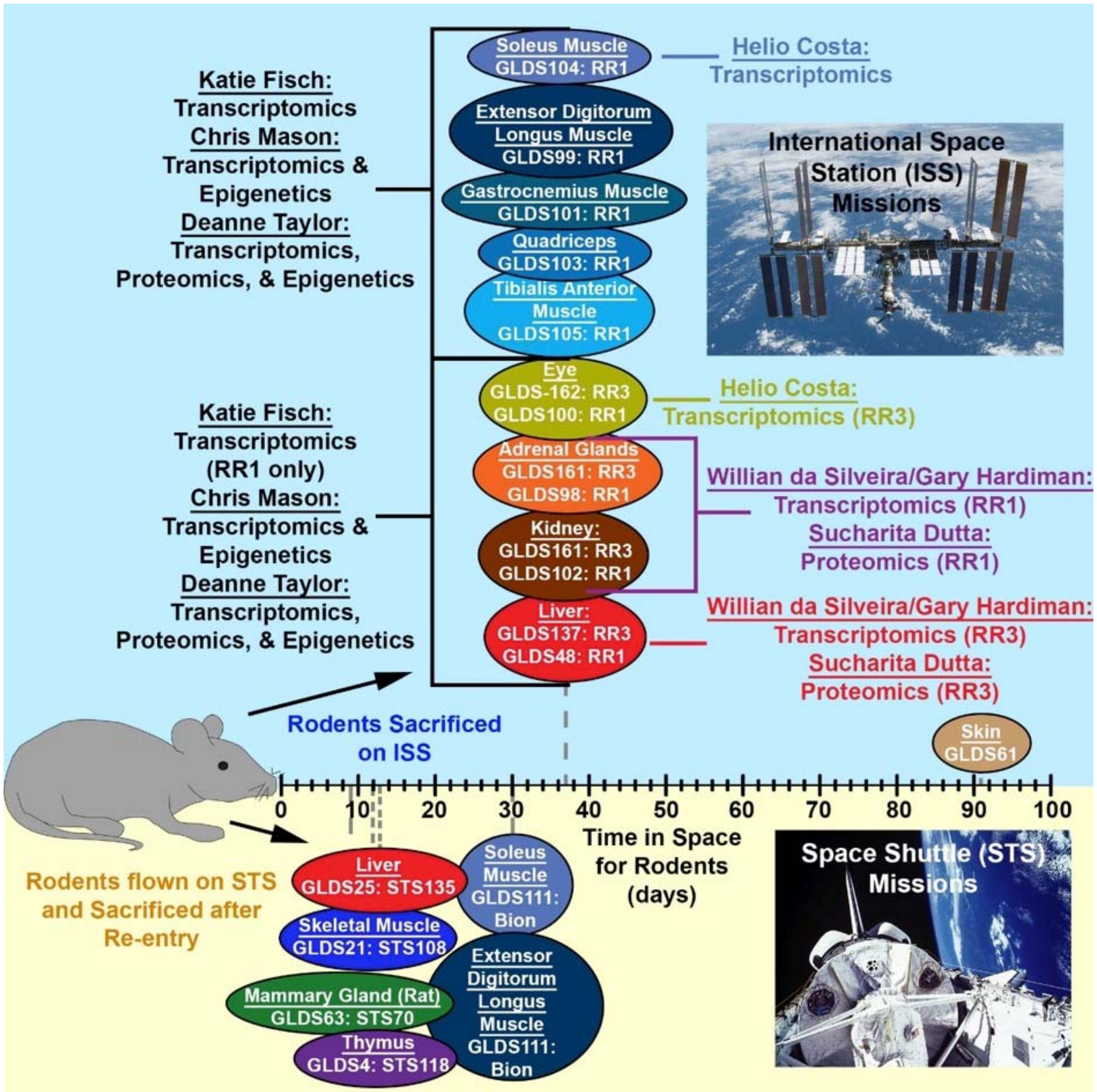
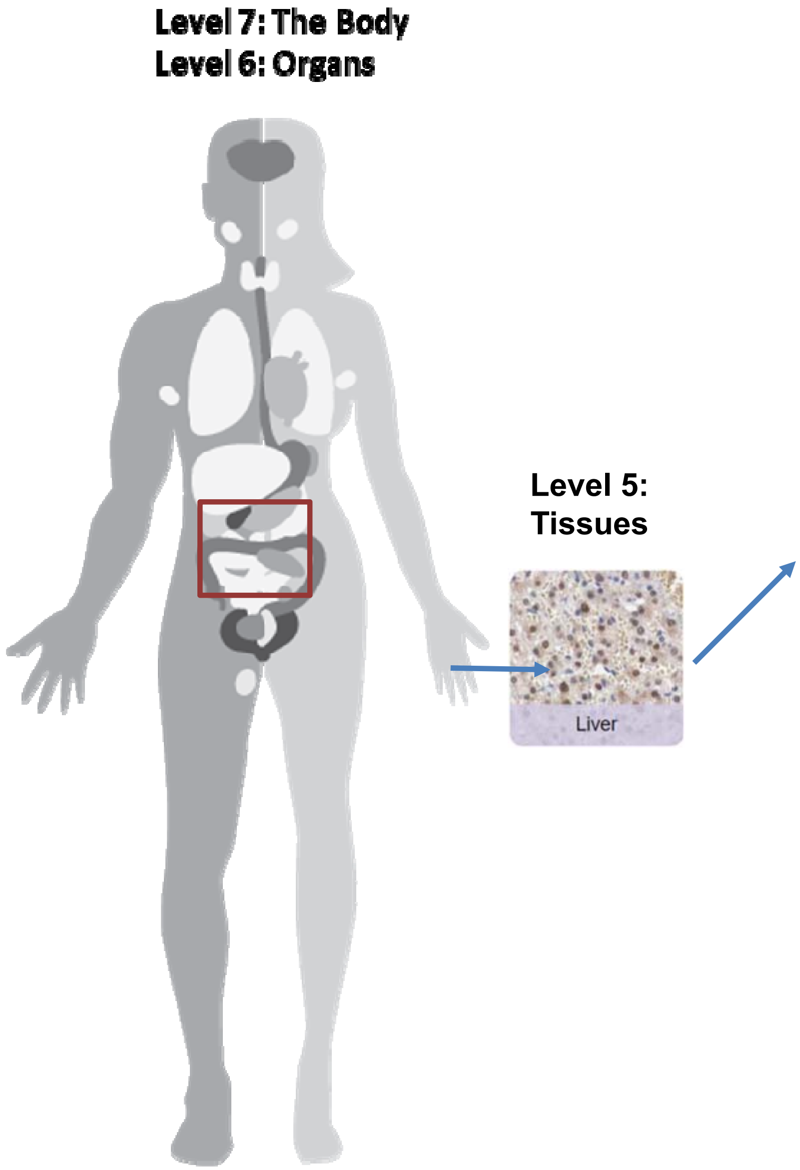
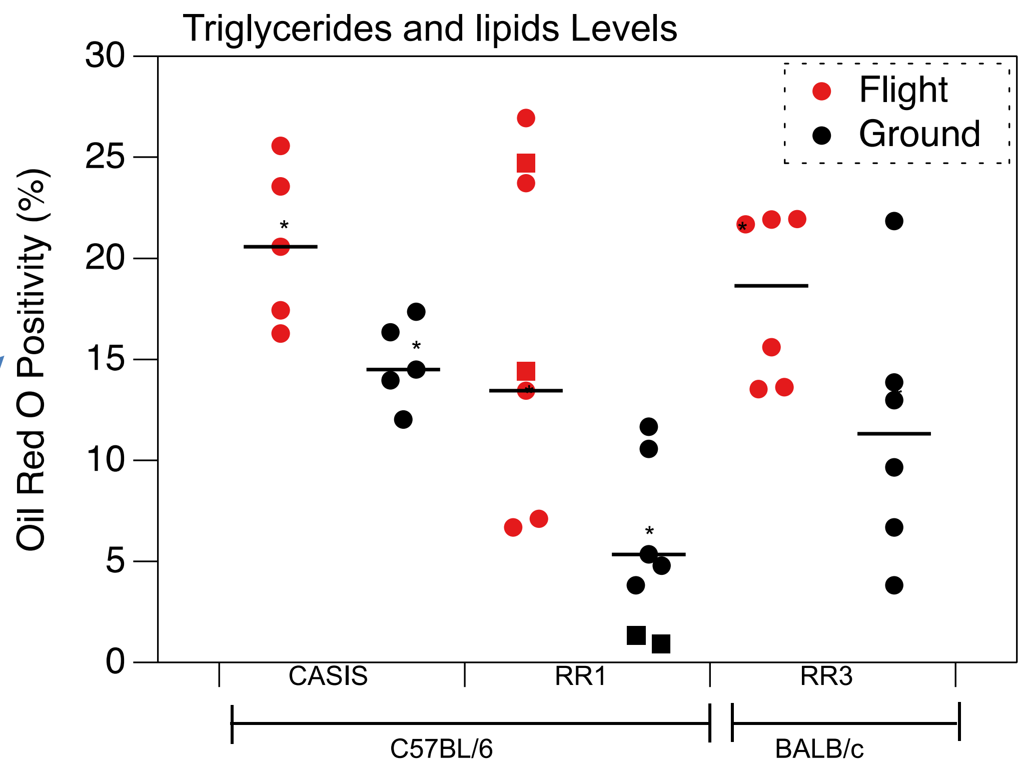
Specific Datasets and Tissues AWG Members Analyzed



- <u>Additional Datasets that are being analyzed:</u>
  - Human datasets
    - GLDS-54, GLDS-174, GLDS-86, GLDS-118, GLDS-53, GLDS-54, GLDS-13. GLDS-52, or GLDS-114 (Tyson McDonald and Yared Kidane)

Lipid Accumulation in the Liver





Lipid Accumulation in the Liver And Ion Diffusion

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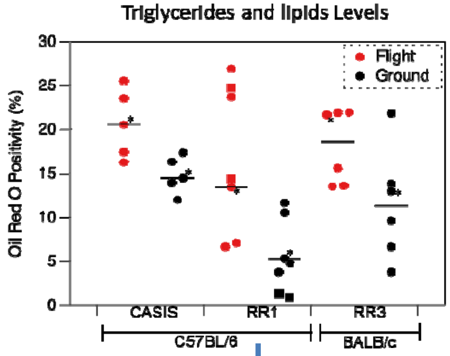
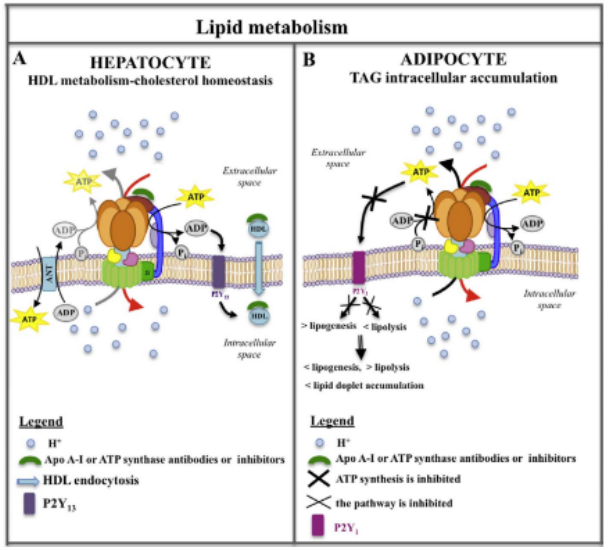
Level 5: Tissues

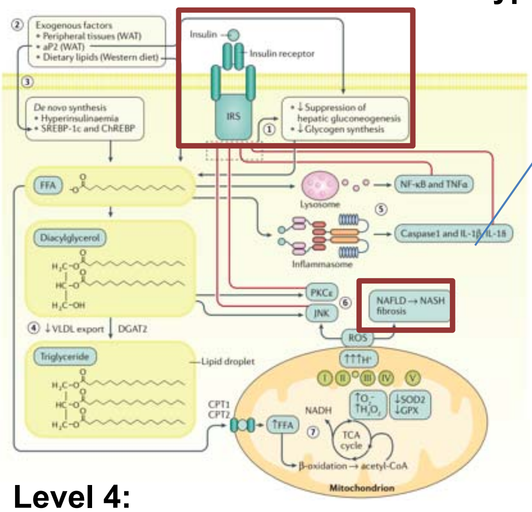


Level 1: Monomeric Units



Diabetes Type 2

Inflammation

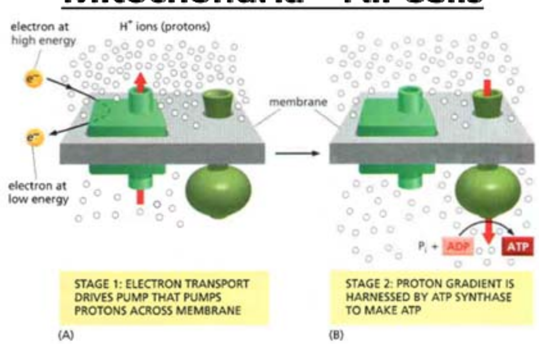


Level 4:
The Cell and its Organelles

Taurino & Gnoni. Exp Mol Pathol. 2018.
Tilg et al. Nat Rev Gastroenterol Hepatol. 2017.

Level 1: Monomeric Units

Mitochondria – All Cells



Mitochondrial Stress

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Liver at the Center of Metabolic Disorders

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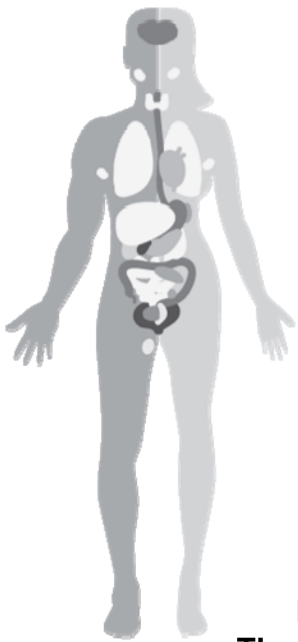
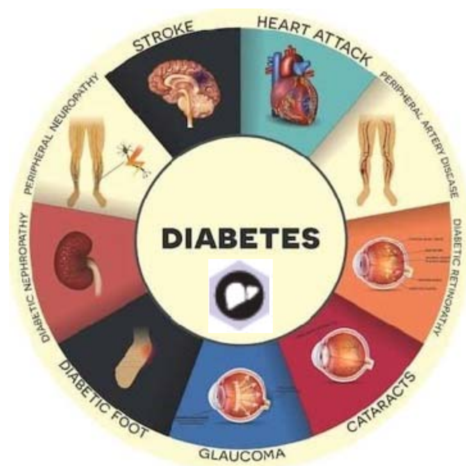
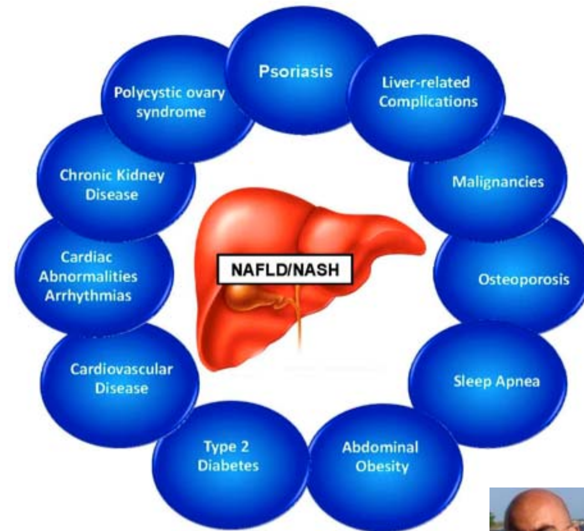
Level 7: The Body
Level 6: Organs



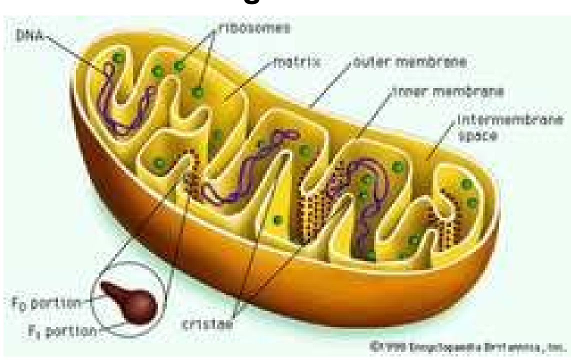
Diabetes Complications

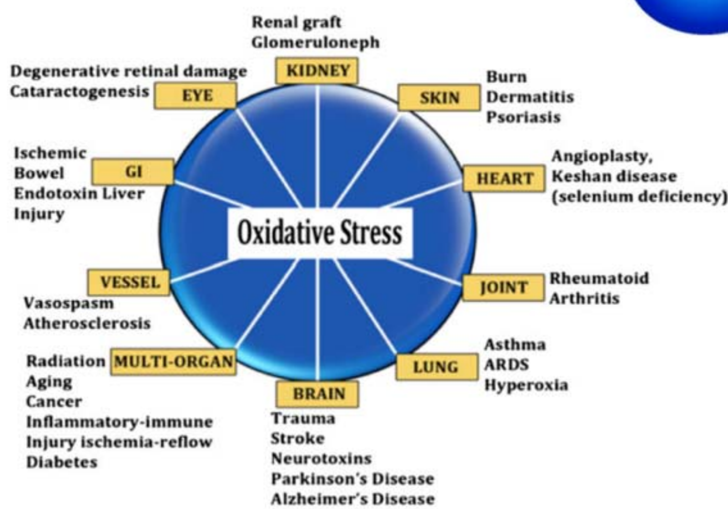


Non-Alcoholic Fatty Liver Disease Complications



Level 4: The Cell and its Organelles





Willian da Silveira

Gary Hardiman

Schmidt & Goodwin, Metabolomics (2013).
Ballestri et al. World J Gastroenterol. 2014.

RR1 and RR3 Mice

RR1: C57BL/6
mice strain
(female)

Diabetes Type 2 induced by High Fat Diet Model:

- Th1 Immune Response (more inflammatory),
- More susceptible to adiposity, liver inflammation, and liver fibrosis

RR3: BALB/c
mice strain
(female)

- Th2 Immune Response (more tolerogenic),
- More susceptible to liver steatosis
- Radiosensitive

RR1 and RR3 Experimental Detail

ISS

RR1 - C57BL/6

RR3 - BALB/c

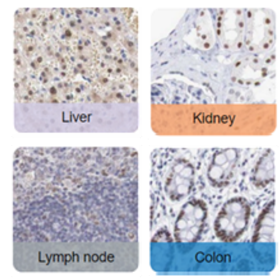
Exposition time: ≈ 40 days

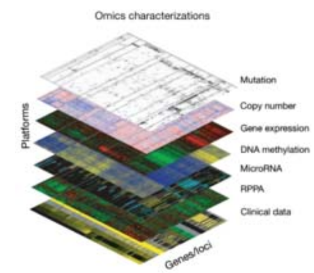
RR1
Space Flight n = 6
Ground Control n = 6

RR3
Space Flight n = 6
Basal Control* n = 6
Ground Control n = 6

Earth

Level 5: Tissues





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RR1 and RR3: Liver Transcriptomics

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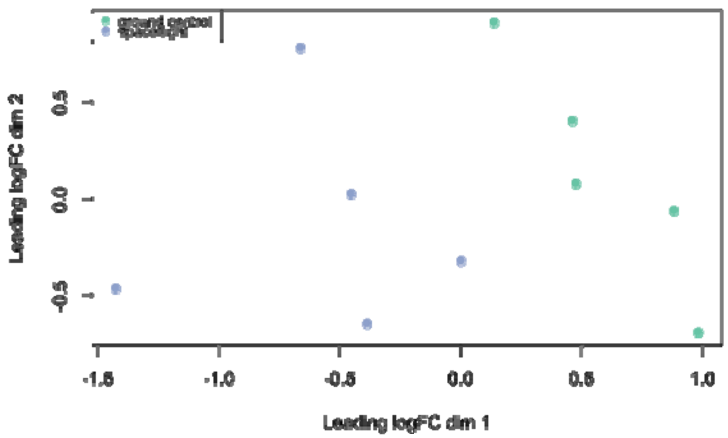
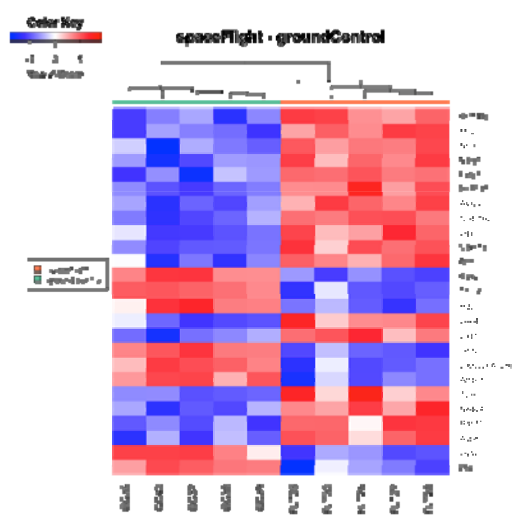
Open Science for Exploration

RR1 Liver (C57BL/6)

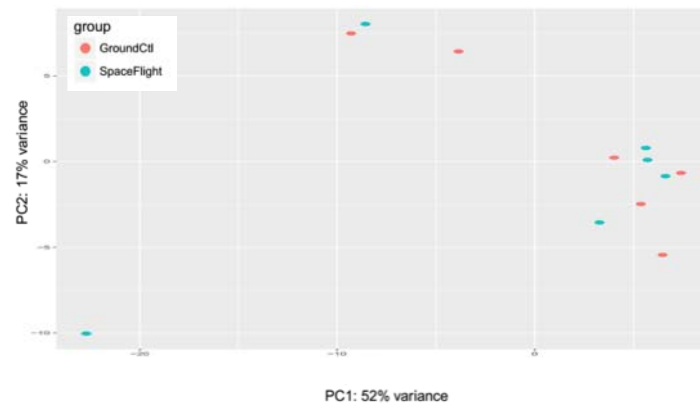
181 DE genes adj.P < 0.05

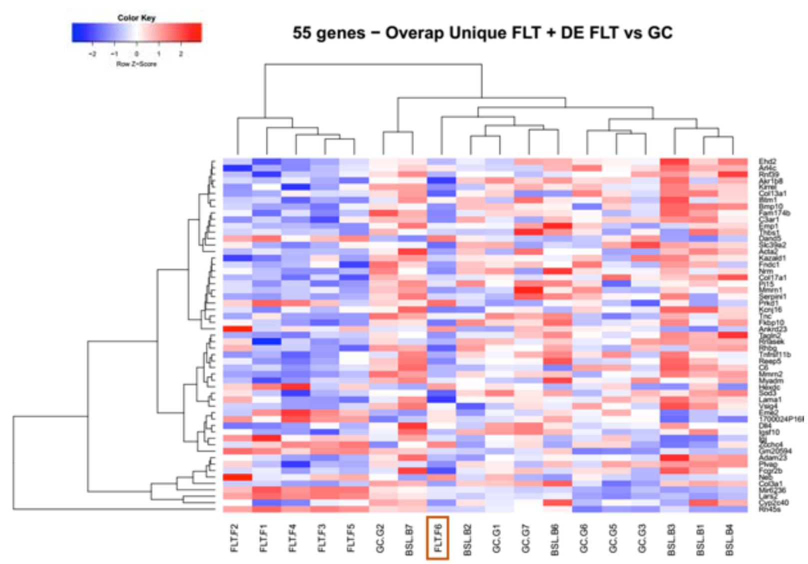




RR3 Liver (BALB/c)

0 DE genes adj.P < 0.05





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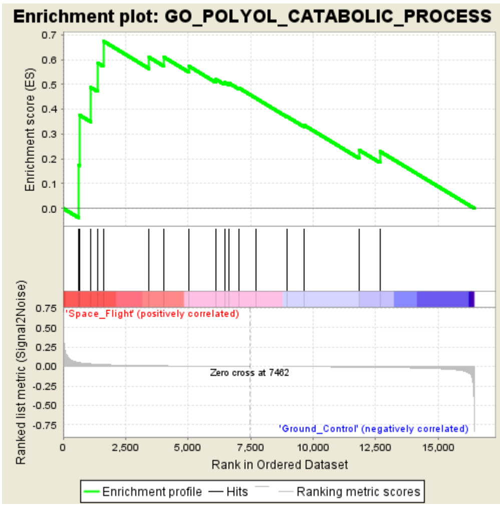
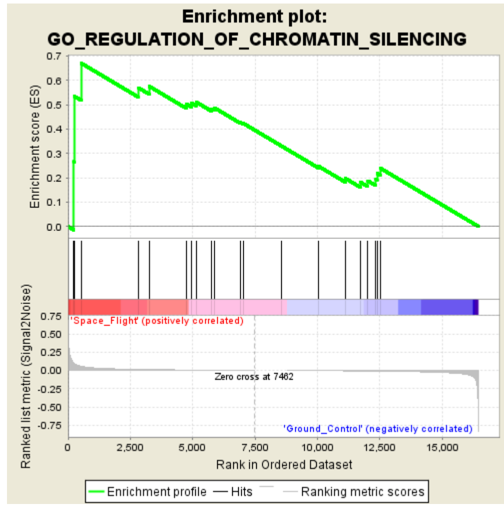
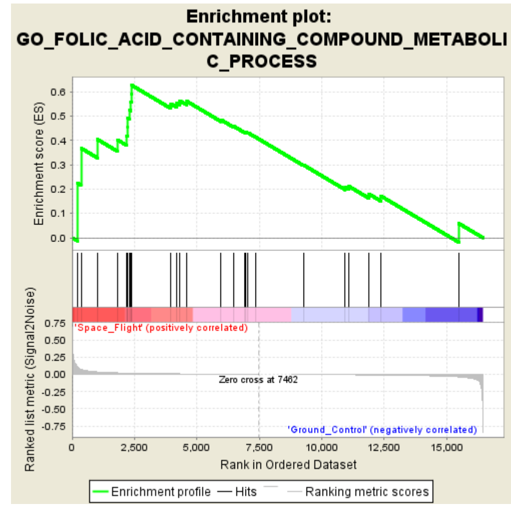
Kathleen Fisch

RR3 (BALB/c) System Level Analysis







GSEA - G.O Biological Process:

NAME	NOM p-val	FDR q-val
GO_POLYOL_CATABOLIC_PROCESS	0.002	0.21
GO_FOLIC_ACID_CONTAINING_COMPOUND_METABOLIC_PROCESS	0.002	0.20
GO_PTERIDINE_CONTAINING_COMPOUND_METABOLIC_PROCESS	<0.001	0.21
GO_RESPONSE_TO_LEAD_ION	<0.002	0.23
GO_REGULATION_OF_CHROMATIN_SILENCING	<0.003	0.22

Related to eye damage and cataract Risk in **Diabetes Type II**

Willian da Silveira

Gary Hardiman

RR3 (BALB/c) System Level Analysis

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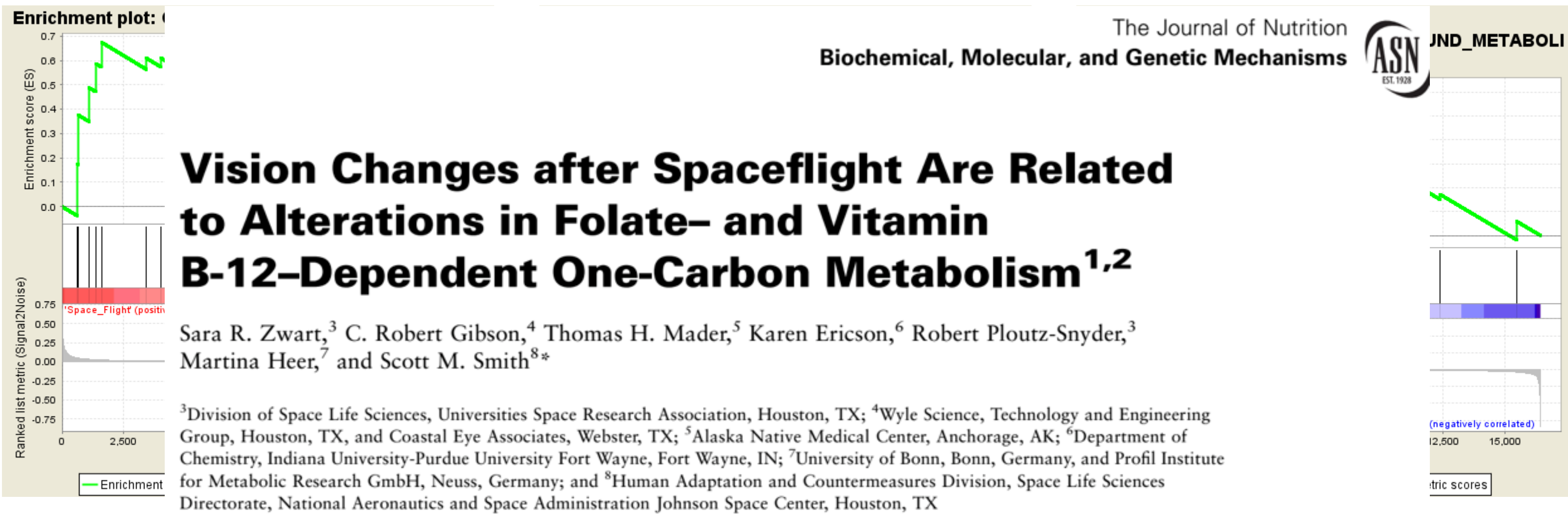

The Journal of Nutrition
Biochemical, Molecular, and Genetic Mechanisms

Vision Changes after Spaceflight Are Related to Alterations in Folate– and Vitamin B-12–Dependent One-Carbon Metabolism[1,2]

Sara R. Zwart,[3] C. Robert Gibson,[4] Thomas H. Mader,[5] Karen Ericson,[6] Robert Ploutz-Snyder,[3] Martina Heer,[7] and Scott M. Smith[8]*

[3]Division of Space Life Sciences, Universities Space Research Association, Houston, TX; [4]Wyle Science, Technology and Engineering Group, Houston, TX, and Coastal Eye Associates, Webster, TX; [5]Alaska Native Medical Center, Anchorage, AK; [6]Department of Chemistry, Indiana University-Purdue University Fort Wayne, Fort Wayne, IN; [7]University of Bonn, Bonn, Germany, and Profil Institute for Metabolic Research GmbH, Neuss, Germany; and [8]Human Adaptation and Countermeasures Division, Space Life Sciences Directorate, National Aeronautics and Space Administration Johnson Space Center, Houston, TX

GSEA - G.O Biological Process:

NAME	NOM p-val	FDR q-val
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GO_RESPONSE_TO_LEAD_ION	<0.002	0.23
GO_REGULATION_OF_CHROMATIN_SILENCING	<0.003	0.22

Related to eye damage and cataract Risk in **Diabetes Type II**

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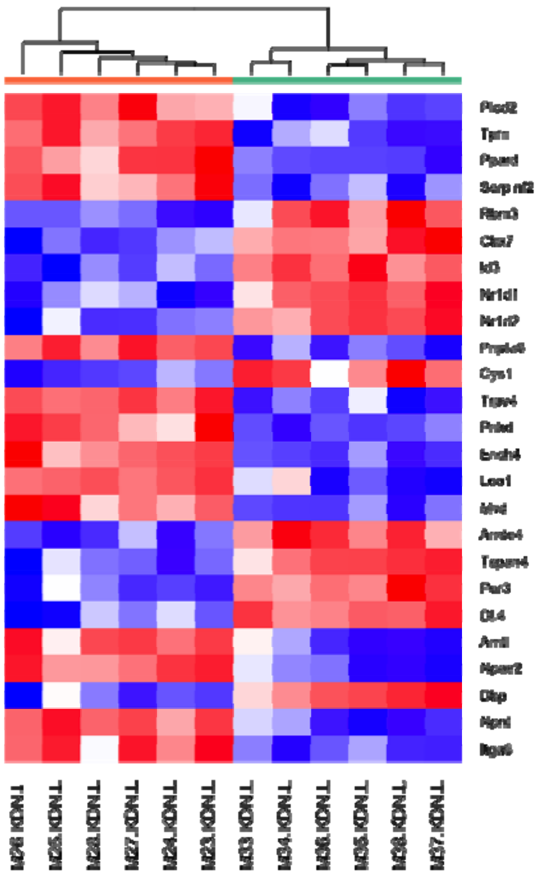
RR1 Differentially Expressed Genes : Space Flight vs Ground Control

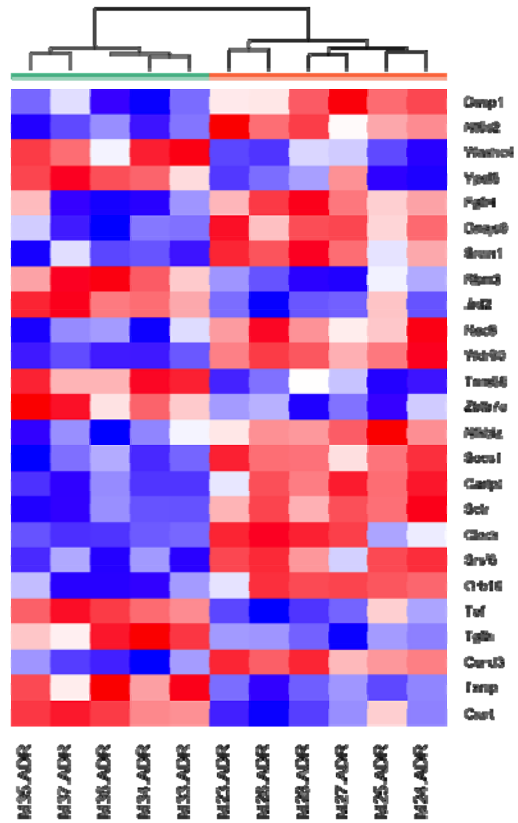
RR1 Kidney

Spaceflight - Ground_control



RR1 Adrenal

Spaceflight - Ground_control



spaceflight
ground control

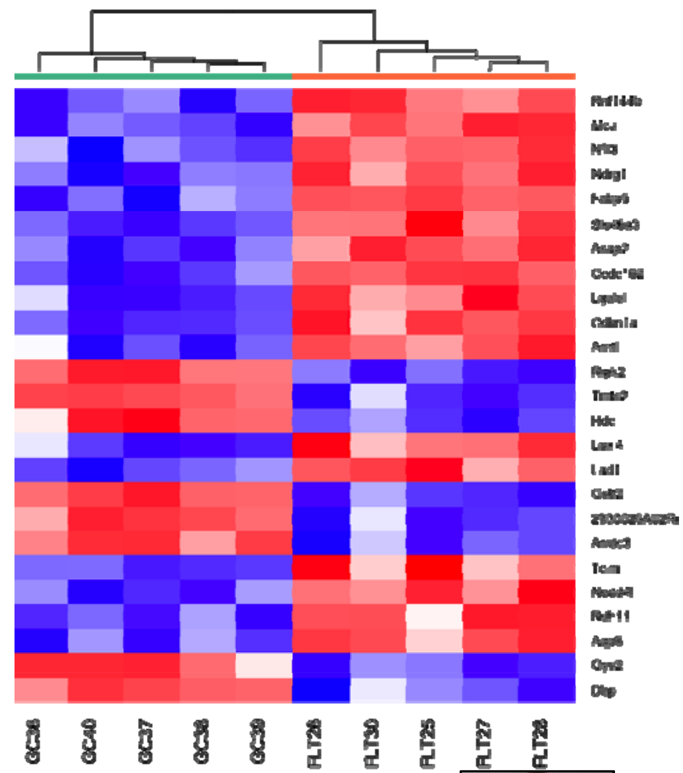
Color Key

-1 0 1

Row Z-Score

RR1 Liver

spaceFlight - groundControl



Brin Rosenthal

Kathleen Fisch

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RR1 Shared DE Genes

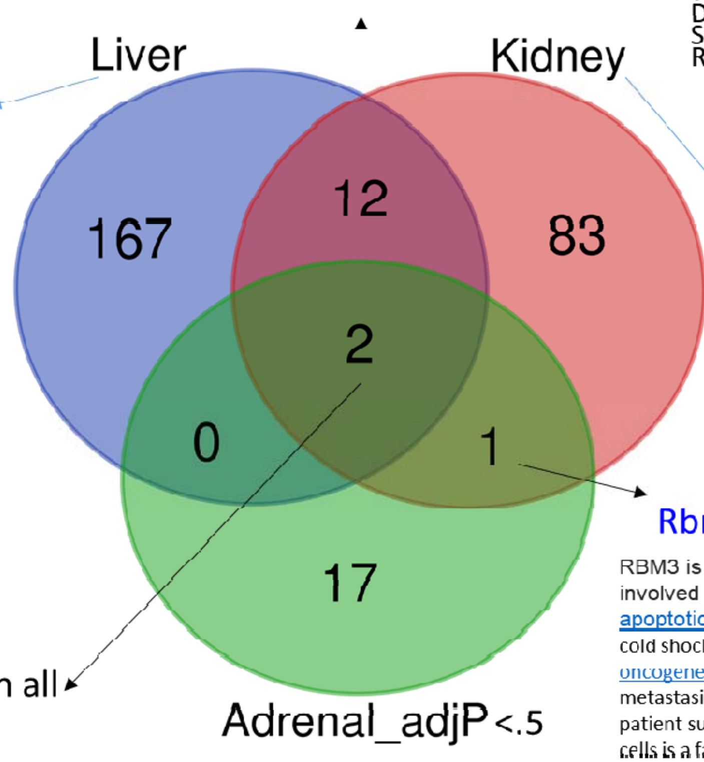
Cbx7 Arntl Cdkn1a Gale Per3 Nfil3 Npas2
Pnkd Loxl4 Bhlhe41 Dbp Leo1

Toppgene

Circadian Rhythm
TF activity
DNA binding
Stress induced premature senescence
Response to redox state

GSEA

Zinc Transporters (Reactome)
Apoptosis by TGFB1 via MAPK1...
Alpha Linolenic Acid Metabolism (KEGG)
PARK2_Hepatocyte_Proliferation...
LGI1_Targets_Up
Amplification hot spot...
FGFR ligand binding... (Reactome)
Response to TGFB1...
Breast Cancer...
Apoptosis by CDKN1A not via TP53...
EGFR signaling...
Systemic lupus erythematosus...



GSEA

Core Duplicon Genes
Signal Attenuation (Reactome)
Post Chaperonin Tubulin (Reactome)

Downregulated in all three conditions
Tef
Txnip

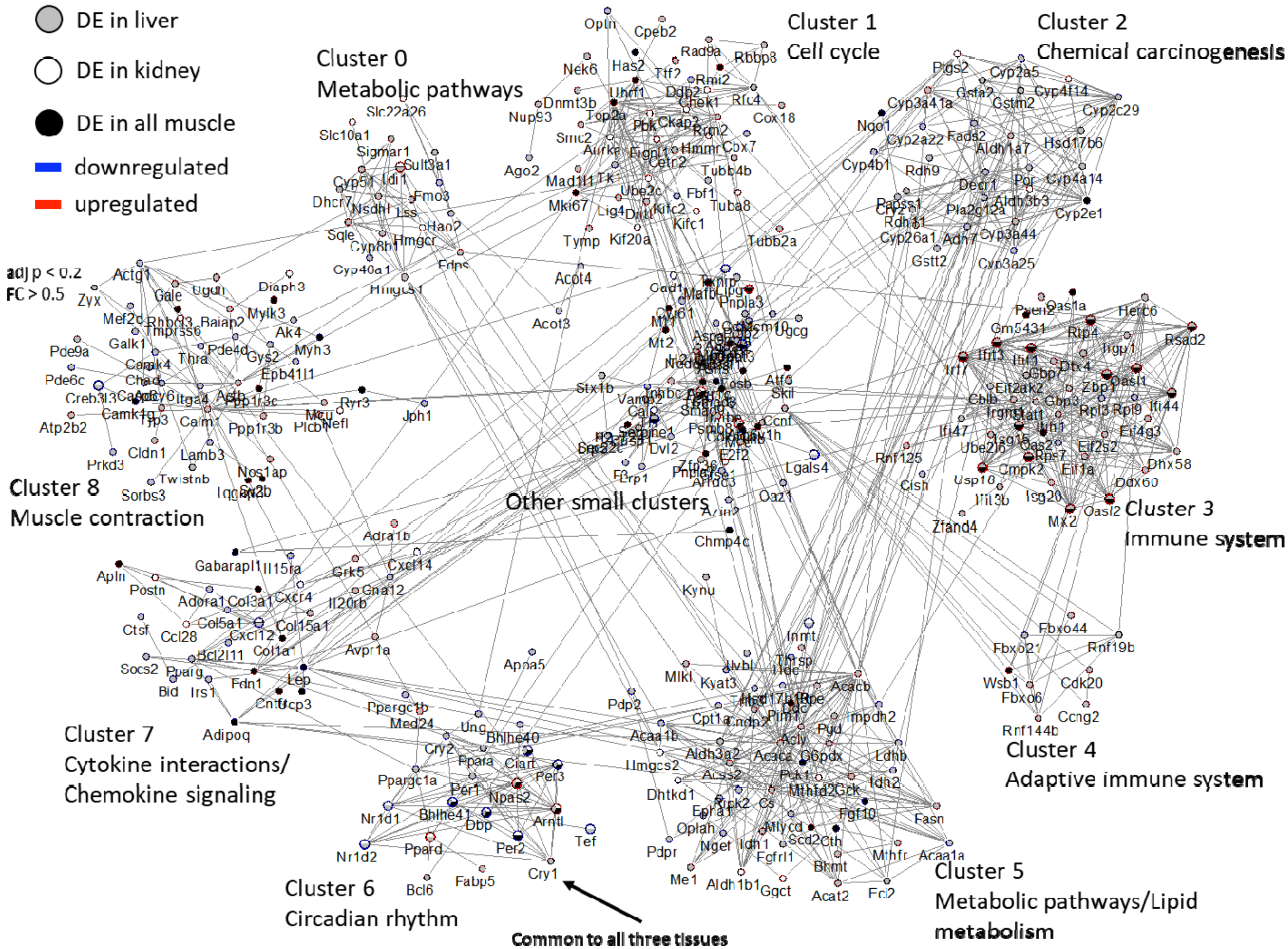
Rbm3 -- downregulated

RBM3 is cold-induced RNA binding protein and is involved in mRNA biogenesis exerts anti-apoptotic effects.[3] Expression of this gene is induced by cold shock and low oxygen tension. RBM3 is a proto-oncogene that is associated with tumor progression and metastasis and is a potential cancer biomarker.[4] Based on patient survival data, high levels of RBM3 protein in tumor cells is a favourable prognostic biomarker in colorectal cancer.[5]

Brin Rosenthal

Kathleen Fisch

RR1 (C57BL/6)
All Tissues Network Analysis



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Kathleen Fisch

RR1 (C57BL/6) : Systems Analysis (GSEA Analysis)

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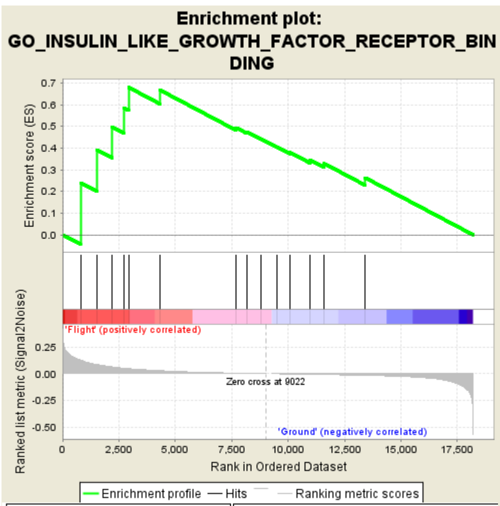
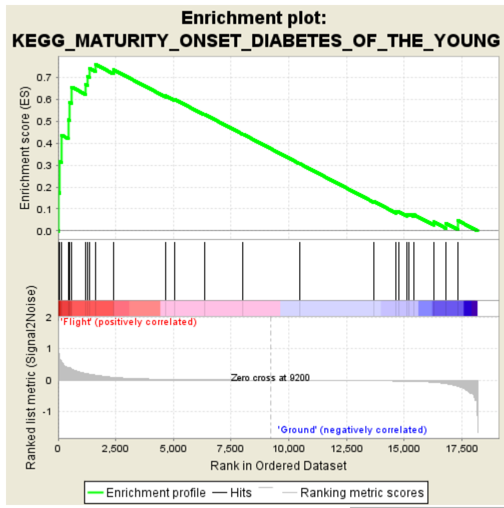
RR1 – ALL Tissues



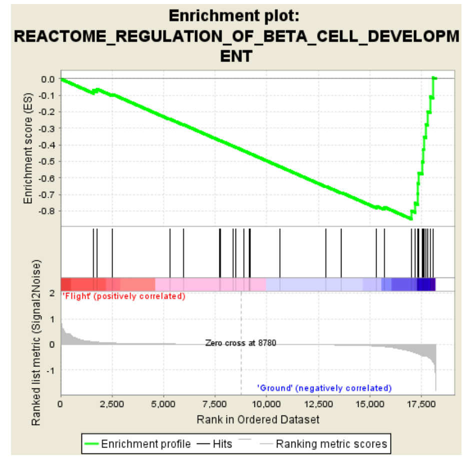
Nominal p-value	0.0
FDR q-value	0.022425935

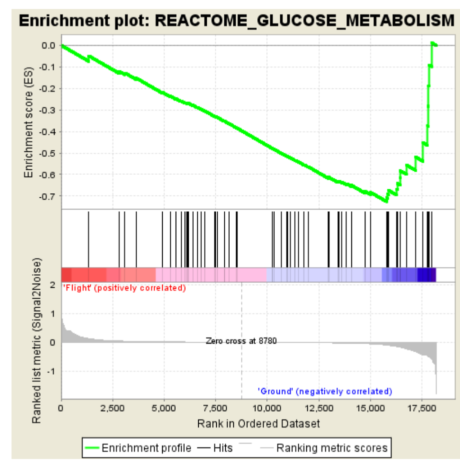
RR1 – Kidney



Nominal p-value	0.012345679
FDR q-value	0.21693978

RR1 – Adrenal Gland





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Gary Hardiman

Brin Rosenthal

Kathleen Fisch

GeneLab
Open Science for Exploration

Vitamin D Role in Space - Literature

Cite this: *Photochem. Photobiol. Sci.*, 2013, **12**, 536

Dietary vitamin D alters the response of the skin to UVB-irradiation depending on the genetic background of the mice†

R. C. Malley,*[a,b] H. K. Muller,[b] M. Norval[c] and G. M. Woods[a,b]

RR3 - BALB/c

RR1 - C57BL/6

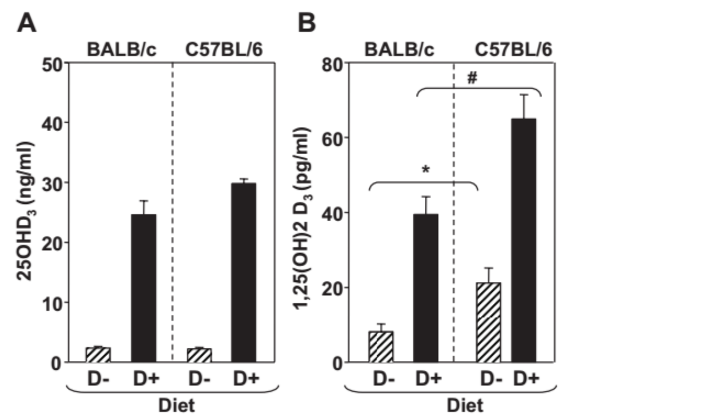
	BALB/c	
	D+	D−
Male	112 ± 14 (n = 14)	21 ± 3 (n = 17)
Female	110 ± 24 (n = 12)	20 ± 5 (n = 23)
	C57BL/6	
	D+	D−
Male	137 ± 32[a] (n = 14)	17 ± 5[b] (n = 24)
Female	129 ± 34[a] (n = 18)	15 ± 5[b] (n = 24)

Mean ± SD, nmol L-1

(*Endocrinology* 150: 1051–1060, 2009)

Vitamin D Deficiency Modulates Graves' Hyperthyroidism Induced in BALB/c Mice by Thyrotropin Receptor Immunization

Alexander Misharin, Martin Hewison, Chun-Rong Chen, Venu Lagishetty, Holly A. Aliesky, Yumiko Mizutori, Basil Rapoport, and Sandra M. McLachlan



In conclusion, we found a strain-specific difference in handling vitamin D, with BALB/c mice having reduced ability (compared with C57BL/6 mice) to generate the active metabolite.

Strains of mice differ in their ability to be suppressed by UVB irradiation: **BALB/c** mice are considered **"sensitive"** and **C57BL/6 "resistant"**. (The) results indicate that dietary vitamin D3 can reduce UVB-induced suppression of the contact hypersensitivity response depending on the genetic background of the mice.

Willian da Silveira

Gary Hardiman

Vitamin D Role in Space

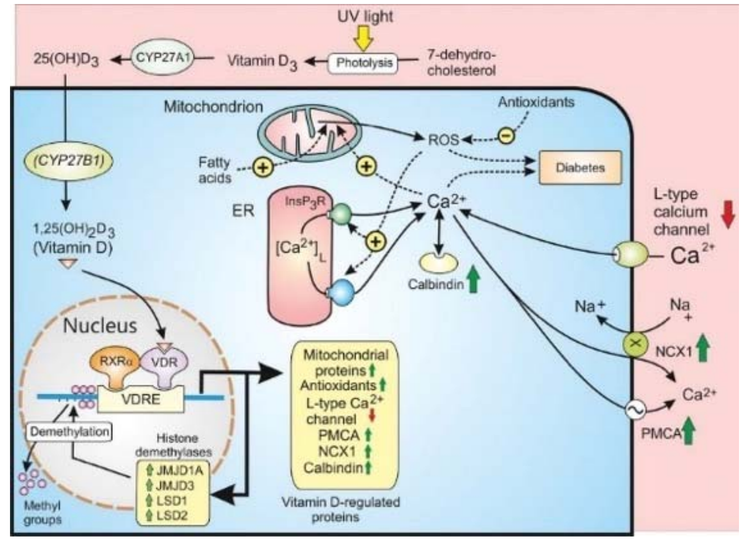
JN THE JOURNAL OF NUTRITION

The Nutritional Status of Astronauts Is Altered after Long-Term Space Flight Aboard the International Space Station[1]

Scott M. Smith,*[2] Sara R. Zwart,* Gladys Block,† Barbara L. Rice,** and Janis E. Davis-Street**

*Human Adaptation and Countermeasures Office, NASA Lyndon B. Johnson Space Center, Houston, TX 77058; †Epidemiology and Public Health Nutrition, University of California-Berkeley, Berkeley, CA 94720; and **Enterprise Advisory Services, Inc., Houston, TX 77058

Despite vitamin D supplement use during flight, serum 25-hydroxycholecalciferol was decreased after flight ($P < 0.01$).



Vitamin D acts to prevent diabetes by maintaining low levels of Ca^{2+} and ROS.
Berridge, 2017

Molecular and Cellular Endocrinology 450 (2017) 24–31

Spotlight on vitamin D receptor, lipid metabolism and mitochondria: Some preliminary emerging issues

Francesca Silvagno*, Gianpiero Pescarmona

Vitamin D Receptor has been defined a <u>gatekeeper of mitochondrial respiratory chain activity.</u>

nutrients

Review

Vitamin D Supplementation and Non-Alcoholic Fatty Liver Disease: Present and Future

Ilaria Barchetta, Flavia Agata Cimini and Maria Gisella Cavallo *

Epidemiological studies point towards an association between hypovitaminosis D and the presence of NAFLD and steatohepatitis (NASH), independently of confounders such as obesity and insulin resistance.

Willian da Silveira

Gary Hardiman

Circadian Rhythm, Vitamin D, and Mitochondria

Antioxid Redox Signal. 2014 Jun 20; 20(18): 2982–2996.
doi: 10.1089/ars.2013.5645
PMCID: PMC4038996
PMID: 24111846

Skin, Reactive Oxygen Species, and Circadian Clocks

Mary A. Ndiaye,[1] Minakshi Nihal,[1] Gary S. Wood,[1,2] and Nihal Ahmad[1,2]

Abstract

Go to:

Significance: Skin, a complex organ and the body's first line of defense against environmental insults, plays a critical role in maintaining homeostasis in an organism. This balance is maintained through a complex network of cellular machinery and signaling events, including those regulating oxidative stress and circadian rhythms. These regulatory mechanisms have developed integral systems to protect skin cells and to signal to the rest of the body in the event of internal and environmental stresses. ***Recent Advances:*** Interestingly, several signaling pathways and many bioactive molecules have been found to be involved and even important in the regulation of oxidative stress and circadian rhythms, especially in the skin. It is becoming increasingly evident that these two regulatory systems may, in fact, be interconnected in the regulation of homeostasis. Important examples of molecules that connect the two systems include serotonin, melatonin, vitamin D, and vitamin A. ***Critical Issues:*** Excessive reactive oxygen species and/or dysregulation of antioxidant system and circadian rhythms can cause critical errors in maintaining proper barrier function and skin health, as well as overall homeostasis. Unfortunately, the modern lifestyle seems to contribute to increasing alterations in redox balance and circadian rhythms, thereby posing a critical problem for normal functioning of the living system. ***Future Directions:*** Since the oxidative stress and circadian rhythm systems seem to have areas of overlap, future research needs to be focused on defining the interactions between these two important systems. This may be especially important in the skin where both systems play critical roles in protecting the whole body. *Antioxid. Redox Signal.* 20, 2982–2996.

Antioxid Redox Signal

RR3 - EYE (BALB/c) :
Up-regulated: Functional Annotation Clustering

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Open Science for Exploration

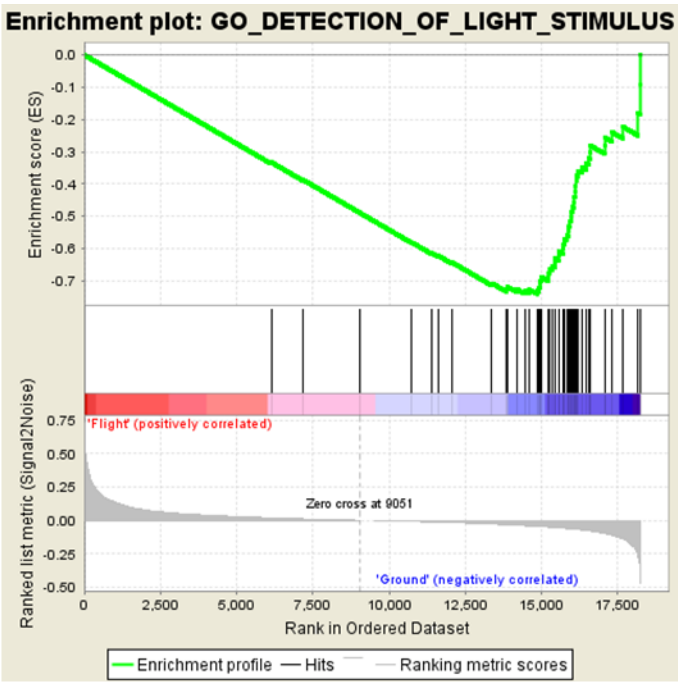
- **Most up-regulated Gene:**
  Gene: Defb7 (ENSMUSG00000037790.3)
  Role: Beta-defensin 7 has bactericidal activity and is involved in defense response to bacteria
  Log_2 fold-change: 22
  Adjusted p-value: 2.94e-7

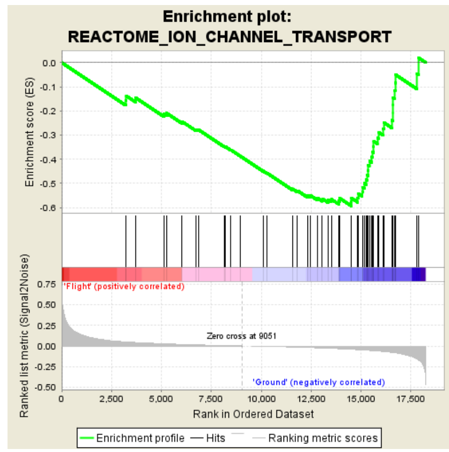
otation Cluster 1	Enrichment Score: 8.69		Count	P_Value	Benjamini
‹M_BP_FAT	fatty acid metabolic process	RT	17	1.9E-10	2.1E-7
‹_KEYWORDS	lipid metabolism	RT	15	2.0E-10	1.7E-8
‹_KEYWORDS	fatty acid metabolism	RT	10	1.6E-8	7.9E-7
_PATHWAY	PPAR signaling pathway	RT	12	2.9E-8	2.5E-6
otation Cluster 2	**Enrichment Score: 7.69**		**Count**	**P_Value**	**Benjamini**
‹M_CC_FAT	peroxisome	RT	17	6.4E-14	8.9E-12
‹M_CC_FAT	microbody	RT	17	6.4E-14	8.9E-12
‹_KEYWORDS	peroxisome	RT	15	1.6E-12	4.2E-10
‹M_CC_FAT	microbody part	RT	8	5.6E-8	3.9E-6
‹M_CC_FAT	peroxisomal part	RT	8	5.6E-8	3.9E-6
‹M_CC_FAT	peroxisomal membrane	RT	6	1.1E-5	2.3E-4
‹M_CC_FAT	microbody membrane	RT	6	1.1E-5	2.3E-4
Q_FEATURE	short sequence motif:Microbody targeting signal	RT	6	1.5E-4	3.8E-2
‹M_BP_FAT	peroxisome organization	RT	4	1.5E-3	6.0E-2
otation Cluster 3	**Enrichment Score: 4.64**		**Count**	**P_Value**	**Benjamini**
‹M_MF_FAT	carboxylic acid binding	RT	11	5.5E-8	1.0E-5
‹M_MF_FAT	vitamin binding	RT	10	1.2E-5	1.5E-3
‹M_MF_FAT	amino acid binding	RT	5	5.7E-4	2.1E-2
‹M_MF_FAT	amine binding	RT	6	7.3E-4	2.2E-2

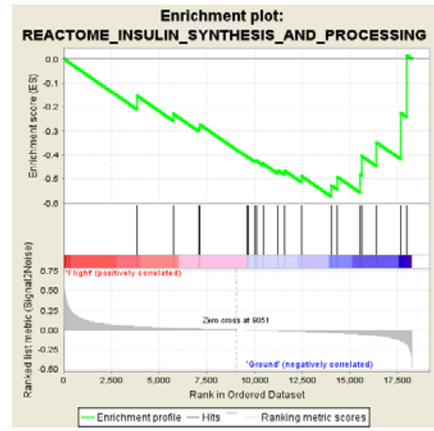

Kathryn Grabek

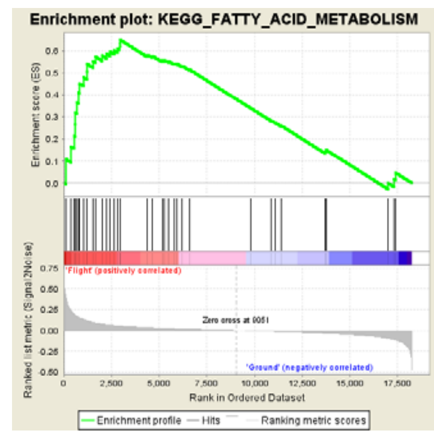

Helio Costa

RR3 - EYE (BALB/c) :
GSEA Analysis









NAME	NOM p-val	FDR q-val
GO_FOLIC_ACID_CONTAINING_COMPOUND_METABOLIC_PROCESS	0.003	0.01
GO_POLYOL_METABOLIC_PROCESS	0.014	0.17
GO_DETECTION_OF_LIGHT_STIMULUS	<0.001	<0.001
REACTOME_ION_CHANNEL_TRANSPORT	<0.001	0.01
REACTOME_INSULIN_SYNTHESIS_AND_PROCESSING	0.044	0.18
KEGG_FATTY_ACID_METABOLISM	<0.001	0.003

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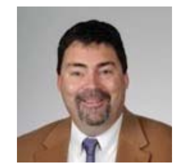
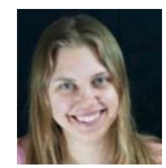


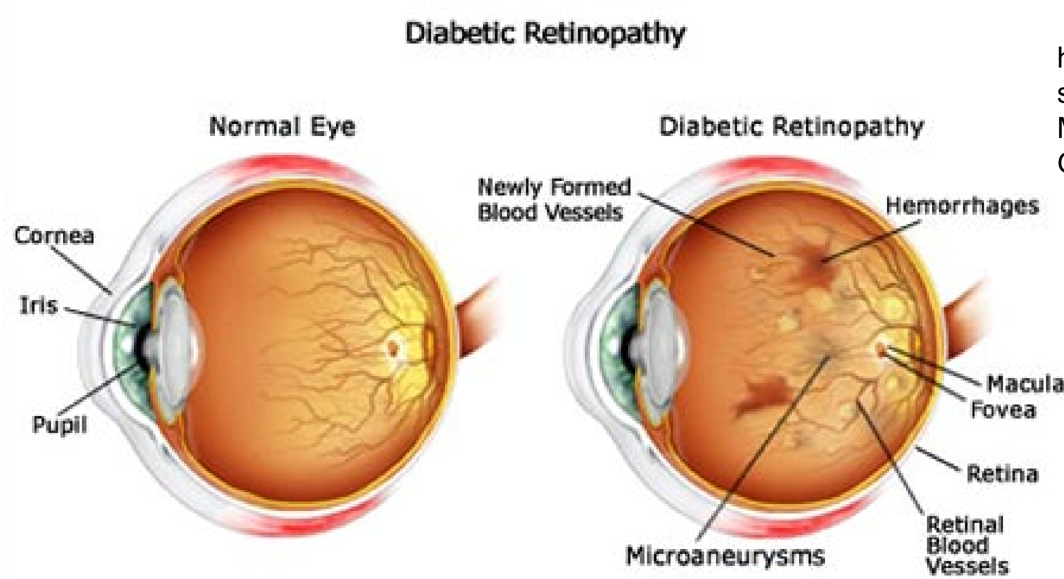
Gary Hardiman



Kathryn Grabek

Helio Costa

Analysis Relating Liver to the Eye



https://www.eyedoctorophthalmologistnyc.com
Molecular Biology of the Cell, Garland Science; 5th edition. 2007.

Willian da Silveira

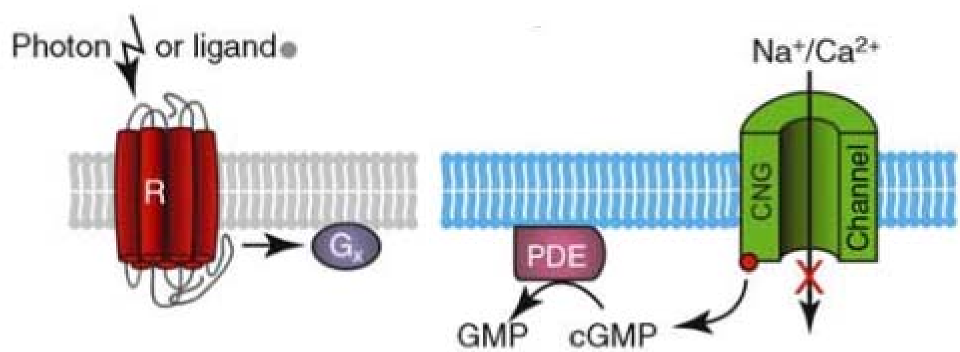
Gary Hardiman

Kathryn Grabek

Helio Costa

Cone Cells - Eye

1st Amplification 2nd Amplification 3rd Amplification



Overcoming Batch Effects: RR3 – Liver: Proteomics

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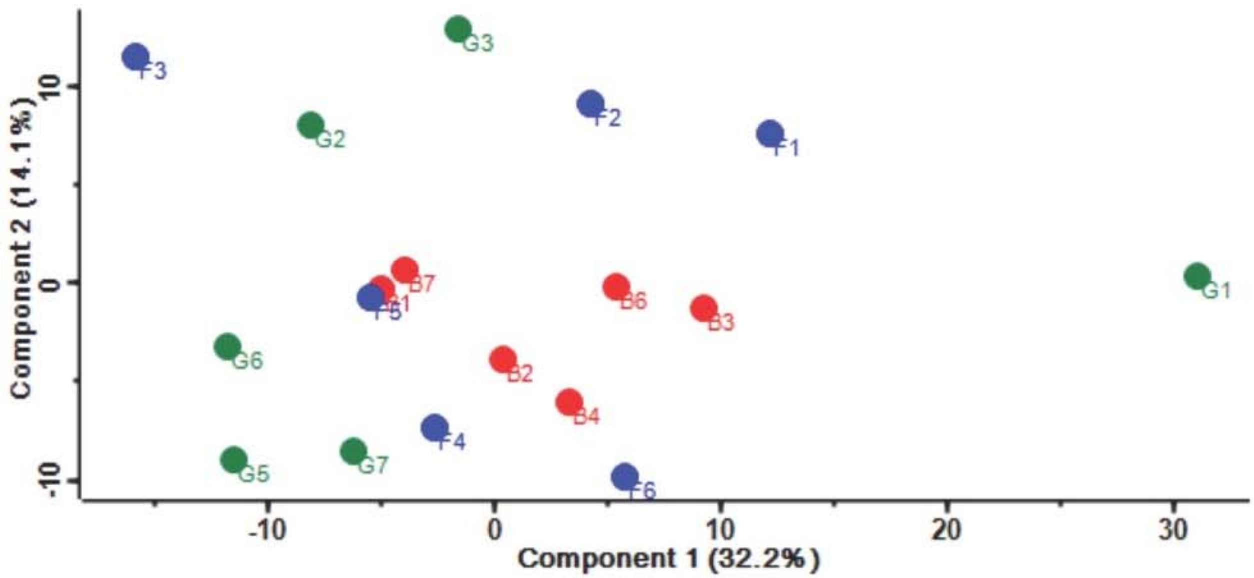
Data processing: PCA plot of normalized & ComBat treated data

Normalized to the proteins of the baseline samples (B)



G1 and F3 seem to be outliers. I removed these two samples for the further analysis.

●Flight ●Ground ●Basel

Deanne Taylor

Hossein Fazelinia

Significantly Expressed Protein RR3 – Liver: Proteomics

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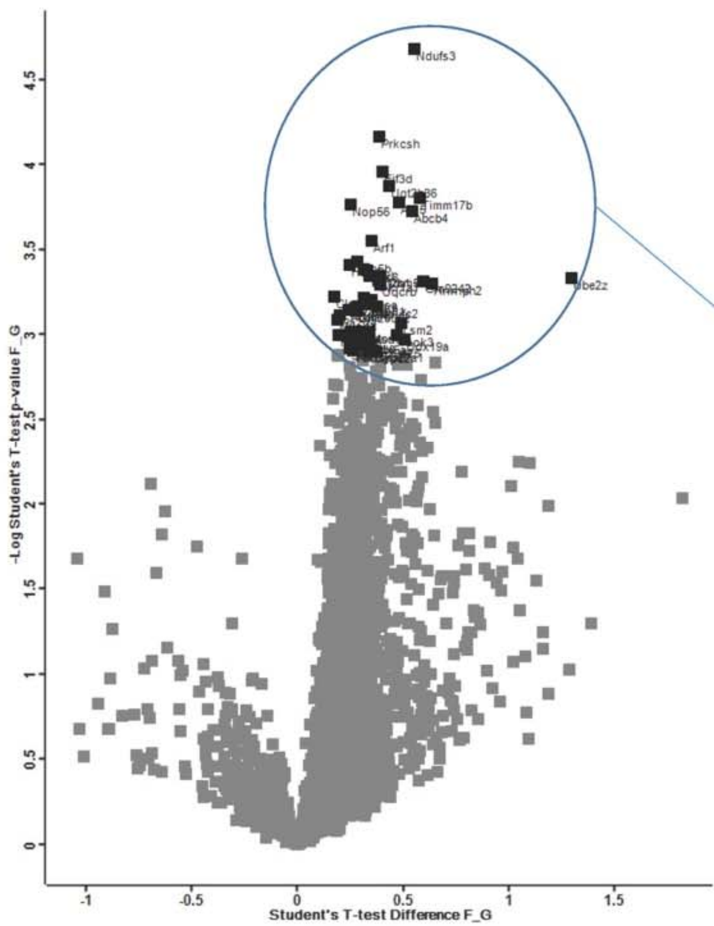
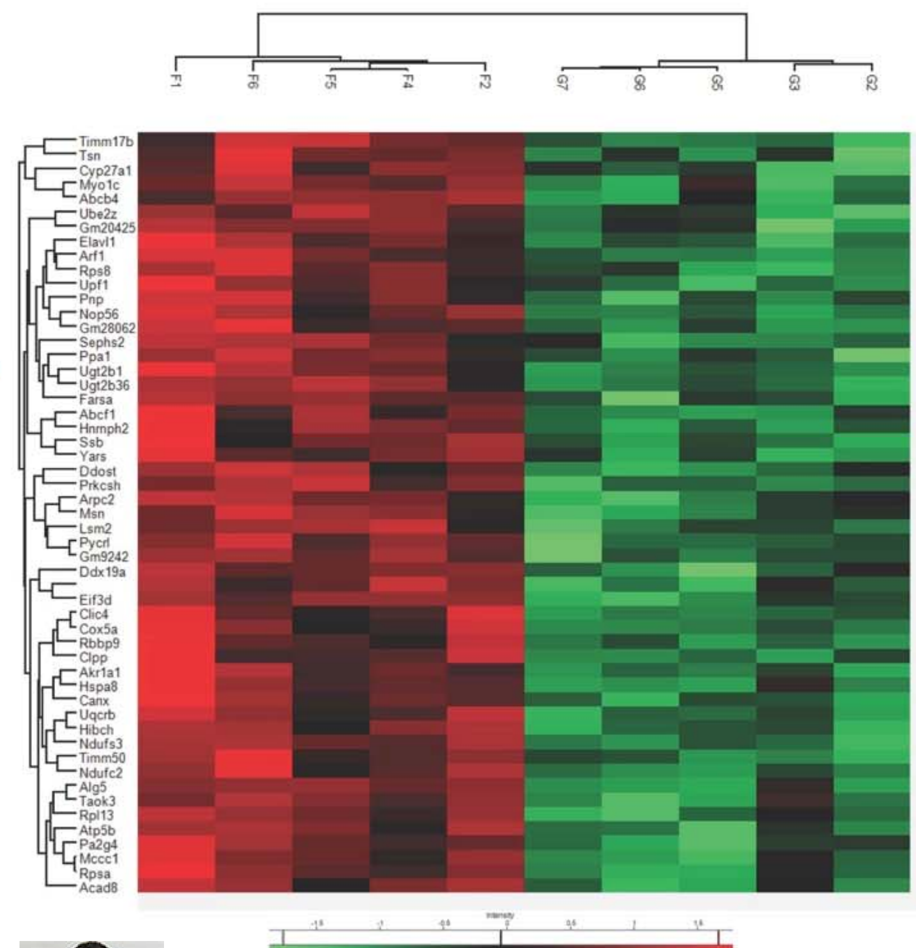
T-test analysis with %5 FDR



Heat map of significantly changed proteins



Deanne Taylor

Hossein Fazelinia

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Open Science for Exploration

Protein Pathway Analysis
RR3 – Liver: Proteomics

Data processing: GO term analysis for significant proteins

#	Molecular functions	Min FDR	In Data
1	RNA binding	1.471E-09	25
2	catalytic activity	8.716E-08	42
3	heterocyclic compound binding	1.472E-05	38
4	ATP binding	1.472E-05	18
5	small molecule binding	1.472E-05	24
6	organic cyclic compound binding	1.478E-05	38
7	adenyl ribonucleotide binding	1.478E-05	18
8	adenyl nucleotide binding	1.478E-05	18
9	purine ribonucleoside triphosphate binding	3.401E-05	19
10	anion binding	3.742E-05	24
11	purine ribonucleotide binding	3.742E-05	19
12	ATPase activity	3.742E-05	10
13	purine nucleotide binding	3.742E-05	19
14	ribonucleotide binding	3.742E-05	19
15	ATPase activity, coupled	4.245E-05	9
16	carbohydrate derivative binding	9.412E-05	20
17	nucleotide binding	9.412E-05	20
18	nucleoside phosphate binding	9.412E-05	20
19	monocarboxylic acid binding	9.412E-05	5
20	ceramide-translocating ATPase activity	1.267E-04	2

#	Processes	Min FDR	In Data
1	small molecule metabolic process	1.496E-06	25
2	aromatic compound catabolic process	1.496E-06	13
3	peptide metabolic process	8.235E-06	14
4	uronic acid metabolic process	8.568E-06	5
5	glucuronate metabolic process	8.568E-06	5
6	cellular amide metabolic process	1.024E-05	15
7	protein targeting	1.075E-05	10
8	organic acid metabolic process	1.075E-05	17
9	carboxylic acid metabolic process	1.075E-05	16
10	organic cyclic compound catabolic process	1.075E-05	12
11	cellular amino acid metabolic process	1.681E-05	10
12	cellular catabolic process	1.752E-05	21
13	translation	2.470E-05	11
14	lysosomal membrane organization	2.709E-05	3
15	purine ribonucleoside triphosphate metabolic process	2.709E-05	9
16	oxoacid metabolic process	2.709E-05	16
17	metabolic process	2.713E-05	53
18	ribonucleoside triphosphate metabolic process	2.787E-05	9
19	purine nucleoside triphosphate metabolic process	2.787E-05	9
20	cellular metabolic process	2.904E-05	50

#	Localizations	Min FDR	In Data
1	cytoplasm	1.491E-10	63
2	cytoplasmic part	1.799E-08	52
3	macromolecular complex	1.349E-07	37
4	inner mitochondrial membrane protein complex	2.003E-07	8
5	intracellular organelle part	2.489E-07	48
6	organelle part	5.429E-07	48
7	mitochondrial protein complex	5.429E-07	8
8	ribonucleoprotein complex	5.429E-07	15
9	intracellular ribonucleoprotein complex	3.692E-06	14
10	mitochondrial part	4.006E-06	15
11	intracellular part	4.006E-06	63
12	mitochondrial membrane part	4.006E-06	8
13	mitochondrial inner membrane	4.038E-06	11
14	organelle inner membrane	1.103E-05	11
15	intracellular	1.315E-05	63
16	mitochondrial membrane	1.725E-05	12
17	organelle envelope	2.340E-05	15
18	envelope	2.340E-05	15
19	mitochondrial envelope	2.492E-05	12
20	myelin sheath	2.492E-05	7

Protein Pathway Analysis RR3 – Liver: Proteomics

GeneLab
Open Science for Exploration

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Related mitochondria functions are revealed from the initial proteomic analysis!!

Protein Pathway Analysis
RR3 – Liver: Proteomics

Data processing: GO term analysis for significant proteins

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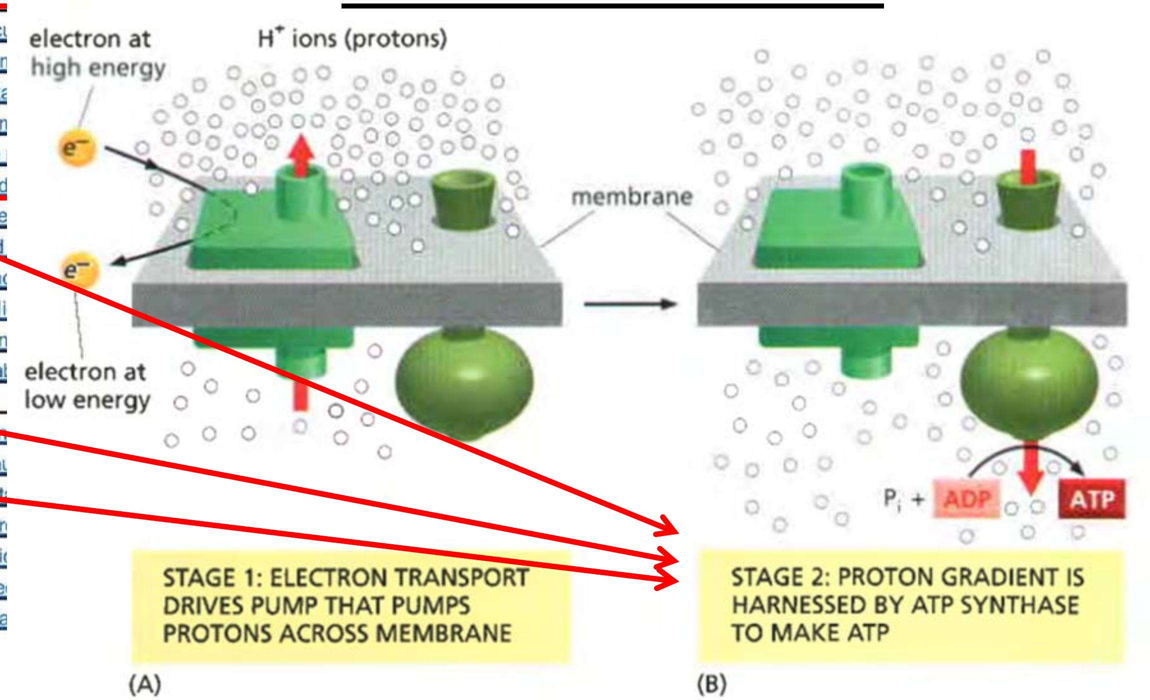
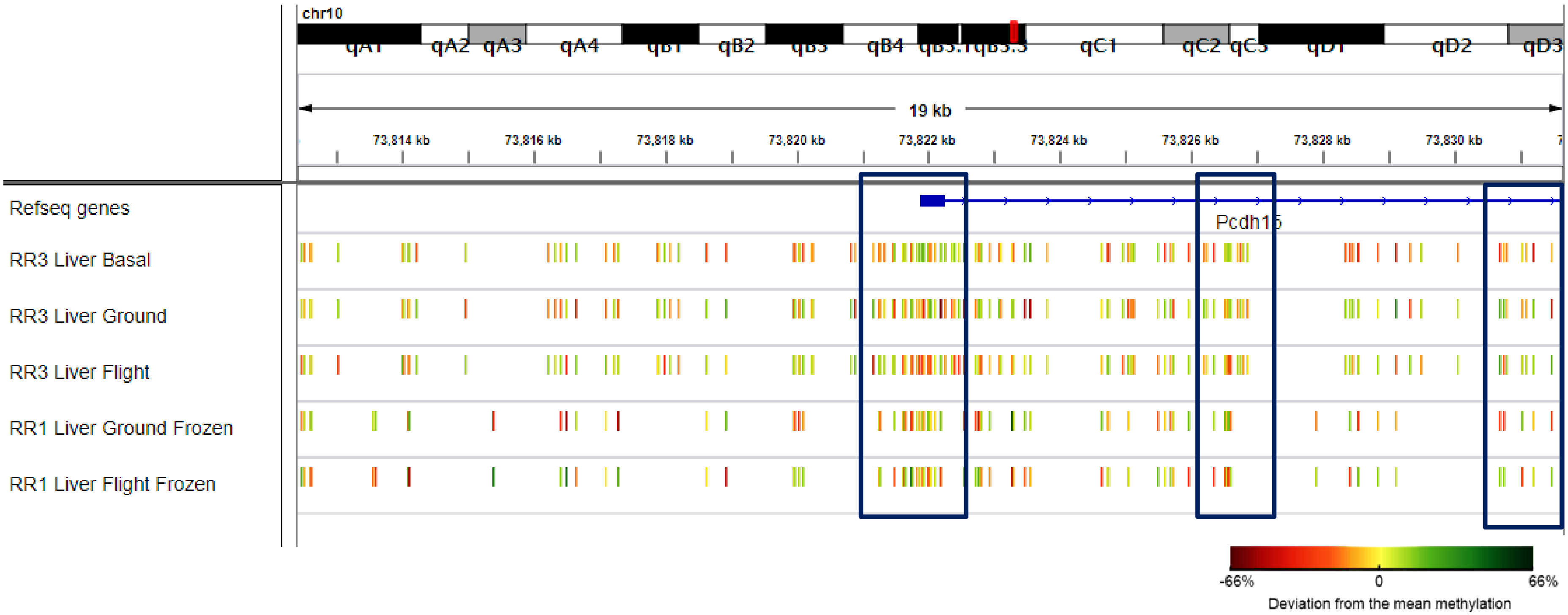
13	translation
14	lysosomal m
15	purine ribonu
16	oxoacid meta
17	metabolic pr
18	ribonucleosi
19	purine nucle
20	cellular meta

Mitochondria – All Cells

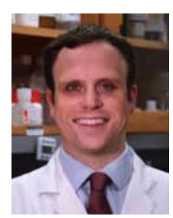


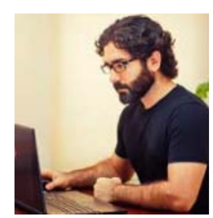
Related mitochondria functions are revealed from the initial proteomic analysis!!

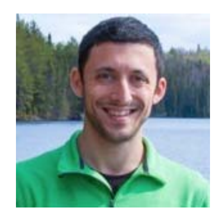
Preliminary Methylation Data for RR1 and RR3 datasets



Deviation from mean
separate for each experiment







Chris Mason **Cem Meydan** **Jonathan Foox**

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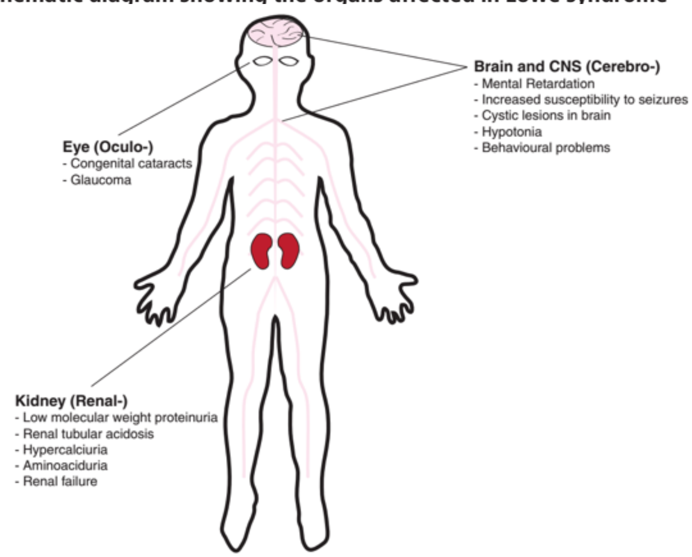
Hypothesis Developed and Being Worked On

- **Spaceflight changes the physical properties of the cell components impacting from the molecular to the whole body level.**
- **The Mitochondria are the principal cellular component affect.**
- **The Liver is the principal organ affected in issues related to the metabolism.**
- **Overall circadian rhythm pathways are being disrupted**
- Possible disease that can be associated with liver damage and pathways is: <u>Oculocerebrorenal Syndrome of Lowe</u>

  - "Extensive research has demonstrated that OCRL-1 is involved in multiple intracellular processes involving endocytic trafficking and actin skeleton dynamics. This explains the multi-organ manifestations of the disease."
  - "The classic form of the oculocerebrorenal syndrome of Lowe (OMIM #309000), first described by Lowe et al. in 1952 [1], is characterized by the triad of congenital cataracts, severe intellectual impairment, and renal tubular dysfunction with slowly progressive renal failure"
  - Patients with this disease manifest Cataract, Glaucoma and Muscle hypotonia.

Schematic diagram showing the organs affected in Lowe syndrome



Mehta, Zenobia B et al. "The Cellular and Physiological Functions of the Lowe Syndrome Protein OCRL1." *Traffic* (2014).

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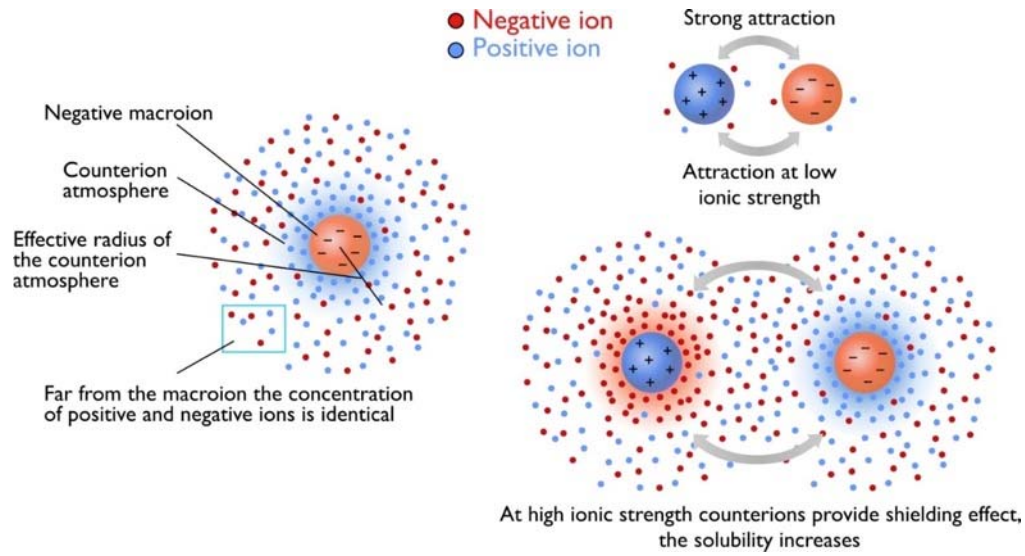
Hypothesis Developed and Being Worked On (Ion Diffusion)

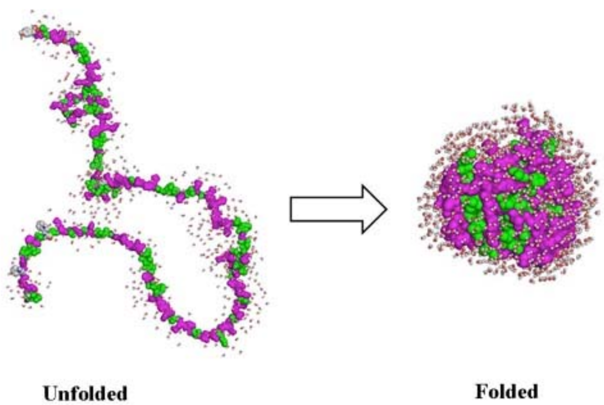
Assumptions:

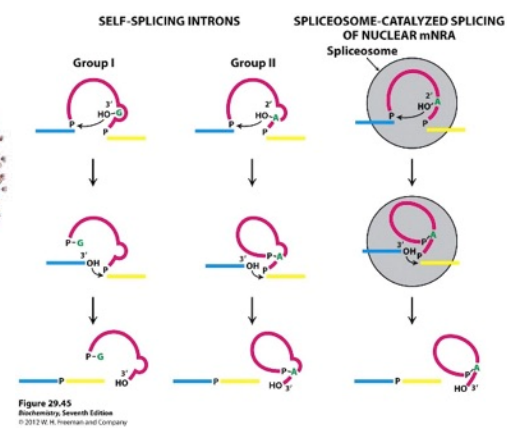
- Gravity is a physical property.
- Alteration in Gravity must have a primary impact in physical properties of a cell, like ion diffusion.
- Eletrostatics properties of proteins influence protein-protein interaction and/or protein folding, the same can happen with RNA strutures.
- Ions are critical for Eletrostatics properties of the proteins, RNAs and etc.

Hypotheses:

- By altering Ion Diffusion, microgravity can influence cellular events by altering Protein-Protein Interaction and "Binding", Protein folding and RNA structures what would influence RNA splicing.
- Is expected that other Physiological properties dependent of Ion diffusion will be impacted too.







http://elte.prompt.hu/sites/default/files/tananyagok/IntroductionToPracticalBiochemistry/ch05s04.html
https://step1.medbullets.com/biochemistry/102094/protein-folding-and-degradation

Hypothesis Developed and Being Worked On (Ions and Mitochondria)

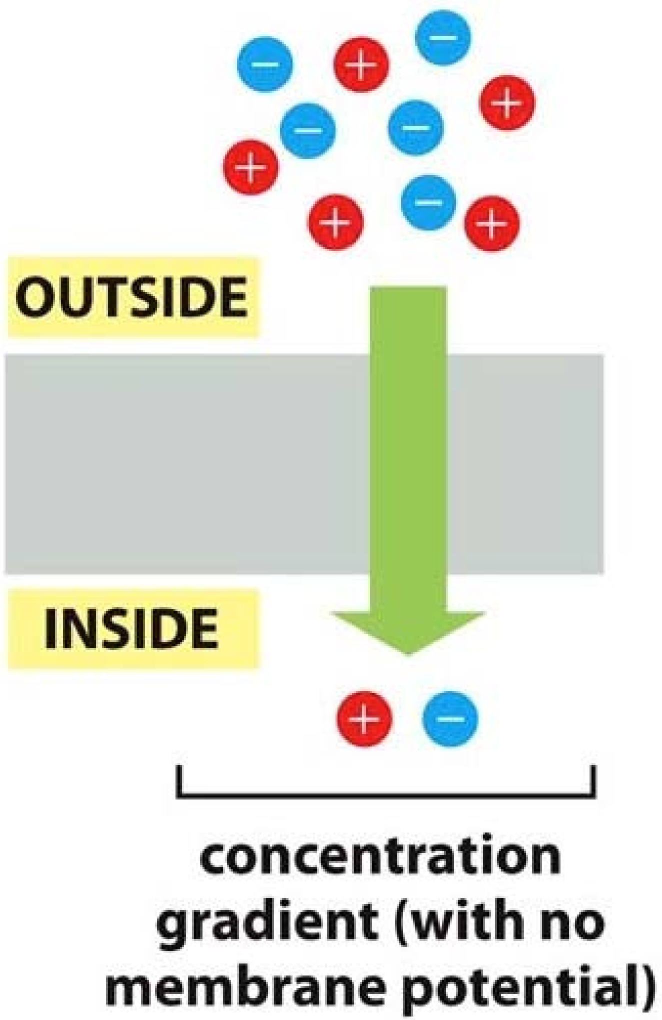
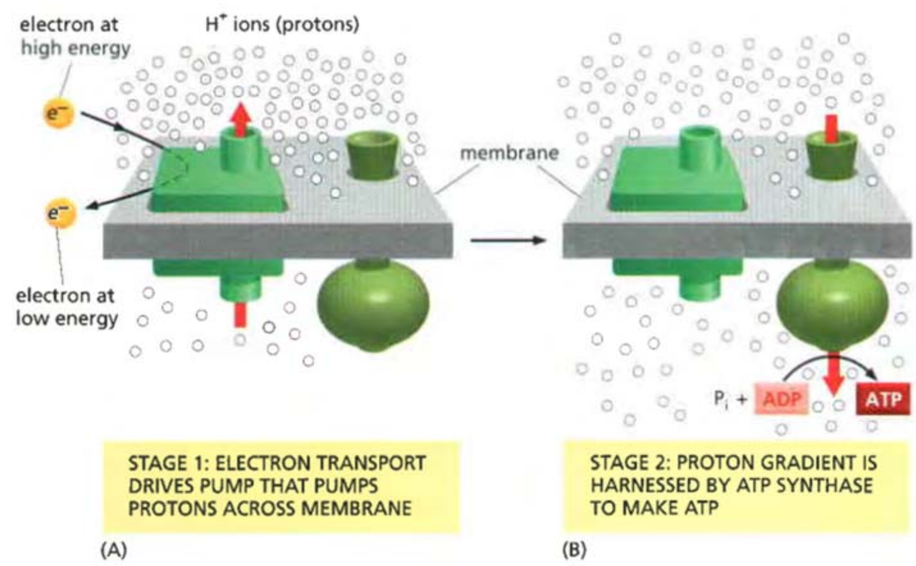
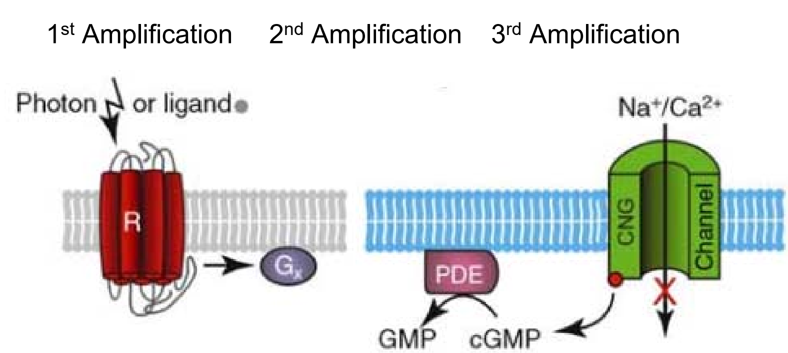


Figure 11-4b Molecular Biology of the Cell 6e (© Garland Science 2015)

Mitochondria – All Cells



Cone Cells - Eye

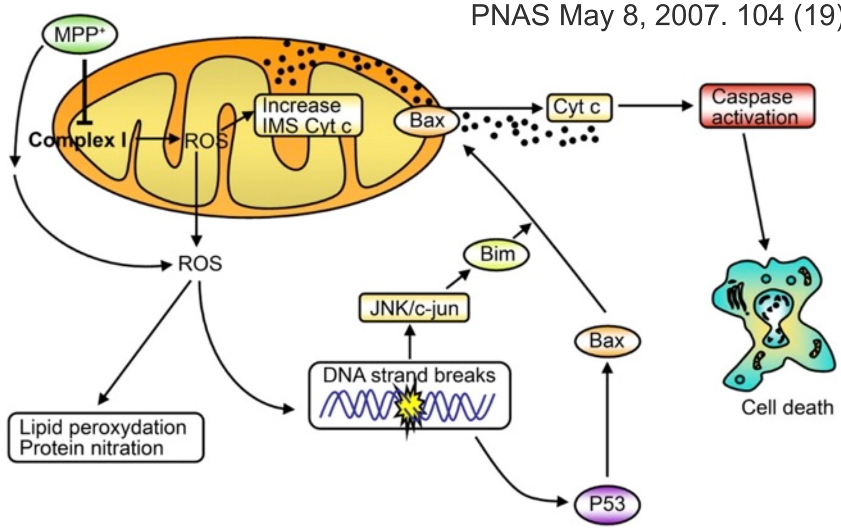


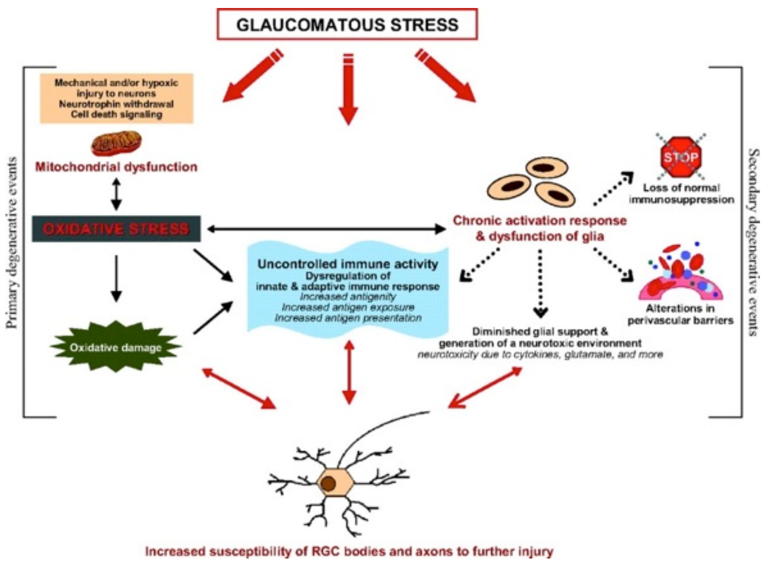
Molecular Biology of the Cell, Garland Science; 5th edition. 2007.

Alternative Hypothesis being Considered (Ions and Mitochondria)

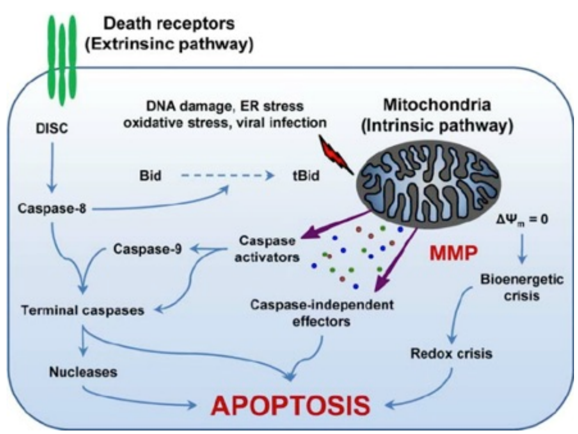
- Mitochondria can be disrupted by one single particle traversal in one single mitochondria and create a cascade of event, including oxidative stress lasting several days in the exposed cell

PNAS May 8, 2007. 104 (19) 8161-8166





Investigative Ophthalmology & Visual Science March 2009, Vol.50, 1001-1012. doi:10.1167/iovs.08-2717



Galluzzi L, Brenner C, Morselli E, Touat Z, Kroemer G (2008) Viral Control of Mitochondrial Apoptosis. PLoS Pathog 4(5): e1000018. https://doi.org/10.1371/journal.ppat.1000018

Systems Biology Analysis Used to Understand Spaceflight Impact on Health Risk

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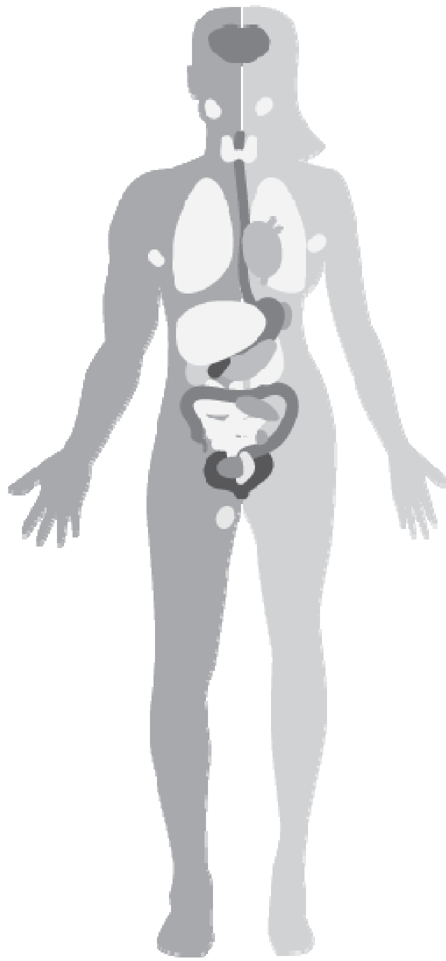
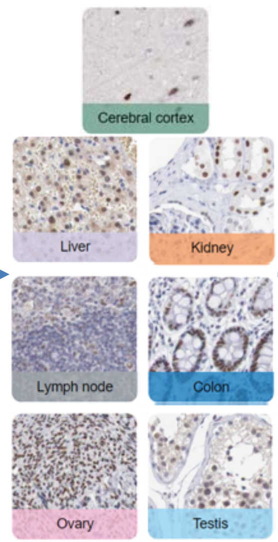
Level 7: The Body
Level 6: Organs



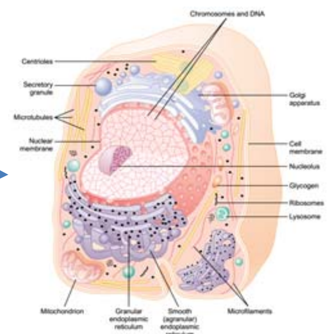
Inflammation, Lipid Accumulation, alteration of cell migration and etc.

Level 5: Tissues



Mitochondrial Stress And Cytoskeleton alteration

Level 4: The Cell and its Organelles



Protein Complexes and The Electron Chain Reaction

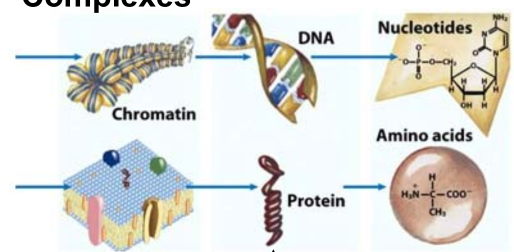
Level 3: Supra molecular Complexes

Electrostatic Properties and Folding

Level 2: Macro molecules

Ion Diffusion

Level 1: Monomeric Units



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Visualization Tools to Implement on GeneLab Platform

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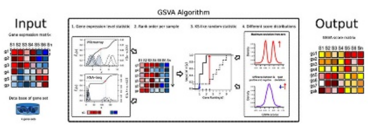
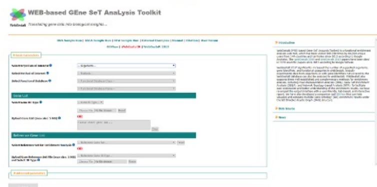
Visualization Tools

Top Picks from AWG

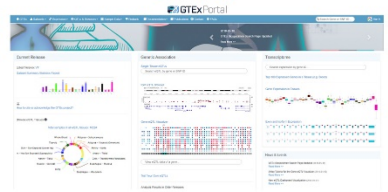
GSVA/GSEA



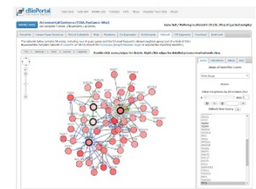
Webgestalt



G-Tex



cBioPortal



Other Open Source Tools

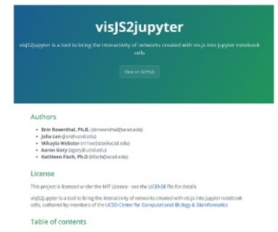
REVIGO

Toppfun

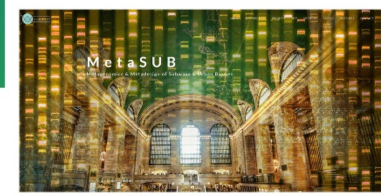
GOrilla

Cytoscape

VisJS2Jupyter

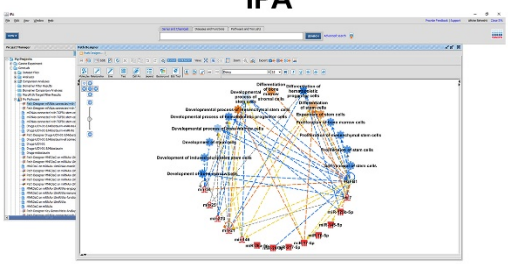


MetaSub

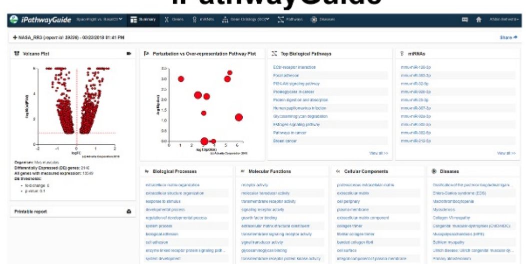


Proprietary Software

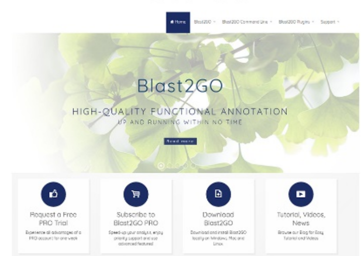
IPA



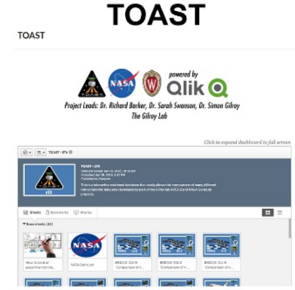
iPathwayGuide



Blast2Go



TOAST



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Visualization Tools to Implement on GeneLab Platform

Visualization Tools

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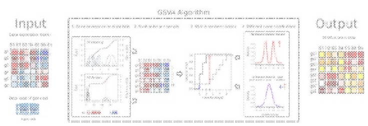

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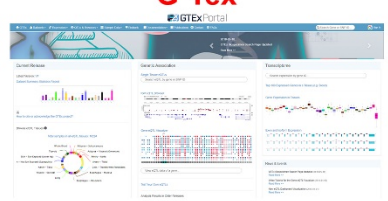

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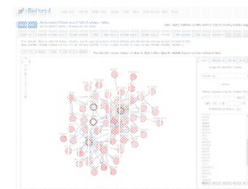

VisJS2Jupyter

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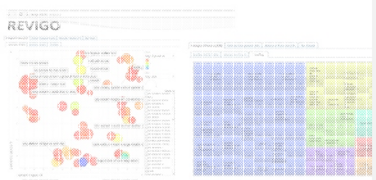
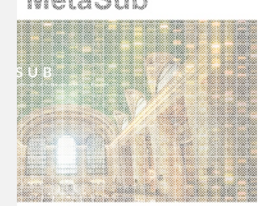


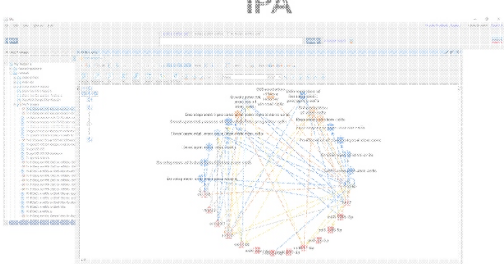
MetaSub



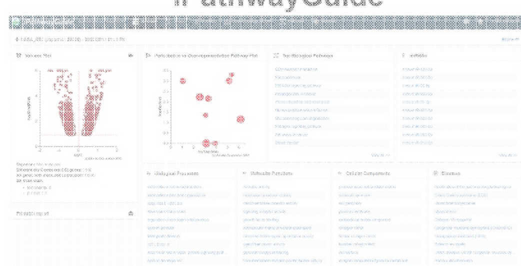
Members of G-Tex have offered to help with development of G-Tex for our GeneLab platform. Multi-Omics AWG member helped make the connection with G-Tex

Proprietary Software

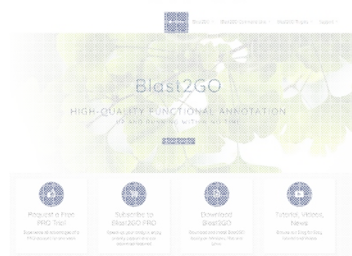
IPA



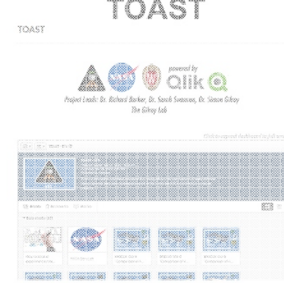
iPathwayGuide



Blast2Go



TOAST



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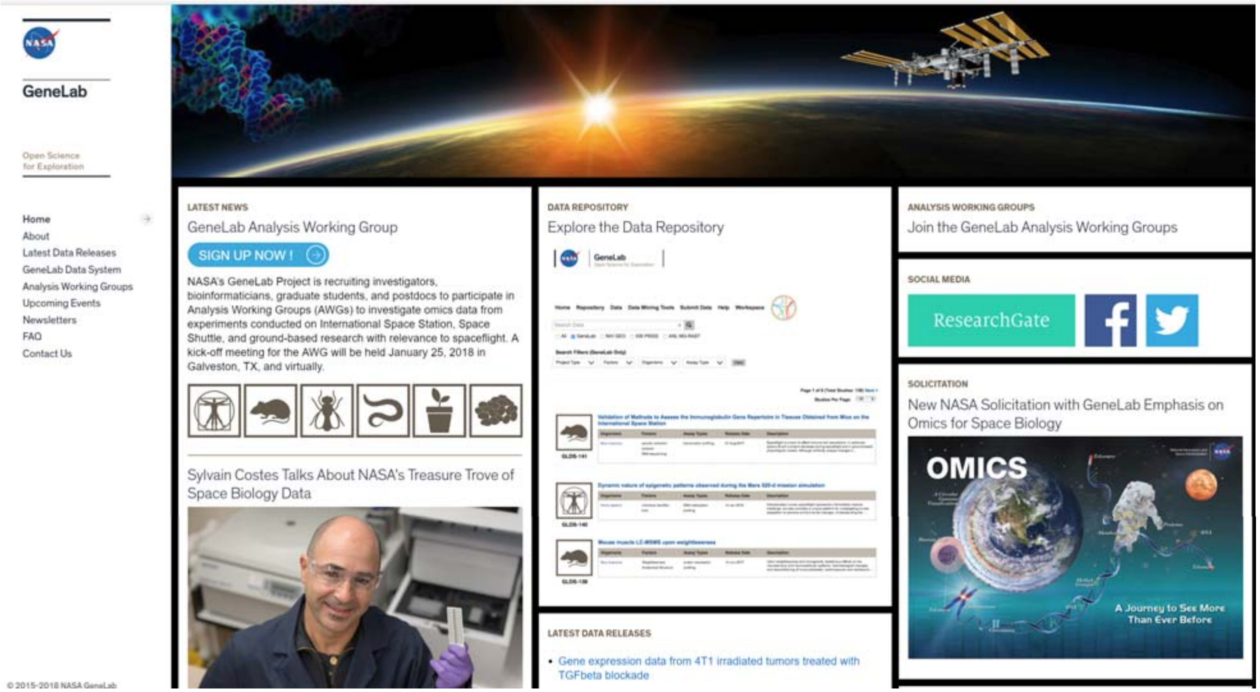
Science Communications



Engage broadest community of researchers, industry, and citizen scientists to advance innovations

https://genelab.nasa.gov

- Weekly social media posts:
  - @NASAAmes **Facebook**
  - **Twitter** #GeneLab
  - **ResearchGate**: https://www.researchgate.net/project/Omics-for-Space-Biology-The-GeneLab-project
- GeneLab database listed in science journals:
  - *Scientific Data*, *Oxford e-Research*
- *GeneLab issues Digital Object Identifiers (DOI) via DataCite*
- Customer Support: Respond and resolve all inquiries from science community, academia, public

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SciComm- Increase Users of the GeneLab Data Repository

– Conferences, Workshops, & Public Outreach Events

- – ASGSR: Presentations, Galaxy platform training sessions
- – AMIA: Learning Showcase – Spotlight on GeneLab
- – AAAS: Session - NASA's GeneLab Project and the Systems Biology of Spaceflight
- – COSPAR, ISSR&D: Presentations
- – Experimental Biology, Plant Biology, Cell Biology, ASM Microbe: Exhibit booths
- – BioData West Open Targets: Workshop & Data-thon
- – California Academy of Sciences, San Francisco Exploratorium

– Social Media, Website, Newsletter, Podcasts, Videos

- Facebook, Twitter, ResearchGate, LinkedIn (weekly posts)
- New Drupal Website (rollout Sept. 28); links to NASA portal, Space Biology
- Quarterly newsletter (700 subscribers)
- NASA Silicon Valley Podcasts
- New GeneLab” video in collaboration with ISS Program Science Office
- GeneLab User Training videos (Oct. 31)

SciComm- Increase Users of the GeneLab Data Repository

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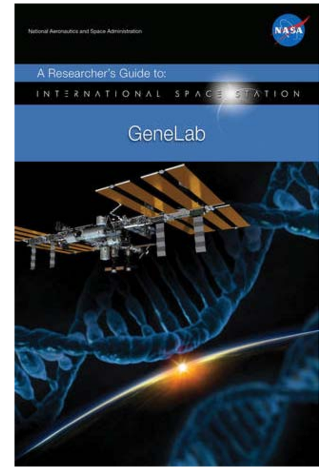

- **Seminars, Webinars**
  - Broad Institute, JPL, JSC, UC San Diego, Stanford, Osaka City Univ - Japan, CSA
  - LabRoots, Genes in Space
- **SciComm Publication**
  - NASA's Researcher's Guide to GeneLab
- **Internship**
  - GeneLab for High Schools
    - Space biology training initiative for high school students on teaching the importance of omics studies and space biology. Students analyze GeneLab datasets and develop research proposals.