

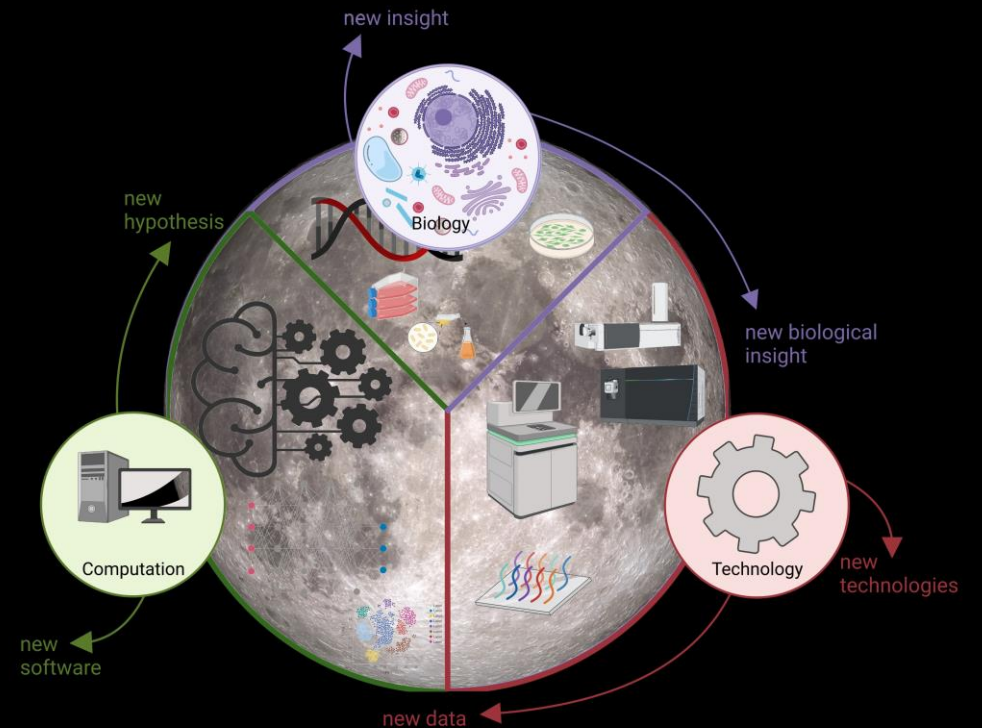
# Computational and systems biology approach utilizing multiple public databases/platforms to address key biological changes associated with health risks occurring during spaceflight

**Afshin Beheshti, PhD**

*Principal Investigator*

*Blue Marble Space Institute of Science*

[afshin.beheshti@bmsis.org](mailto:afshin.beheshti@bmsis.org)



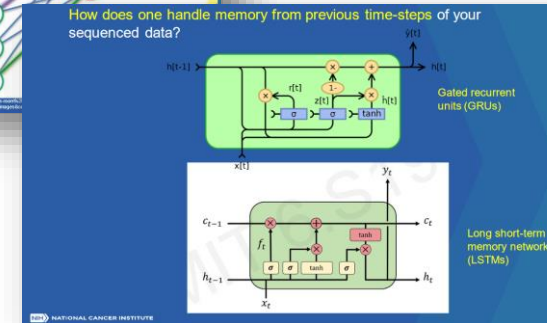
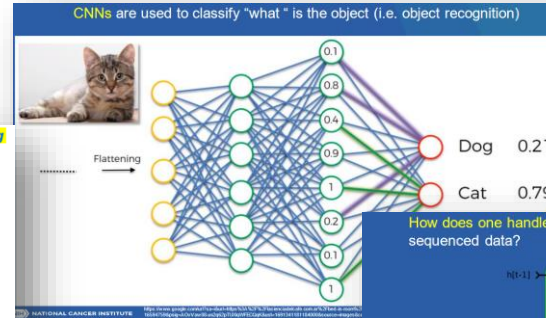
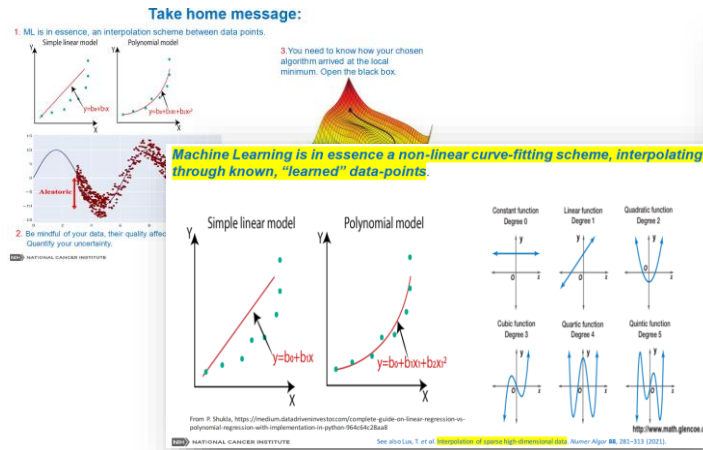
Part of the work was performed under the Funding from NASA's Biological and Physical Sciences Division to NASA Ames under the Task: ID016GLS under KBR Contract Number: NNA14AB82C.

Created with BioRender

# Lessons Learned From Our Previous Speakers



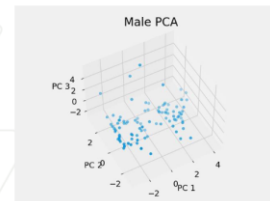
Ceferino Obcemea,  
Ph.D.



**ML models are great curve-fitting tools and provide key analysis for object recognition!!!**

**AI → CFPD → Advanced Mathematics**  
**Singular Value Decomposition: Principal Component Analysis**

Extracts the dimension or "Component" in the data with more linear variance.  
Essentially it looks for the direction in which the data is most spread

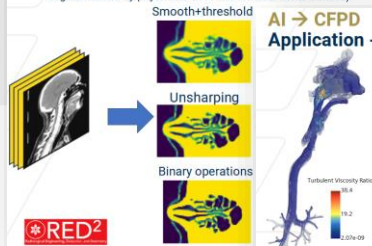


RED<sup>2</sup>

**AI → CFPD**  
**Morphological Techniques: CT Segmentation Upper HRT**

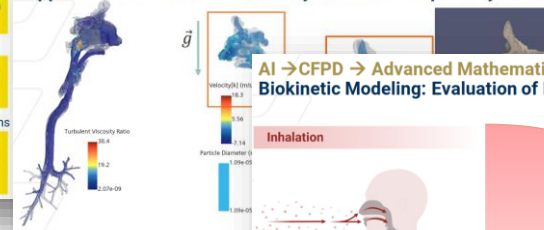
Nasal cavity, automatic segmentation algorithm:

- Complex geometry
- Very challenging to capture all the sinus (in fact most of the manual segmentations by physicians does not consider some cavities)



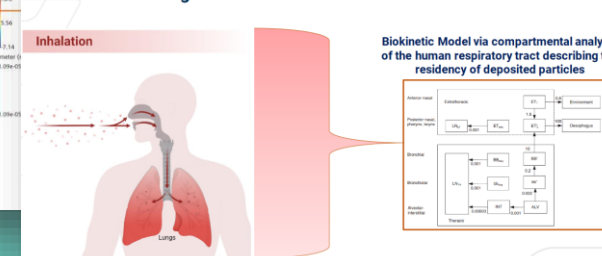
RED<sup>2</sup>

**AI → CFPD**  
**Application - Fluid and Particle Dynamics in Respiratory Tract**



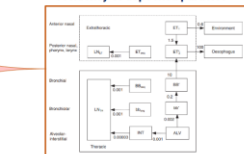
RED<sup>2</sup>

**AI → CFPD → Advanced Mathematics → AI → Advanced Mathematics**  
**Biokinetic Modeling: Evaluation of Radiation Mechanism**



RED<sup>2</sup>

Biokinetic Model via compartmental analysis of the human respiratory tract describing the residency of deposited particles



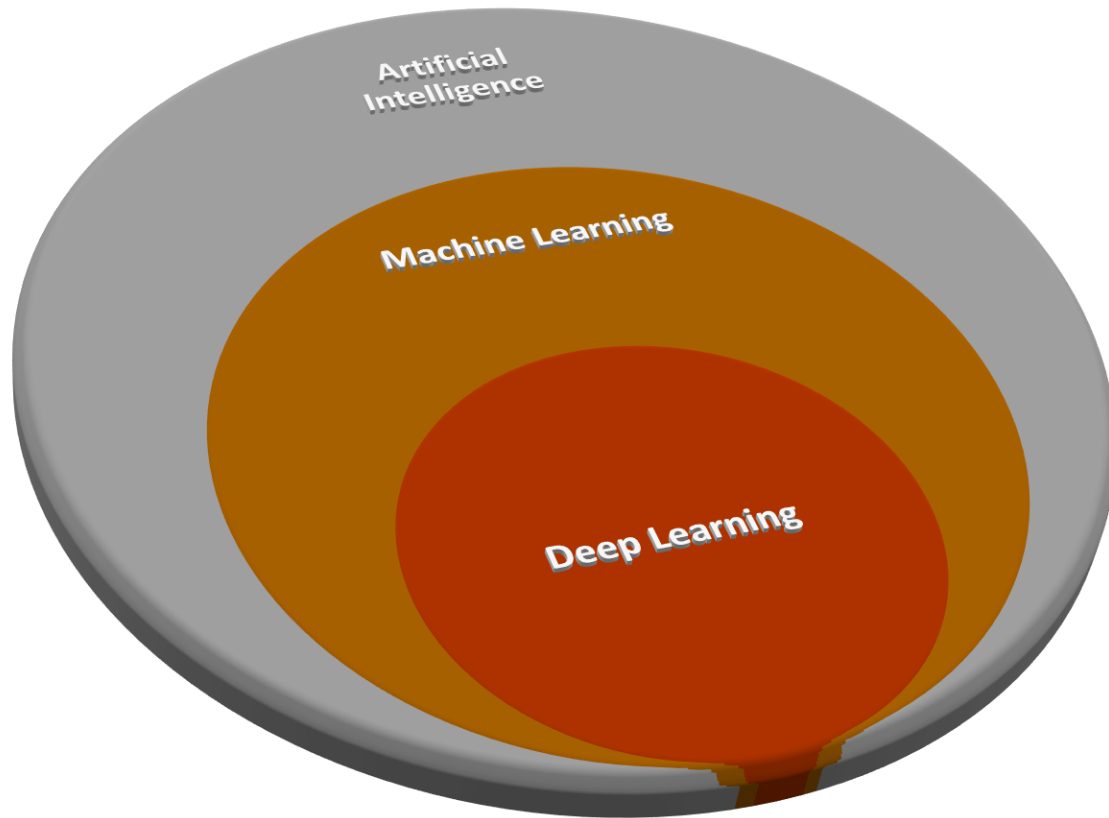
Georgia Tech



Shaheen A.  
Dewji, Ph.D.

**AI/ML models key in producing novel findings with publicly available data on images and big datasets!!!**

# Computational Modeling in Biology



## **Artificial Intelligence**

Computational technique that enables mimic of human intelligence

## **Machine Learning**

A field of AI that utilizes statistical methods/algorithm to enable computers to learn from experience to improve performance as it is exposed to more data over time

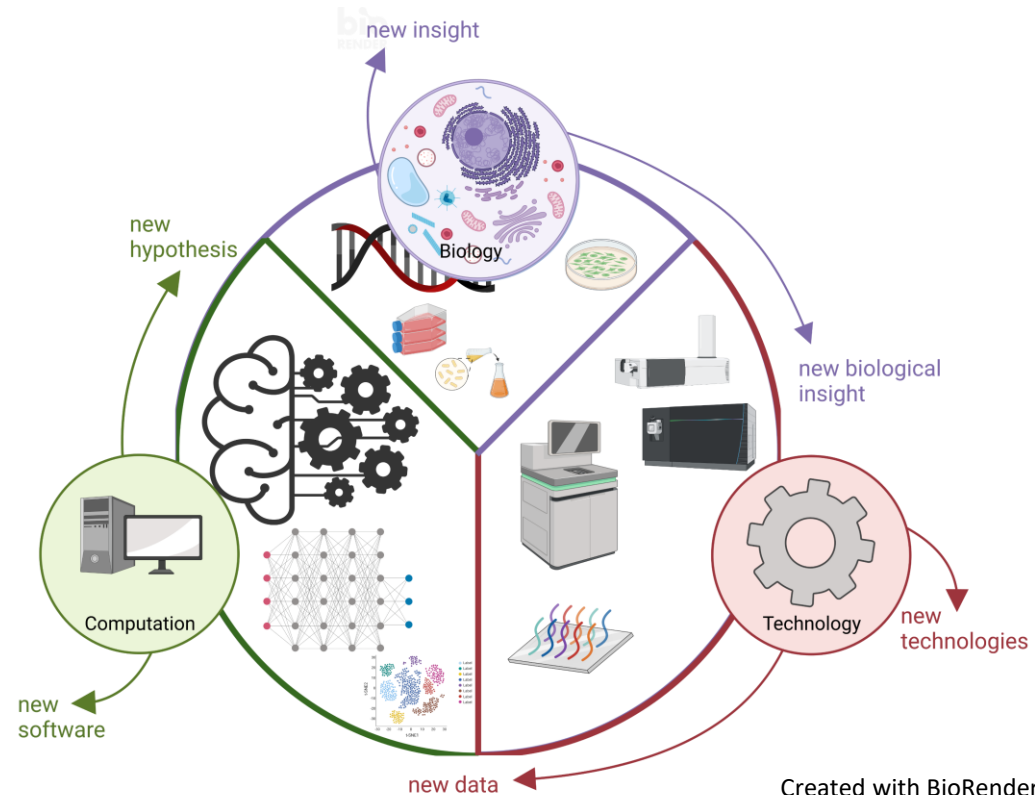
## **Deep Learning**

Subset of machine learning utilizing multilayer neural networks to learn from vast amount of data

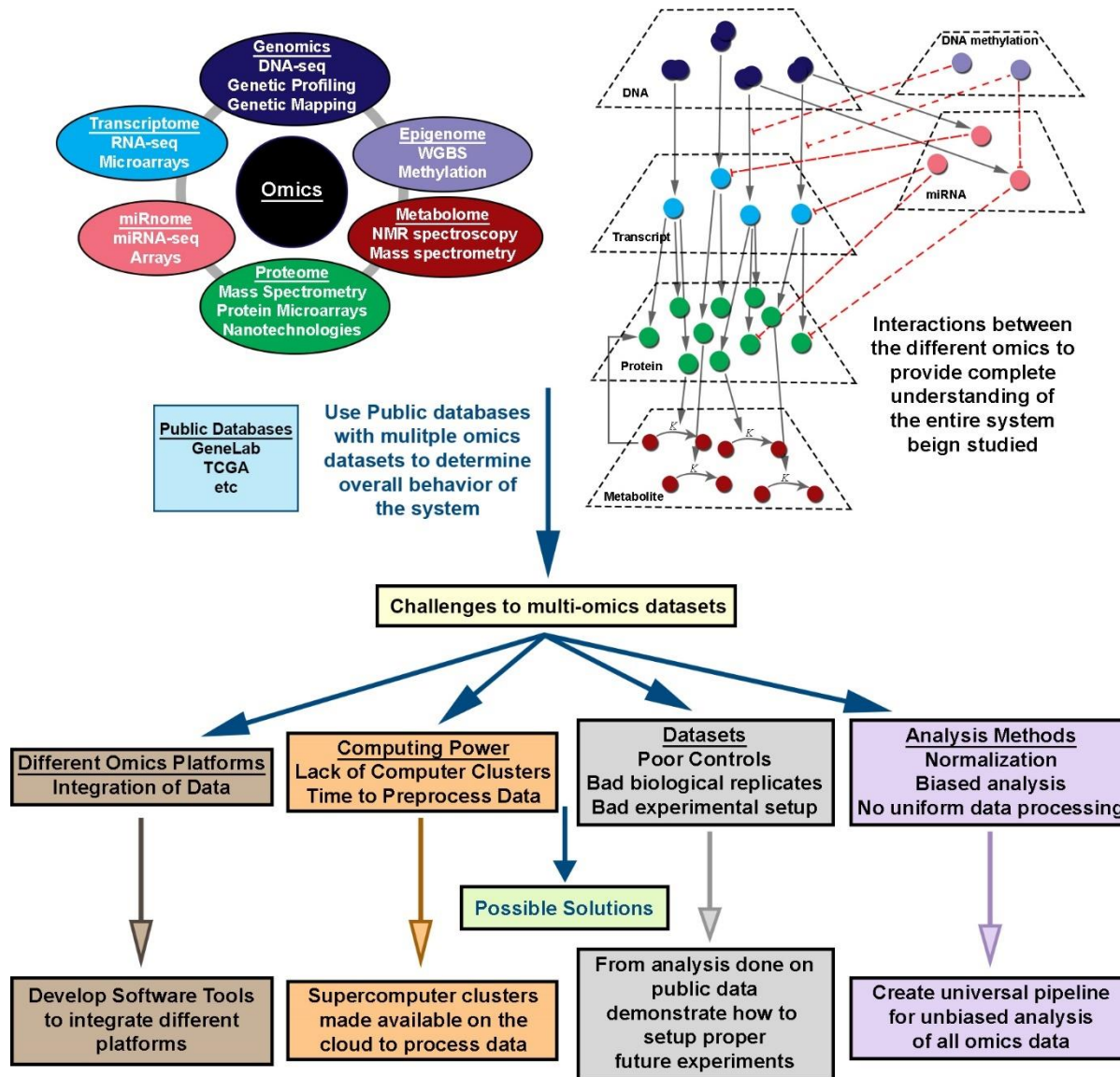
**Relating Systems Biology techniques key to integrate with AI/ML tools!!!**

# What is Systems Biology?

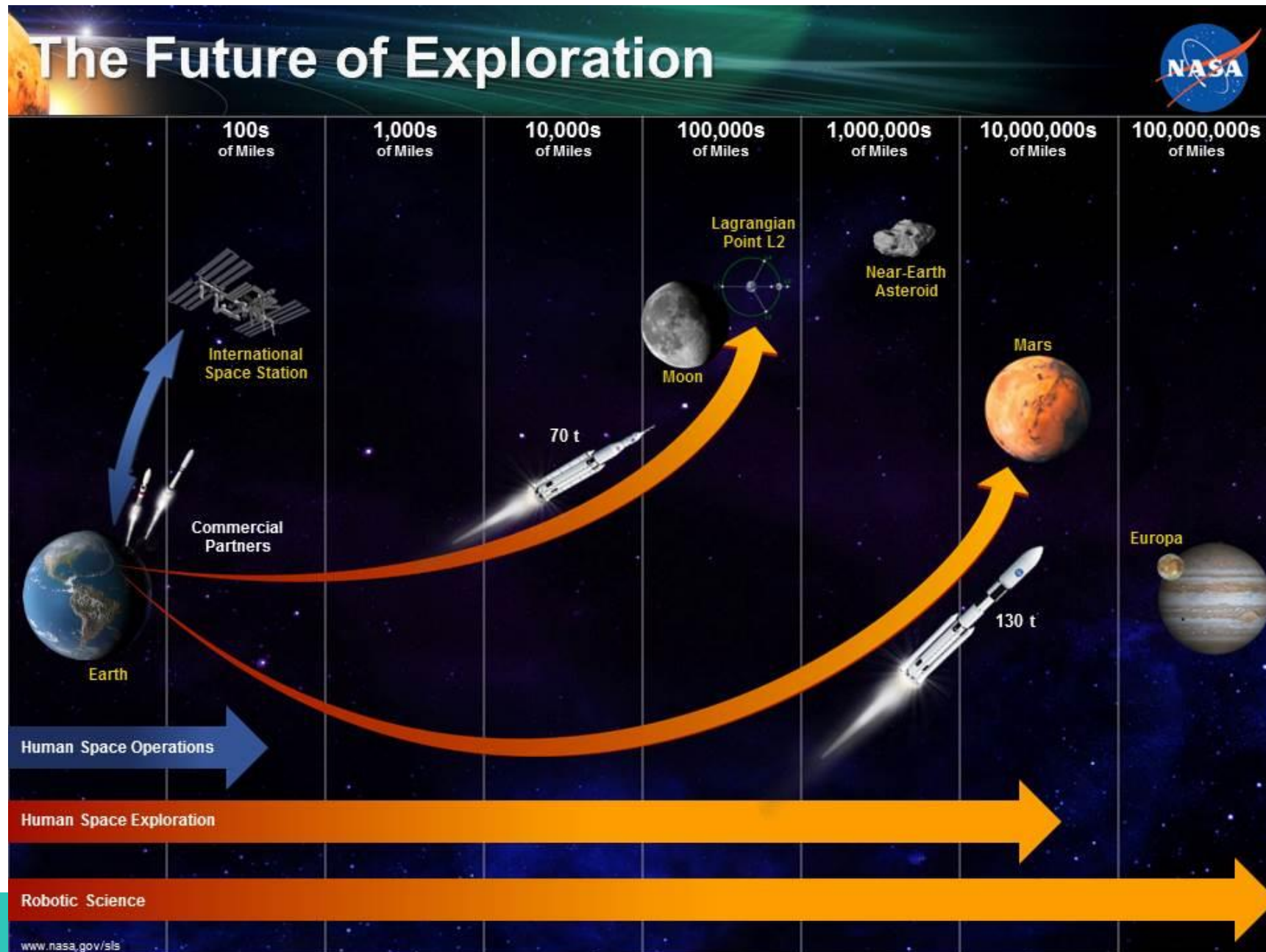
- Systems biology attempts to understand biological organisms or systems as a whole rather than researching their individual components in isolation from one another.
- NIH defines Systems Biology as: “Systems biology is an approach in biomedical research to understanding the larger picture—be it at the level of the organism, tissue, or cell—by putting its pieces together. It’s in stark contrast to decades of reductionist biology, which involves taking the pieces apart.”



# What is Omics?



# Why Care About Spaceflight?



# Space Environment

## Cell

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

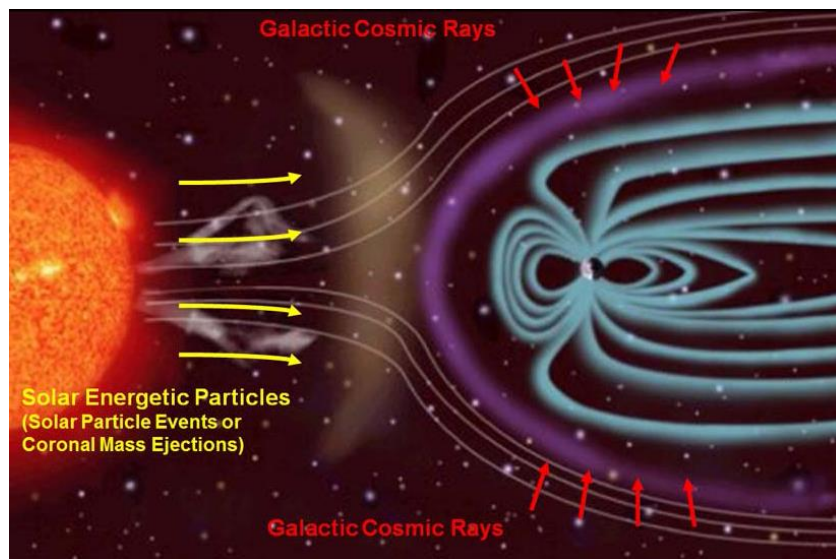
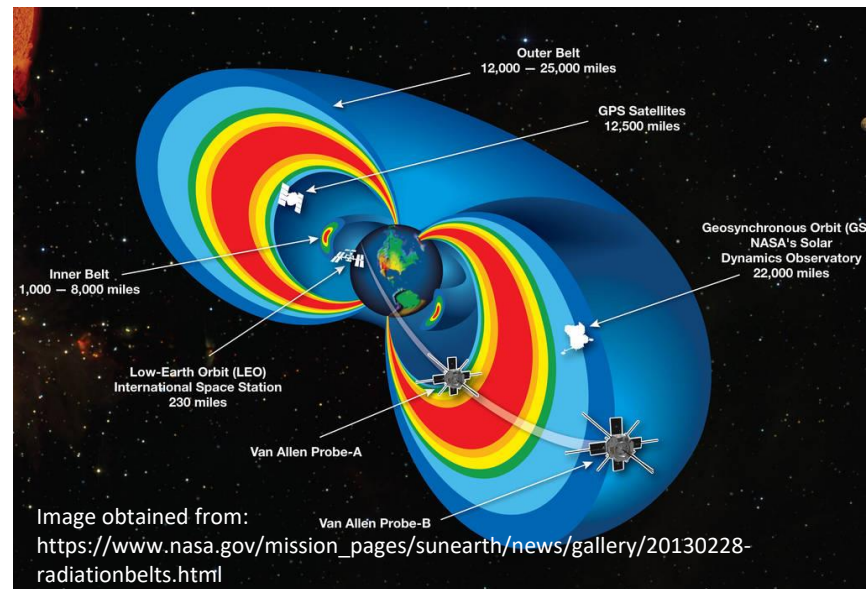
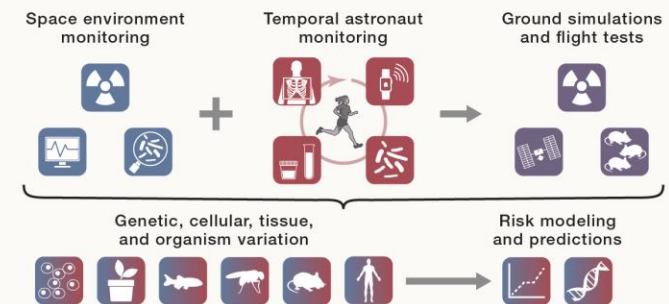
Ebrahim Afshineke <sup>1</sup> • Ryan T. Scott <sup>2</sup> • Matthew J. MacKay <sup>3</sup> • Sylvain V. Costes <sup>4</sup> • Christopher E. Mason <sup>5</sup> • Afshin Beheshti <sup>6</sup> • Show all authors • Show footnotes

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

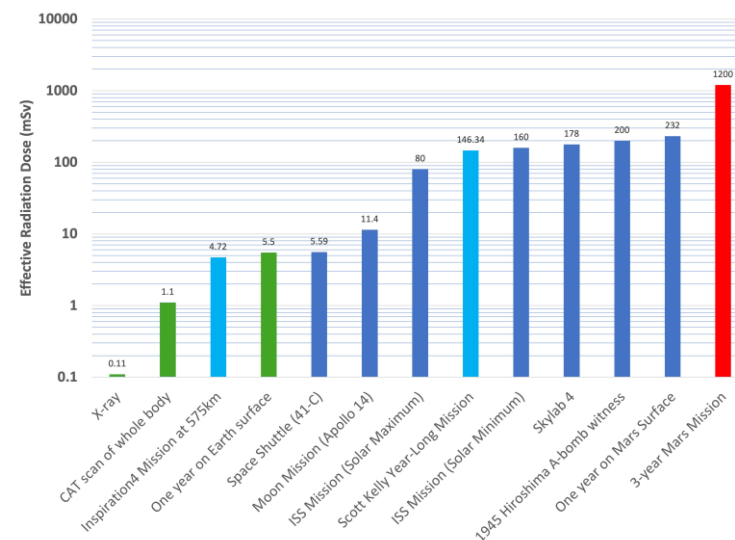
| Space risks                     |                                                 |
|---------------------------------|-------------------------------------------------|
| NASA hazards                    | Risks and health consequences                   |
| Distance                        | Limited health care<br>Support and resources    |
| Confinement                     | Fitness                                         |
| Hostile and closed environments | Infections                                      |
| Gravity                         | Muscle atrophy                                  |
| Radiation                       | Cancer                                          |
|                                 | Nutrition and mood                              |
|                                 | Sleep disruption                                |
|                                 | Stress                                          |
|                                 | Oxidative stress<br>Vision changes<br>Bone loss |
|                                 | Cardio, immune and hypercapnia                  |

Identification of new risks

### Analyses and experimentation



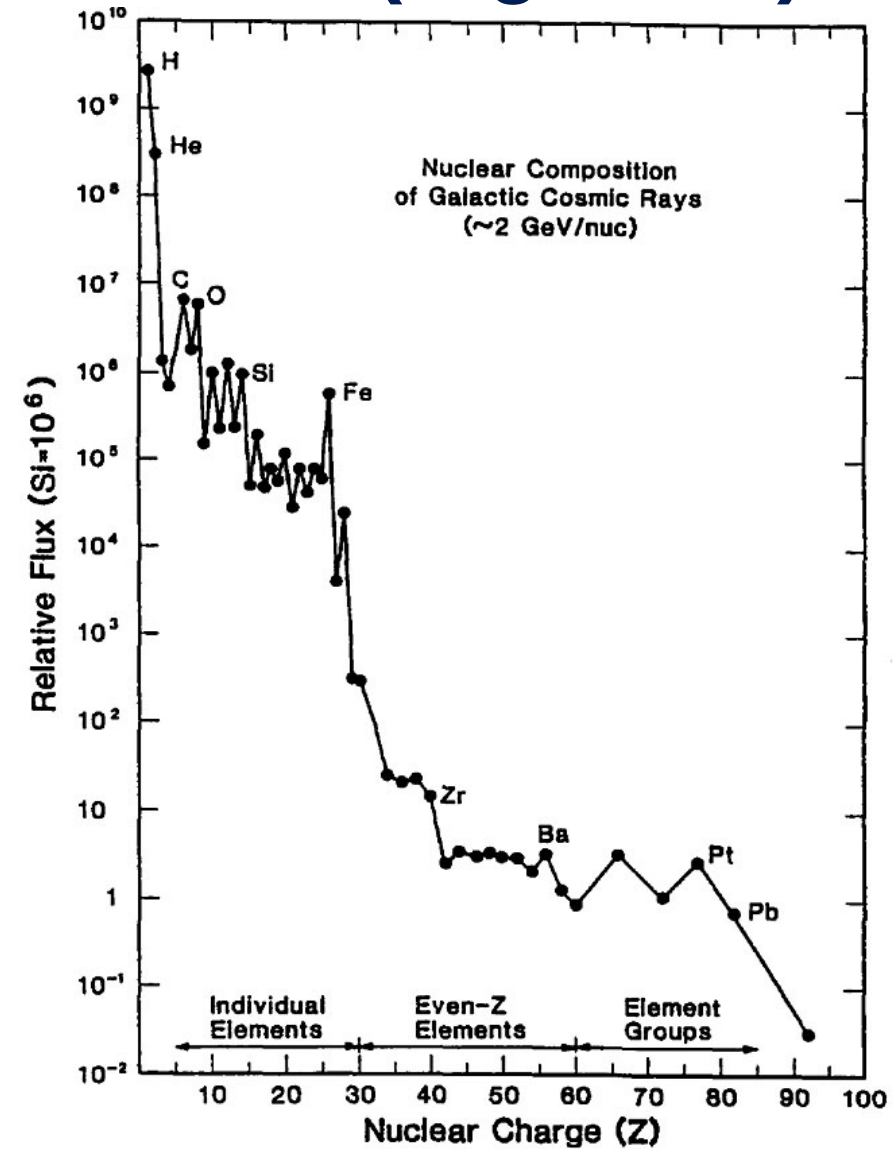
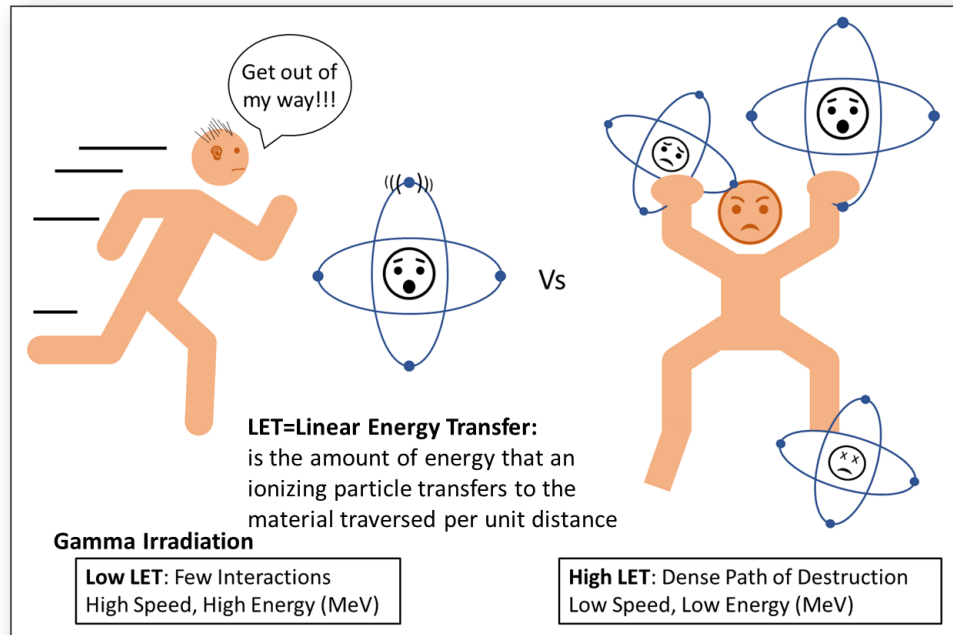
NASA/JPL-Caltech/SwRI - <http://photojournal.jpl.nasa.gov/jpeg/PIA16938.jpg>



## Microgravity



# Galactic Cosmic Radiation (High LET)



# Space Environment Health Risks On Astronauts

Cell

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

Ebrahim Abshenkeoo<sup>1</sup> • Ryan T. Scott<sup>2</sup> • Matthew J. McKay<sup>3</sup> • ... Sylvain V. Costes<sup>4</sup> • Christopher E. Mason<sup>5</sup> • Afshan Beheshti<sup>6</sup> • Show all authors • Show footnotes

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



## FEMALE ASTRONAUT



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



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



Women mount more potent immune responses



Struvite kidney stones more common in women



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



Female astronauts are more susceptible to orthostatic intolerance



Urinary tract infections are more common in female astronauts



Large individual variability to muscle and bone loss in women



Health effect observed on Earth

<https://www.nasa.gov/content/men-women-spaceflight-adaptation>

## MALE ASTRONAUT



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



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



Men mount less potent immune responses



Calcium oxalate kidney stones more common in men



Some male astronauts exhibit clinically significant visual impairment



Male astronauts less susceptible to orthostatic intolerance



Urinary tract infections less common in male astronauts



Large individual variability to muscle and bone loss in men



Health effect observed in space



## A Mission and long-term health risks

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

## B Planned human missions



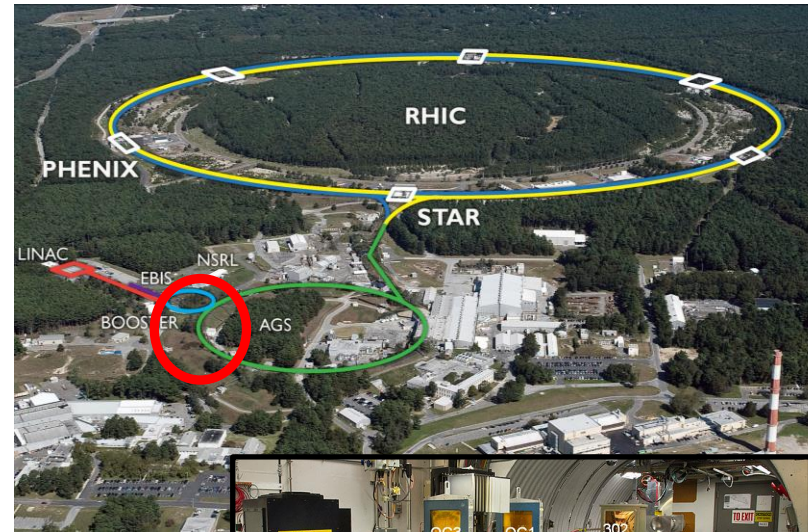
# Type of Experiments Related to Space Biology

## Experiments Done in Space

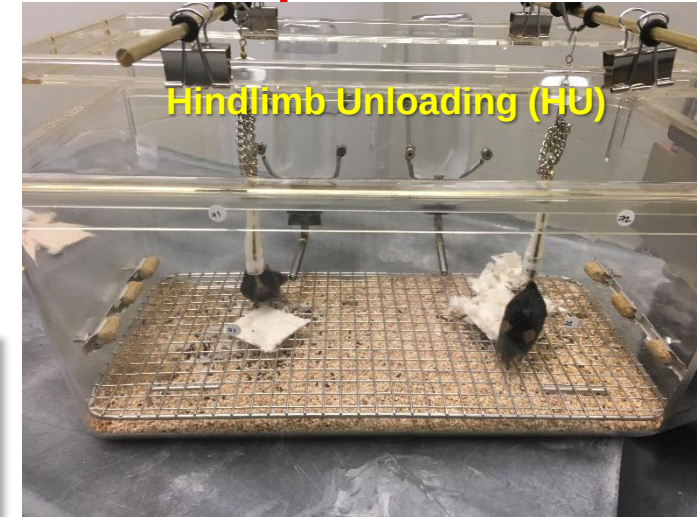


## Space Radiation Simulated Experiments

Brookhaven National Laboratory



## Microgravity Simulated Experiments



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ABSTRACT INTRODUCTION PROTOCOL RESULTS

### GENETICS

Exploring the Effects of Spaceflight on Mouse Physiology using the Open Access NASA GeneLab Platform

Afshin Beheshti<sup>1</sup>, Yasaman Shirazi-Fard<sup>2</sup>, Sungshin Choi<sup>1</sup>, Daniel Berrios<sup>3</sup>, Samrawit G. Gebre<sup>1</sup>, Jonathan M. Galazka<sup>2</sup>, Sylvain V. Costes<sup>2</sup>  
<sup>1</sup>WYLL Labs, Space Biosciences Division, NASA Ames Research Center, <sup>2</sup>Space Biosciences Division, NASA Ames Research Center, <sup>3</sup>USRA, NASA Ames Research Center

# Space Omics Platform that The Public can Use!!



Open Science for Life in Space

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Keywords



## GeneLab (genelab.nasa.gov)



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



### Data Repository

Search and upload spaceflight datasets



### Analyze Data

Perform large-scale analysis of biological omics data



### Environmental Data

Radiation data collected during experiments conducted in space



### Collaborative Workspace

Share, organize and store files



### Submit Data BETA

Have space-relevant data to submit to GeneLab?



### Visualize Data

Interact with GeneLab processed data

## Question:

**Can we leverage other publicly available data platforms to determine novel hypothesis and data for advancing both clinical and spaceflight related issues?**

## Short Answer: Yes!!

**www.import.org**



ImmPort is funded by the NIH, NIAID and DAIT in support of the NIH mission to share data with the public. Data shared through ImmPort has been provided by NIH-funded programs, other research organizations and individual scientists ensuring these discoveries will be the foundation of future research.

Data uploading or sharing questions? Please contact [ImmPort\\_Helpdesk@immport.org](mailto:ImmPort_Helpdesk@immport.org).



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- [API Documentation](#)
- [Ask ImmPort Questions](#)

News

30-May-23 ImmPort Data Release 48 is out! 58 new studies. For details please see the Data Release notes. [🔗](#)

Program specific resource links:

AMP RA/SLE

**Bill & Melinda Gates Foundation**

HIPC

### March of Dimes

**SeroNet**

Enter text (or) Click 'Search' to explore ImmPort shared data e.g. influenza, COVID-19, SDY1 ...

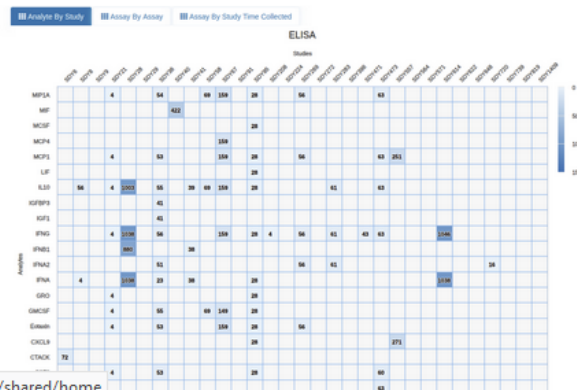
Q Search



[Data Summary: Release 48, May 2023](#)

[Click on the counts with links to visualize the count breakdown](#)

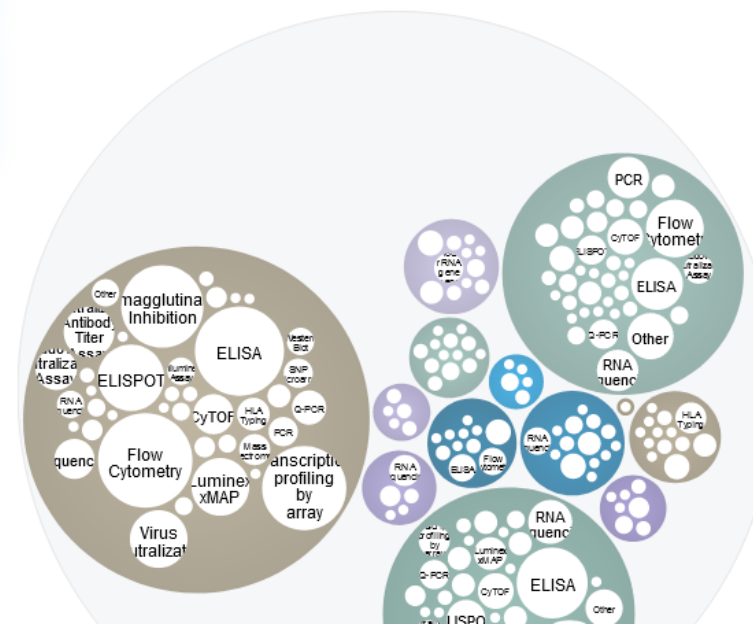
|                                                                                                                                                                                             |                                                                                                                                                                                                  |                                                                                                     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
|  Studies<br> 721      |  Subjects<br> 91877        | Diseases<br> 148 |
|  Experiments<br> 2686 |  Total Results<br> 6528595 | Lab Tests<br>1279770                                                                                |

[Matrix Summary - Analyte By Study](#)

[🔗 Bubble Summary: Research Focus by Assay Type](#)

Click on a research focus to zoom in

### Research Focus by Assay Type



**Hypothesis:**

**Does spaceflight increase the chance of  
potential birth defects?**

# Dataset on ImmPort Related to Small-for-gestational-age fetuses (SGA)

ImmPort

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<https://www.immport.org/shared/study/SDY1871>

## SDY1871 - Maternal plasma miRNAs as potential biomarkers for detecting risk of SGA

Download

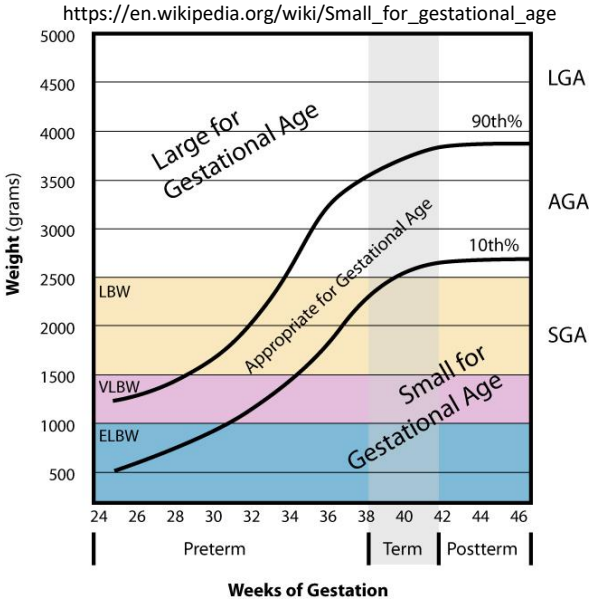
- Summary
- Design
- Adverse Event
- Assessment
- Interventions
- Medications
- Substance
- Demographics
- Lab Tests
- Mechanistic Assays
- Study Files

+ -

### Summary

|                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|----------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Accession            | SDY1871                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Title                | Maternal plasma miRNAs as potential biomarkers for detecting risk of SGA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| DOI                  | 10.21430/M3TU8P1DQ0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Brief Description    | To investigate the miRNA biomarkers associated with the <b>Small-for-gestational-age fetuses</b> (SGA) condition, maternal plasma samples from 29 women (N=16 normal, N=13 SGA) were selected to form a discovery cohort in which expression data for a total of 800 miRNAs was determined using the Nanostring nCounter miRNA assay. Differential expression of two miRNA markers; hsa-miR-374a-5p (p = 0.0176) and hsa-let-7d-5p (p = 0.0036), were validated in an independent population of 95 women (SGA n = 12, Control n = 83).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Research Focus       | Pregnancy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Condition Studied    | Small for Gestational Age                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Start Date           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Detailed Description | Small-for-gestational-age fetuses (SGA) (birthweight <10th centile) are at high risk for stillbirth or long-term adverse outcomes. Here, we investigate the ability of circulating maternal plasma miRNAs to determine the risk of SGA births. Maternal plasma samples from 29 women of whom 16 subsequently delivered normally grown babies and 13 delivered SGA (birthweight <5th centile) were selected from a total of 511 women recruited to form a discovery cohort in which expression data for a total of 800 miRNAs was determined using the Nanostring nCounter miRNA assay. Validation by RT-qPCR was performed in an independent cohort. Findings: Partial least-squares discriminant analysis (PLS-DA) of the Nanostring nCounter miRNA assay initially identified seven miRNAs at 12+14+6 weeks gestation, which discriminated between SGA cases and controls. Four of these were technically validated by RT-qPCR. Differential expression of two miRNA markers; hsa-miR-374a-5p (p = 0.0176) and hsa-let-7d-5p (p = 0.0036), were validated in an independent population of 95 women (SGA n = 12, Control n = 83). In the validation cohort, which was enriched for SGA cases, the ROC AUCs were 0.71 for hsa-miR-374a-5p, and 0.74 for hsa-let-7d-5p, and 0.77 for the two combined. Whilst larger population-wide studies are required to validate their performance, these findings highlight the potential of circulating miRNAs to act as biomarkers for early prediction of SGA births |

Maternal plasma samples were extracted from whole blood and collected prospectively at three time-points; 12<sup>+0</sup> - 14<sup>+6</sup> (time-point A), 15<sup>+0</sup> - 17<sup>+6</sup> (time-point B) and/or 18<sup>+0</sup> – 21<sup>+6</sup> (time-point C) weeks gestation.



# Dataset on ImmPort Related to Small-for-gestational-age fetuses (SGA)

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<https://www.immport.org/shared/study/SDY1871>  
SDY1871 - Maternal plasma miRNAs as potential biomarkers for detecting risk of SGA

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- Summary
- Design
- Adverse Event
- Assessment
- Interventions
- Medications
- Substance
- Demographics
- Lab Tests
- Mechanistic Assays
- Study Files

Are miRNAs associated with SGA elevated in the plasma of females during spaceflight and can increase the risk of birth defects after returning to Earth???

Accession

Title

DOI

Brief Description

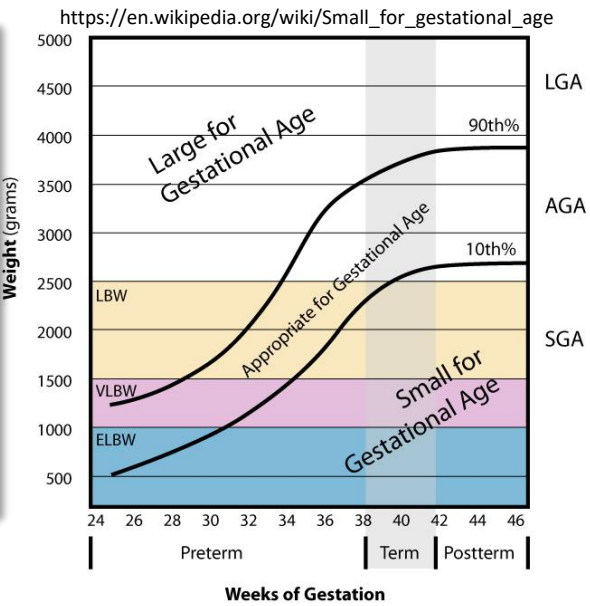
Research

Condition Studied

Start Date

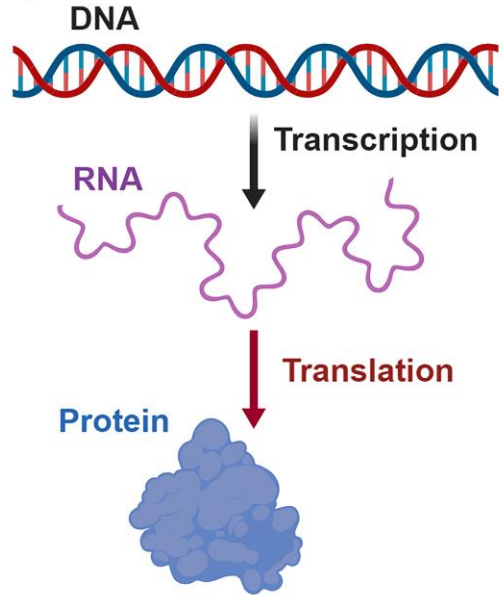
Detailed Description

Small-for-gestational-age fetuses (SGA) (birthweight <10th centile) are at high risk for stillbirth or long-term adverse outcomes. Here, we investigate the ability of circulating maternal plasma miRNAs to determine the risk of SGA births. Maternal plasma samples from 29 women of whom 16 subsequently delivered normally grown babies and 13 delivered SGA (birthweight <5th centile) were selected from a total of 511 women recruited to form a discovery cohort in which expression data for a total of 800 miRNAs was determined using the Nanostring nCounter miRNA assay. Validation by RT-qPCR was performed in an independent cohort. Findings: Partial least-squares discriminant analysis (PLS-DA) of the Nanostring nCounter miRNA assay initially identified seven miRNAs at 12 $\pm$ 14+6 weeks gestation, which discriminated between SGA cases and controls. Four of these were technically validated by RT-qPCR. Differential expression of two miRNA markers; hsa-miR-374a-5p (p = 0.0176) and hsa-let-7d-5p (p = 0.0036), were validated in an independent population of 95 women (SGA n = 12, Control n = 83). In the validation cohort, which was enriched for SGA cases, the ROC AUCs were 0.71 for hsa-miR-374a-5p, and 0.74 for hsa-let-7d-5p, and 0.77 for the two combined. Whilst larger population-wide studies are required to validate their performance, these findings highlight the potential of circulating miRNAs to act as biomarkers for early prediction of SGA births

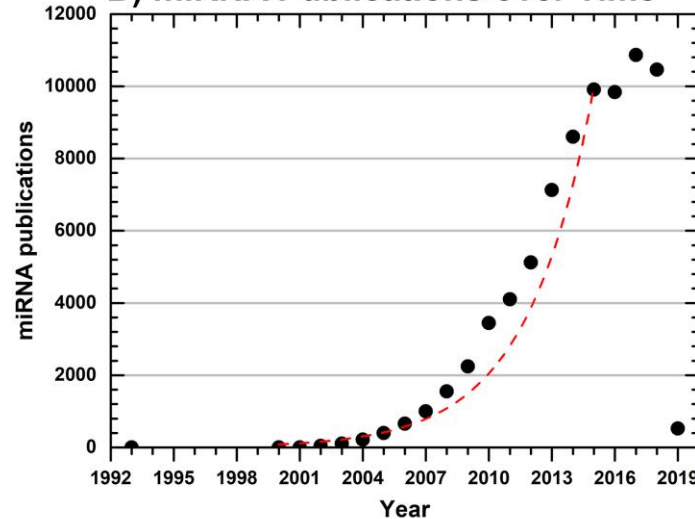


# What are miRNAs and why study miRNAs?

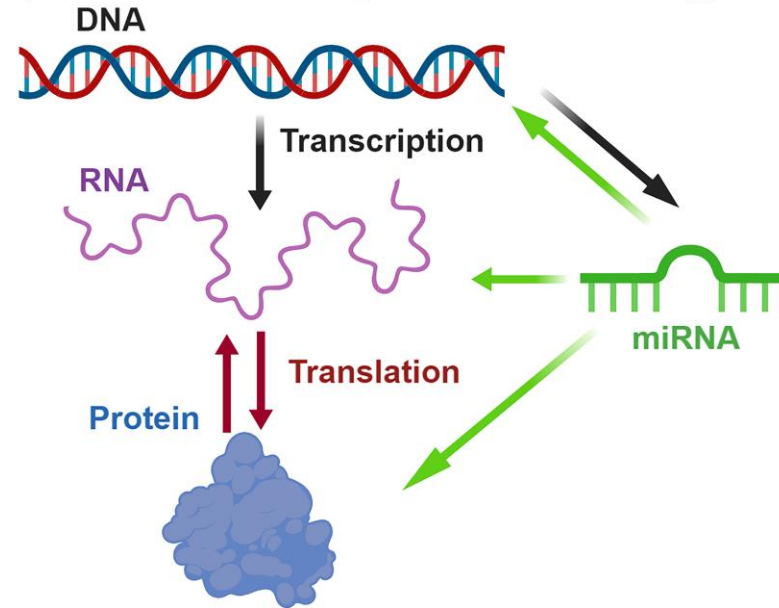
A) Classical View of Molecular Biology



B) miRNA Publications over Time



C) New Understanding of Molecular Biology



Entire figure from Vanderburg and Beheshti, MicroRNAs (miRNAs), the Final Frontier: The Hidden Master Regulators Impacting Biological Response in All Organisms Due to Spaceflight, THREE, 2020.

(<https://three.jsc.nasa.gov/Encyclopedia/Article/80>)



- A single miRNA has been estimated to regulate 100s to 1000s of 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 are highly conserved across species.

# miRNAs and Space: What I have done so far!

## Cell Reports

ARTICLE | ONLINE NOW 108448

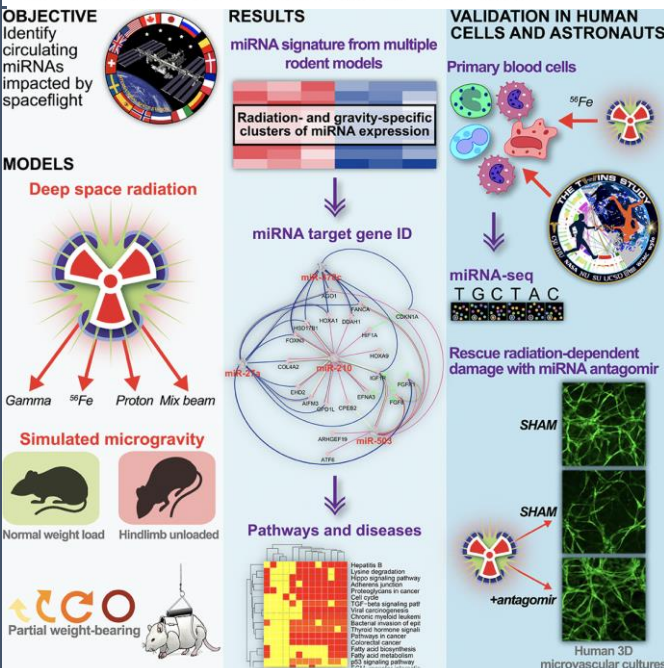
### Circulating miRNA Spaceflight Signature Reveals Targets for Countermeasure Development

Sherina Malkani <sup>22</sup> • Christopher R. Chin <sup>22</sup> • Egle Cekanaviciute <sup>22</sup> • ... Peter Grabham •  
 Christopher E. Mason <sup>23</sup> • Afshin Beheshti <sup>23, 24</sup> • Show all authors • Show footnotes  
 Open Access • Published: November 25, 2020 • DOI: <https://doi.org/10.1016/j.celrep.2020.108448>

PlumX Metrics

**Highlights**

- Spaceflight miRNA signature validated in multiple organism models
- Components of miRNA signature related to space radiation and microgravity
- Downstream targets and circulating dependence of miRNAs in NASA Twins Study
- Inhibition of key microvasculature miRNAs mitigates space radiation impact



## iScience

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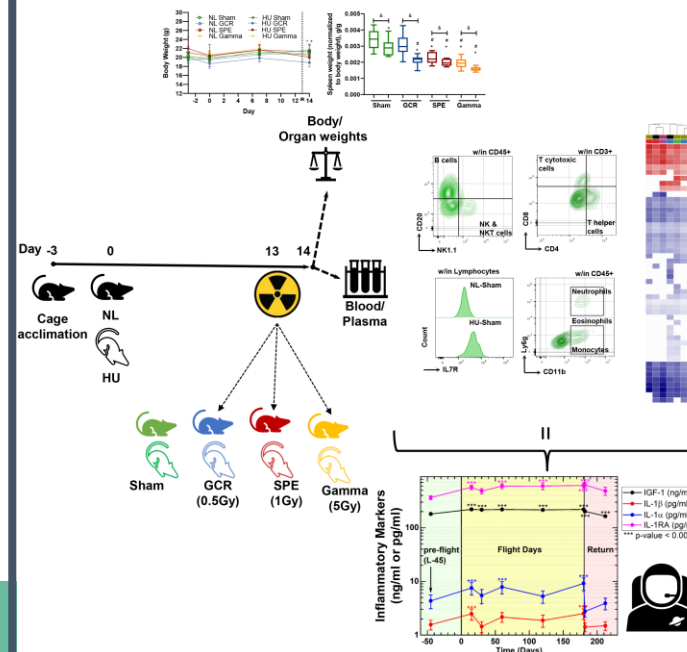
ARTICLE | VOLUME 23, ISSUE 12, 101747, DECEMBER 18, 2020

### Beyond Low-Earth Orbit: Characterizing Immune and microRNA Differentials following Simulated Deep Spaceflight Conditions in Mice

Amber M. Paul • Margareth Cheng-Campbell • Elizabeth A. Blaber • ... Robert Meller • Peter Grabham •  
 Afshin Beheshti • Show all authors • Show footnotes  
 Open Access • Published: November 25, 2020 • DOI: <https://doi.org/10.1016/j.isci.2020.101747>

**Highlights**

- Murine immune profiles from simulated deep spaceflight conditions
- Immune profiling revealed unique immune diversity with each experimental condition
- Plasma microRNA sequence analysis revealed involvement in immune system dysregulation



## iScience

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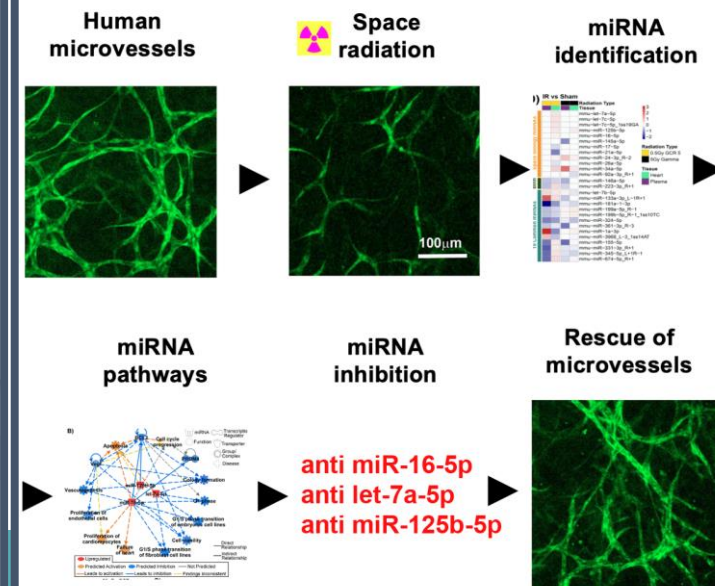
ARTICLE | VOLUME 23, ISSUE 12, 101748, DECEMBER 18, 2020

### LET-Dependent Low Dose and Synergistic Inhibition of Human Angiogenesis by Charged Particles: Validation of miRNAs that Drive Inhibition

Yen-Ruh Wu • Burong Hu • Hazeem Okunola • ... Margareth Cheng-Campbell • Afshin Beheshti • Peter Grabham •  
 Show all authors • Show footnotes  
 Open Access • Published: November 25, 2020 • DOI: <https://doi.org/10.1016/j.isci.2020.101748>

**Highlights**

- Space radiation inhibits angiogenesis synergistically at low doses by 2 mechanisms
- Candidates for bystander transmission are microRNAs
- Three previously identified miRNAs showed downregulation of their angiogenesis targets
- Synthetic miRNA inhibitors were used to reverse the inhibition of angiogenesis



## miRNAs and Space: What I have done so far!

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ARTICLE | [ONLINE NOW](#), 108448

## Circulating miRNA Spaceflight Signature Reveals Targets for Countermeasure Development

Sherina Malkani<sup>22</sup> • Christopher R. Chin<sup>22</sup> • Egle Cekanaviciute<sup>22</sup> • ...

Christopher E. Mason <sup>23</sup>  Afshin Beheshti <sup>23, 24</sup>  [Show all authors](#)

Open Access • Published: November 25, 2020 • DOI: <https://doi.org/10.1016/j.celrep.2020.107600> Reports

## Highlights

- Spaceflight miRNA signature validated in multiple organism models
- Components of miRNA signature related to space radiation and microgravity
- Downstream targets and circulating dependence of miRNAs in NASA Twins Study
- Inhibition of key microvasculature miRNAs mitigates space radiation impact

## OBJECTIVE

Identify circulating miRNAs impacted by spaceflight



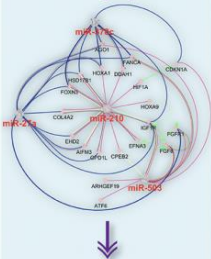
## RESULTS

miRNA signature from multiple rodent models



**Radiation- and gravity-specific clusters of miRNA expression**

miRNA target gene ID



## Pathways and diseases

Hepatitis B  
Lysine degradation  
G-protein signaling pathway  
Adhesion junction  
Proteoglycans in cancer  
Cell cycle  
TGF- $\beta$  signaling  
Viral carcinogenesis  
Chronic myeloid leukaemia  
Basaloid invasion of epithelium  
Thyroid hormone signaling  
Pathways in cancer  
Colorectal cancer  
Fatty acid biosynthesis  
Fatty acid metabolism  
G1S signaling pathway

+antagomir

Human 3D microarray culture

## VALIDATION IN HUMAN CELLS AND ASTRONAUTS

### Primary blood cells

A diagram illustrating the decay of  $^{56}\text{Fe}$ . A central red arrow points from a red and white nuclear symbol labeled  $^{56}\text{Fe}$  to four different isotopes: a green one with a blue nucleus, a purple one with a blue nucleus, a blue one with a blue nucleus, and a red one with a blue nucleus.



TGCTAC

Rescue radiation-dependent damage with miRNA antagomir



SHAM



SHAM



+antagomir

Human 3D  
microvascular cultures

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  PDF

Article

## So Long, and Thanks for All the Antagomirs: Space Radiation Damage Rescued by Inhibition of Key Spaceflight Associated miRNAs

J. Tyson McDonald, Lily Farmerie, Meghan Johnson, Jiwoon Park, and 19 more

This is a preprint; it has not been peer reviewed by a journal.

<https://doi.org/10.21203/rs.3.rs-2370597/v1>  
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**Status:** Under Review

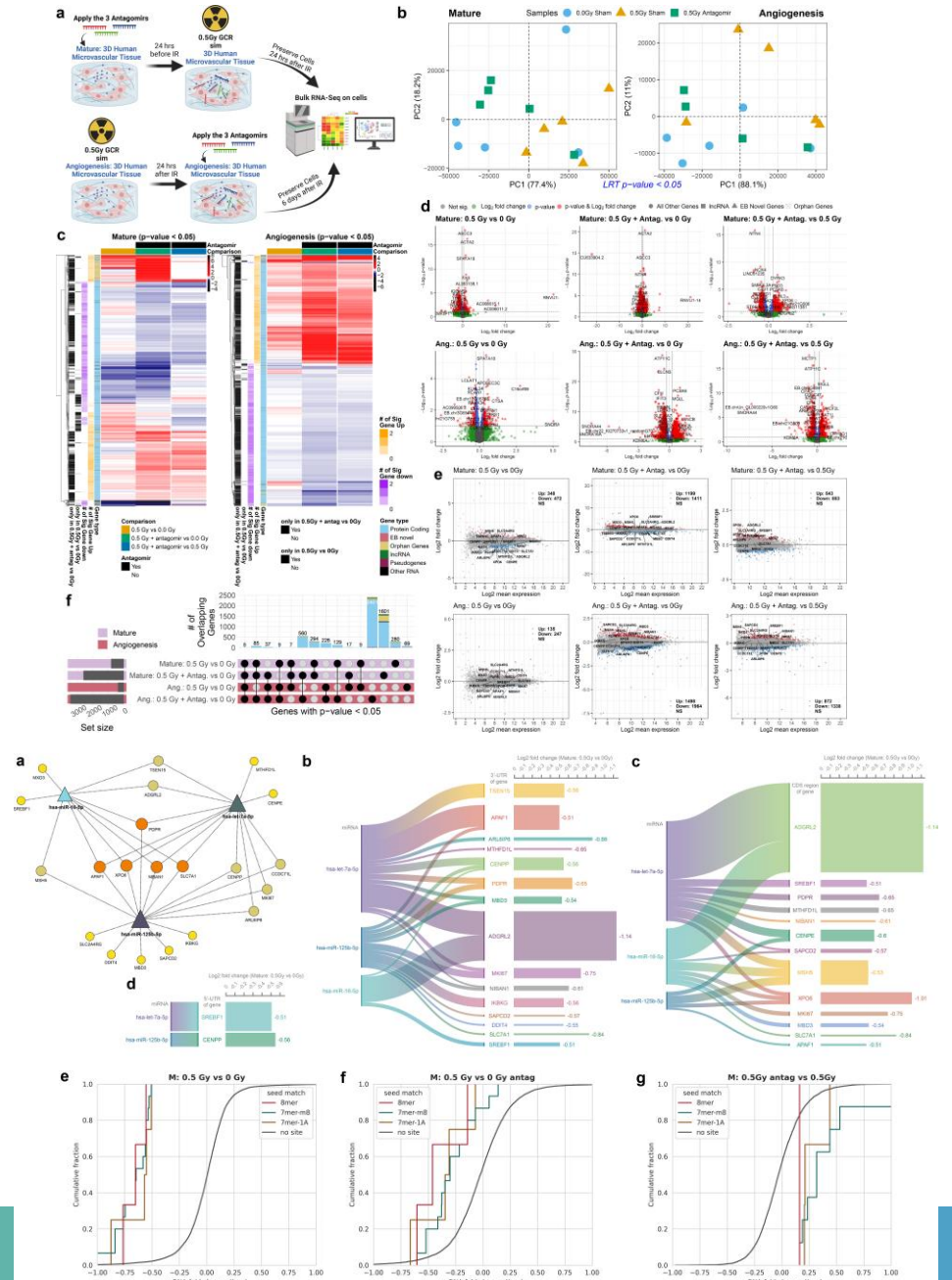
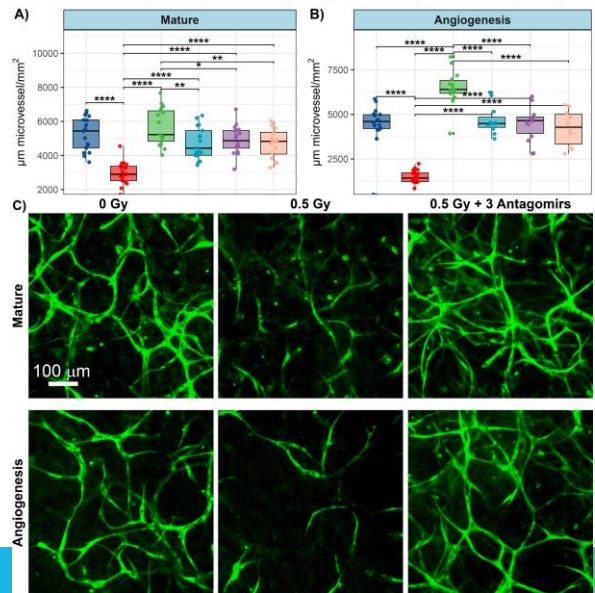
nature portfolio

Version 1

posted 09 Jan, 2023

**Antagomir Treatment on 3D Microvascular Tissues after GCR**

**Condition** ■ 0.0 Gy ■ 0.5 Gy + 3 antagomirs ■ 0.5 Gy + miR-16-5p antagomir  
■ 0.5 Gy ■ 0.5 Gy + let-7a-5p antagomir ■ 0.5 Gy + miR-125b-5p antagomir



# Relating Spaceflight Data to Clinical Data



Home About ▾ Data & Tools ▾ Working Groups ▾ Help ▾



Version 2



OSD-336 Version 2

miRNA signature detection and countermeasures against HZE radiation exposure for tissue degeneration-Plasma

17.72 GB

Study

GeneLab ID: GLDS-336  
DOI: 10.26030/qasa-rr29

Cite this Study

<https://osdr.nasa.gov/bio/repo/data/studies/OSD-336>

## Description

### Description

Biological risks associated with space radiation and microgravity are major concerns for long-term space travel. Through a Systems Biology approach, our previous NASA work has shown both TGF $\beta$  signaling pathways and miRNAs have a critical impact on defining health risks with and without space irradiation. We hypothesize that circulating microRNA (miRNA) signatures are driving microvascular disease and muscle degeneration associated with accelerating aging and will be enhanced by exposure to the space environment (radiation and microgravity). We investigated this hypothesis both in vivo and in vitro and test novel antagonist therapies to these miRNA signatures as countermeasures to reduce space radiation-induced health risks. A comprehensive Systems Biology approach was used to

Normal Loaded (NL) Hindlimb Unloaded (HU)

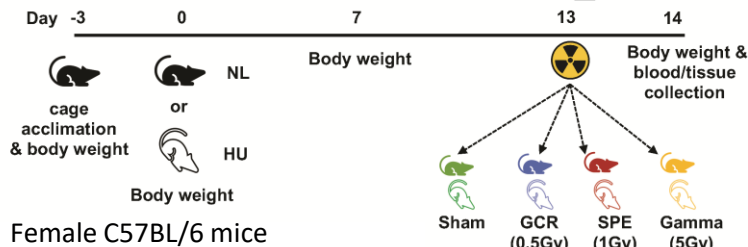


Figure from: Paul et al., Beheshti A. Beyond Low-Earth Orbit: Characterizing Immune and microRNA Differentials following Simulated Deep Spaceflight Conditions in Mice. iScience. 2020 Nov 25;23(12):101747. doi: 10.1016/j.isci.2020.101747. PMID: 33376970; PMCID: PMC7756144.

Submitted Date:  
29-Sep-2020  
Initial Release Date:  
10-Dec-2020



Version 1



OSD-55 Version 1

microRNA expression profiles in human peripheral blood lymphocytes cultured in modeled microgravity

265.87 KB

Study

GeneLab ID: GLDS-55  
DOI: 10.26030/9thk-dv75  
Source Accession: E-GEOD-57400

Cite this Study

PBLs = Peripheral Blood Lymphocytes

## Description

### Description

In the present study we analyzed miRNA and mRNA expression profiles in human peripheral blood lymphocytes (PBLs) incubated in microgravity condition, simulated by a ground-based Rotating Wall Vessel (RWV) bioreactor. Our results show that 42 miRNAs were differentially expressed in MMG-incubated PBLs compared with 1g-incubated ones. Among these, miR-9-5p, miR-9-3p, miR-155-5p, miR-150-3p, and miR-378-3p were the most dysregulated. To improve the detection of functional miRNA-mRNA pairs we performed gene expression profiles on the same samples assayed for miRNA profiling and we integrated miRNA and mRNA expression data. The functional classification of miRNA-correlated genes evidenced significant enrichments 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 between miR-9-3p, miR-155-5p, miR-150-3p and miR-378-3p expression with that of genes involved in immune/inflammatory response (eg. IFNG and IL17F), apoptosis (eg. PDCD4 and PTEN) and cell proliferation (eg. 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. microRNA expression profiling were carried out on total RNA extracted from PBLs of twelve healthy donors at the end of 24h-incubation time in MMG and in 1g conditions. Analyses were performed by using the Human miRNA Microarray kit (V2) (Agilent Technologies), that allows the detection of 723 known human (miRBase v.10.1) and 76 human viral miRNAs. By comparing the expression profile of MMG-incubated vs. 1g-incubated PBLs of the same donor, we found 42 differentially expressed miRNAs, 25 up-regulated and 17 down-regulated.

Submitted Date:  
07-May-2014  
Initial Release Date:  
17-Jul-2014



## Simplified GCR Sim

| Ion species      | Energy (MeV/n) | LET (keV/ $\mu$ m) | Dose (mGy) | Dose fraction (mGy) |
|------------------|----------------|--------------------|------------|---------------------|
| Proton           | 1000           | 0.2                | 175        | 0.35                |
| <sup>28</sup> Si | 600            | 50.4               | 5          | 0.01                |
| <sup>4</sup> He  | 250            | 1.6                | 90         | 0.18                |
| <sup>16</sup> O  | 350            | 20.9               | 30         | 0.06                |
| <sup>56</sup> Fe | 600            | 173.8              | 5          | 0.01                |
| Proton           | 250            | 0.4                | 195        | 0.39                |

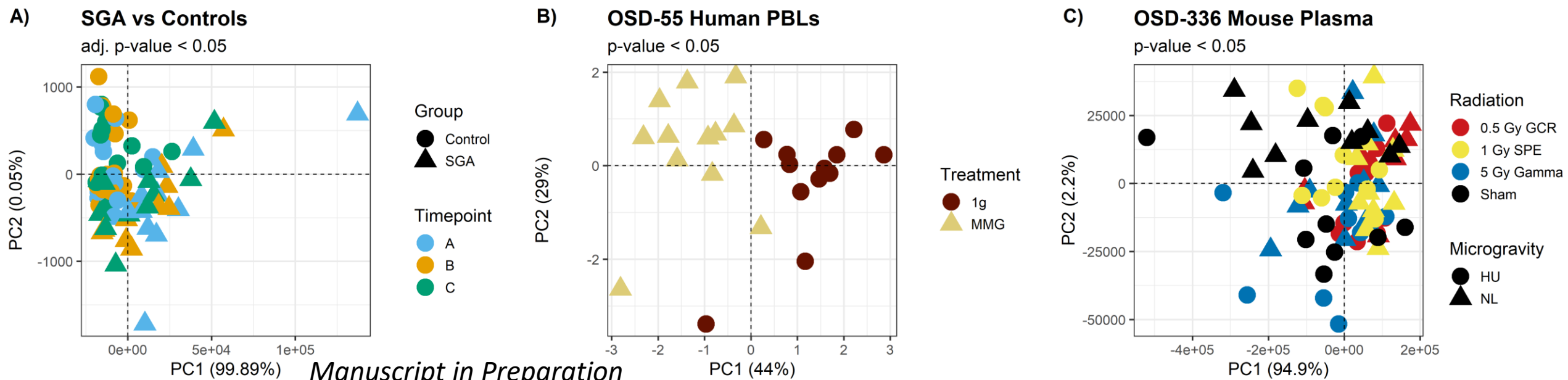
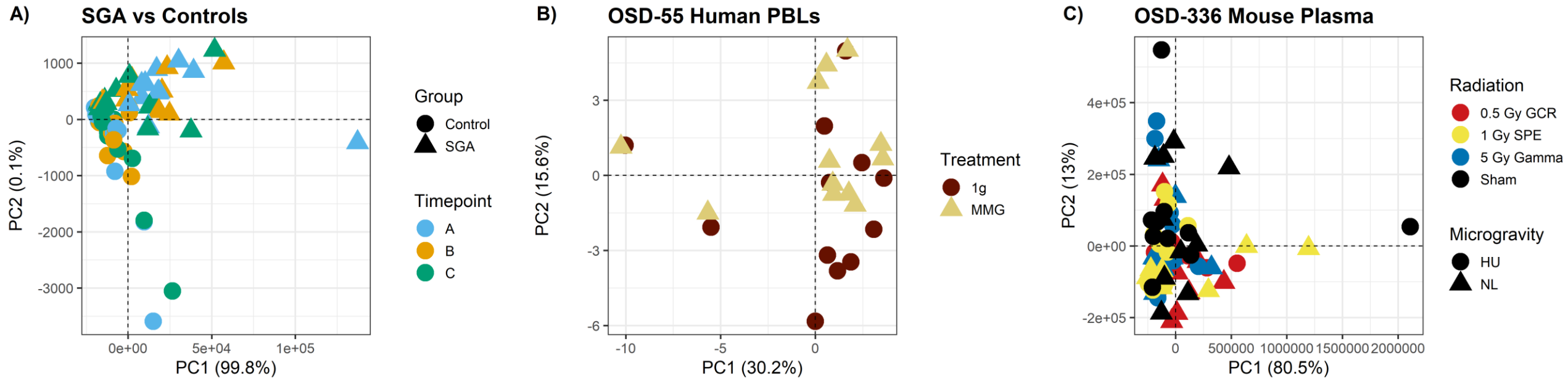
## SPE Sim

| Ion species | Energy (MeV/n) | Dose (cGy) |
|-------------|----------------|------------|
| Proton      | 50             | 91.7       |
| Proton      | 60             | 2.9        |
| Proton      | 70             | 2.0        |
| Proton      | 80             | 1.5        |
| Proton      | 90             | 1.1        |
| Proton      | 100            | 0.8        |
| Proton      | 110            | 0.6        |
| Proton      | 120            | 0.4        |
| Proton      | 130            | 0.3        |
| Proton      | 140            | 0.2        |
| Proton      | 150            | 0.1        |

<https://osdr.nasa.gov/bio/repo/data/studies/OSD-55>

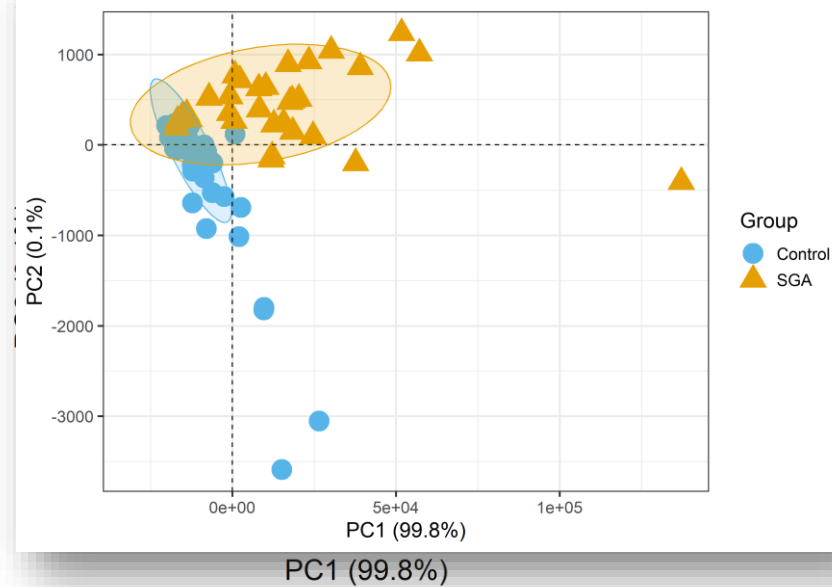


# Overall Pattern of miRNAs Compared to Controls

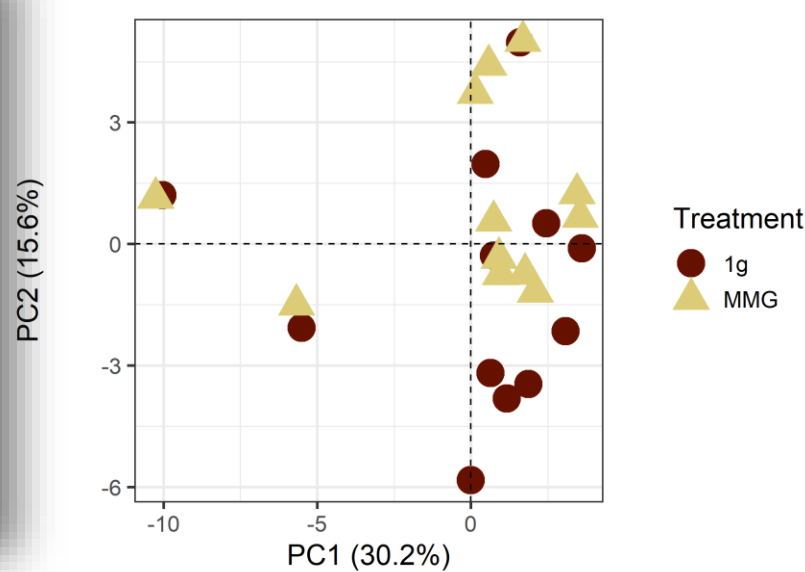


# Overall Pattern of miRNAs Compared to Controls

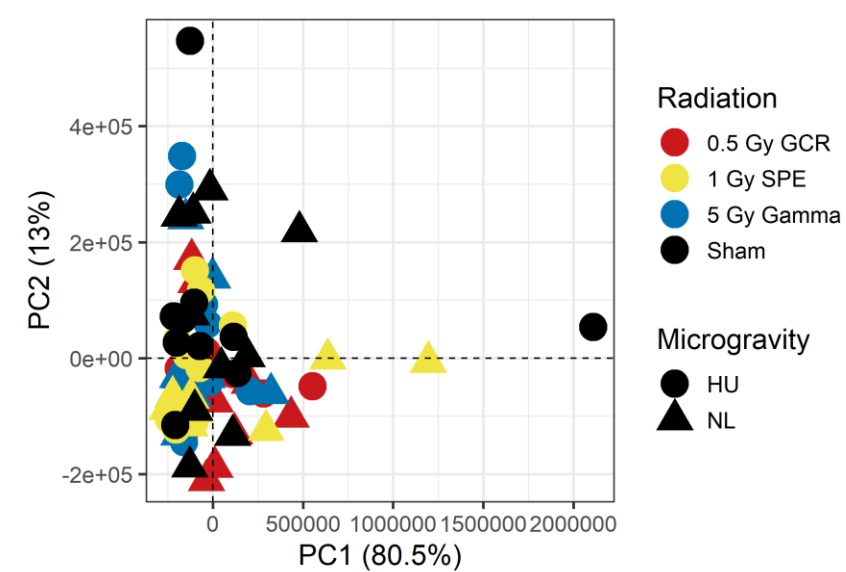
SGA vs Controls



B) OSD-55 Human PBLs

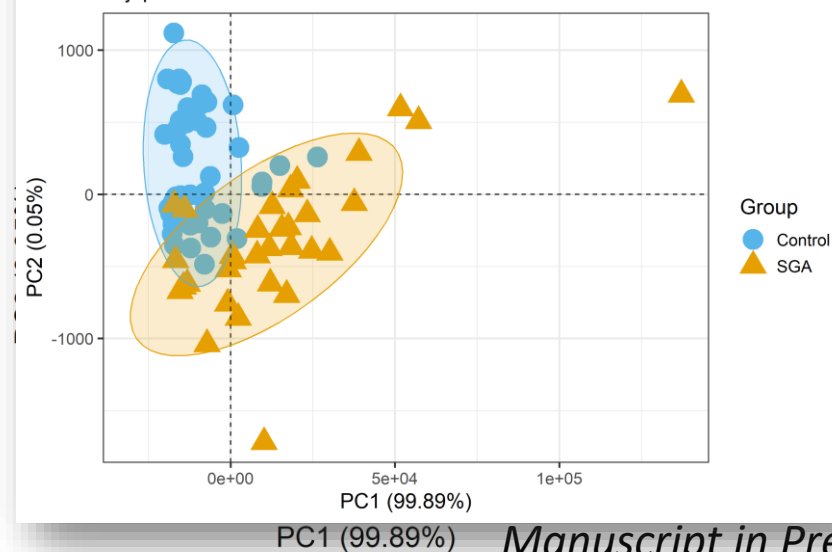


C) OSD-336 Mouse Plasma



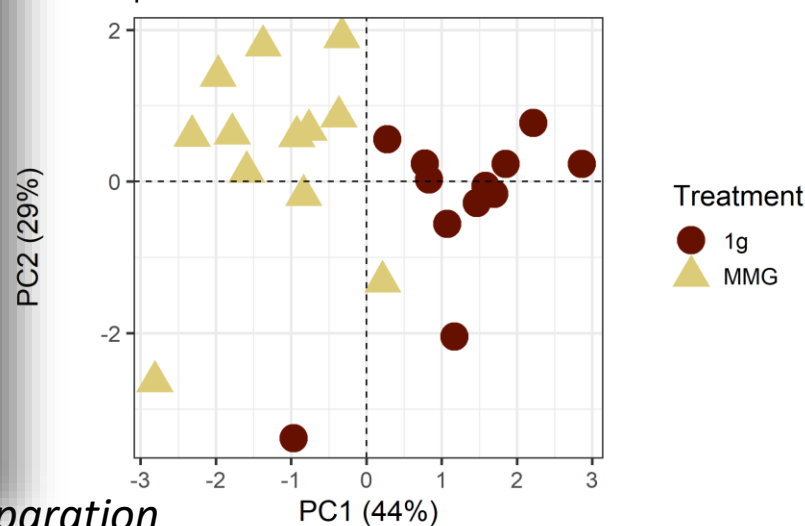
SGA vs Controls

adj. p-value < 0.05



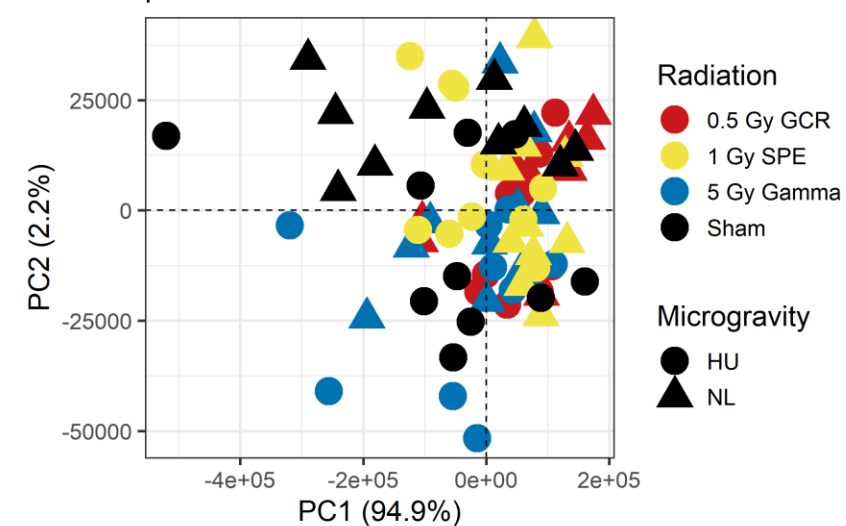
B) OSD-55 Human PBLs

p-value < 0.05



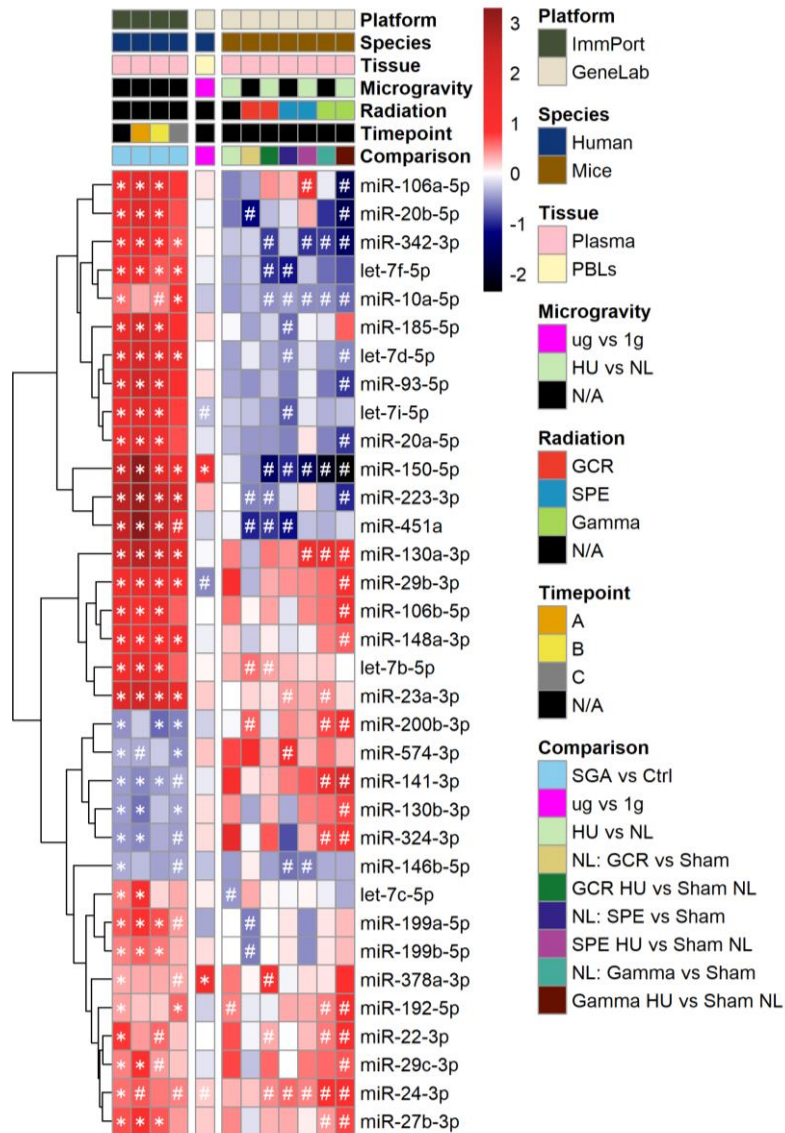
C) OSD-336 Mouse Plasma

p-value < 0.05

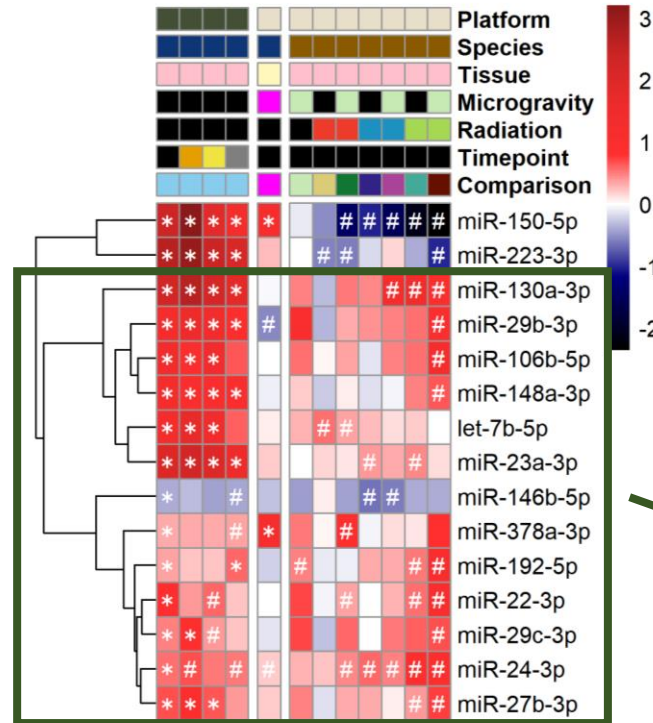


# Common Circulating miRNAs Between SGA and Spaceflight

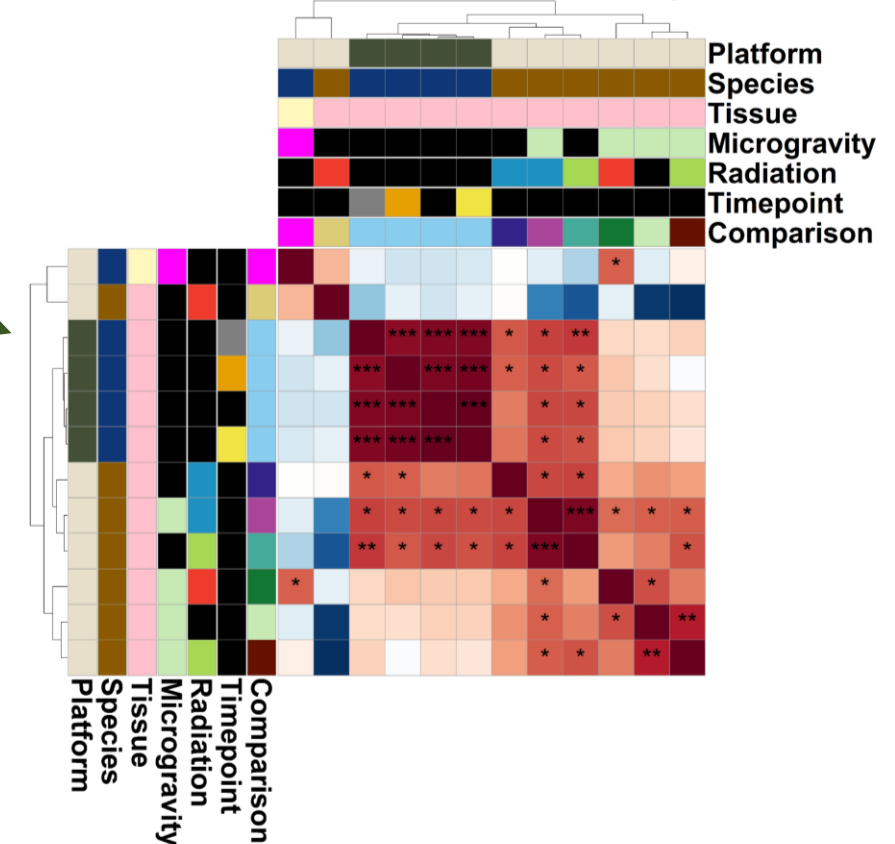
Common miRNAs between SGA  
and Space Environment  
(\* adj. p < 0.05 and # p < 0.05)



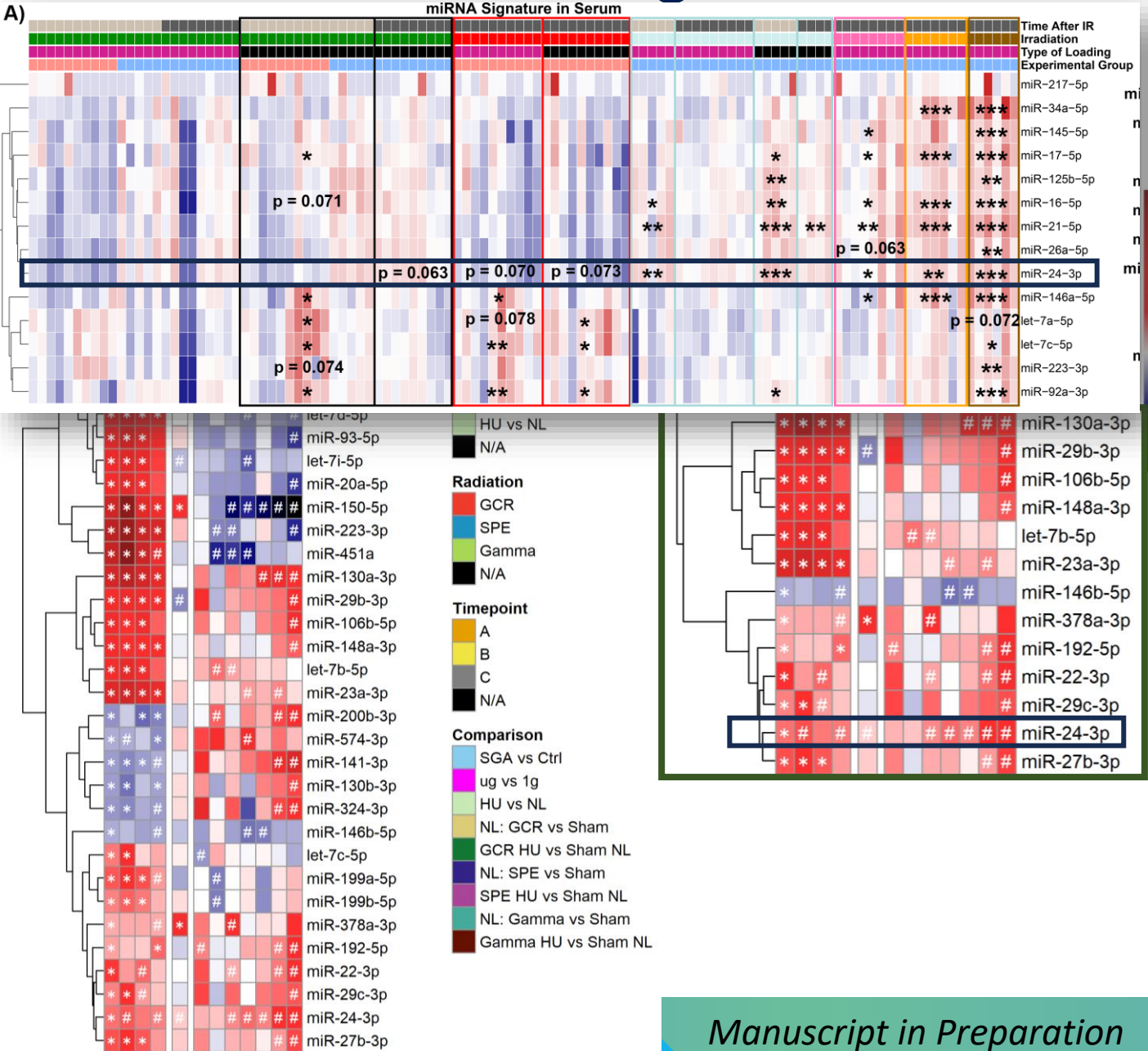
Common miRNAs between SGA  
and Space Environment  
(\* adj. p < 0.05 and # p < 0.05)



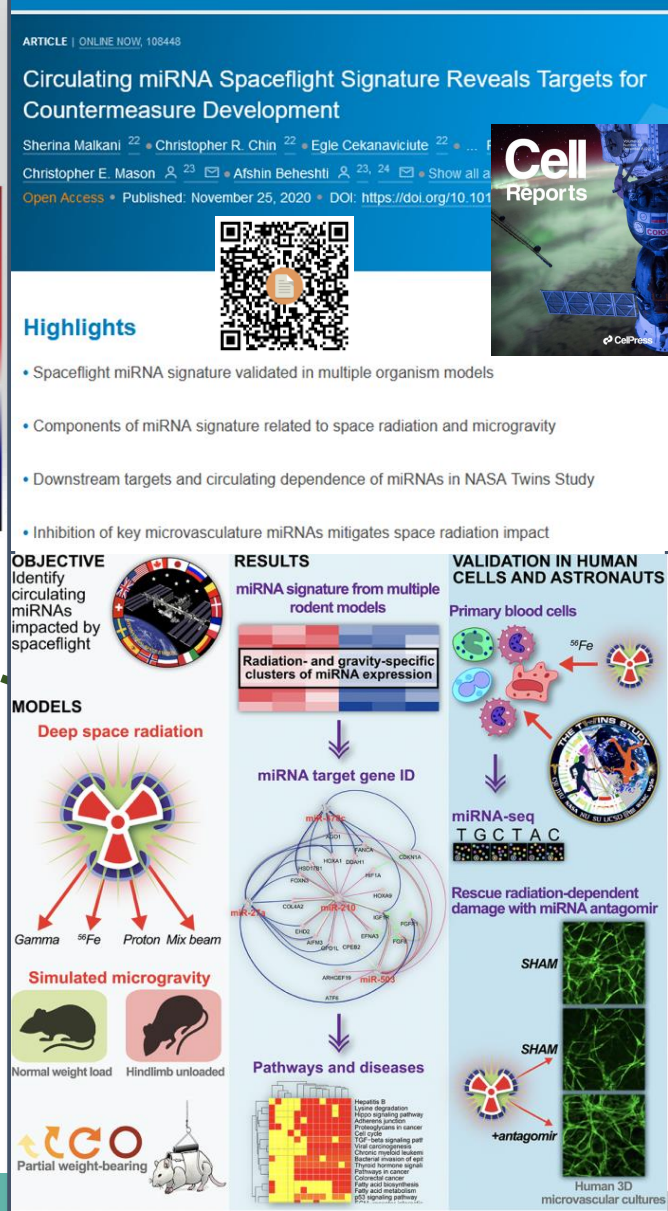
Common miRNAs between SGA and Space Environment



# Common Circulating miRNAs Between SGA and Spaceflight

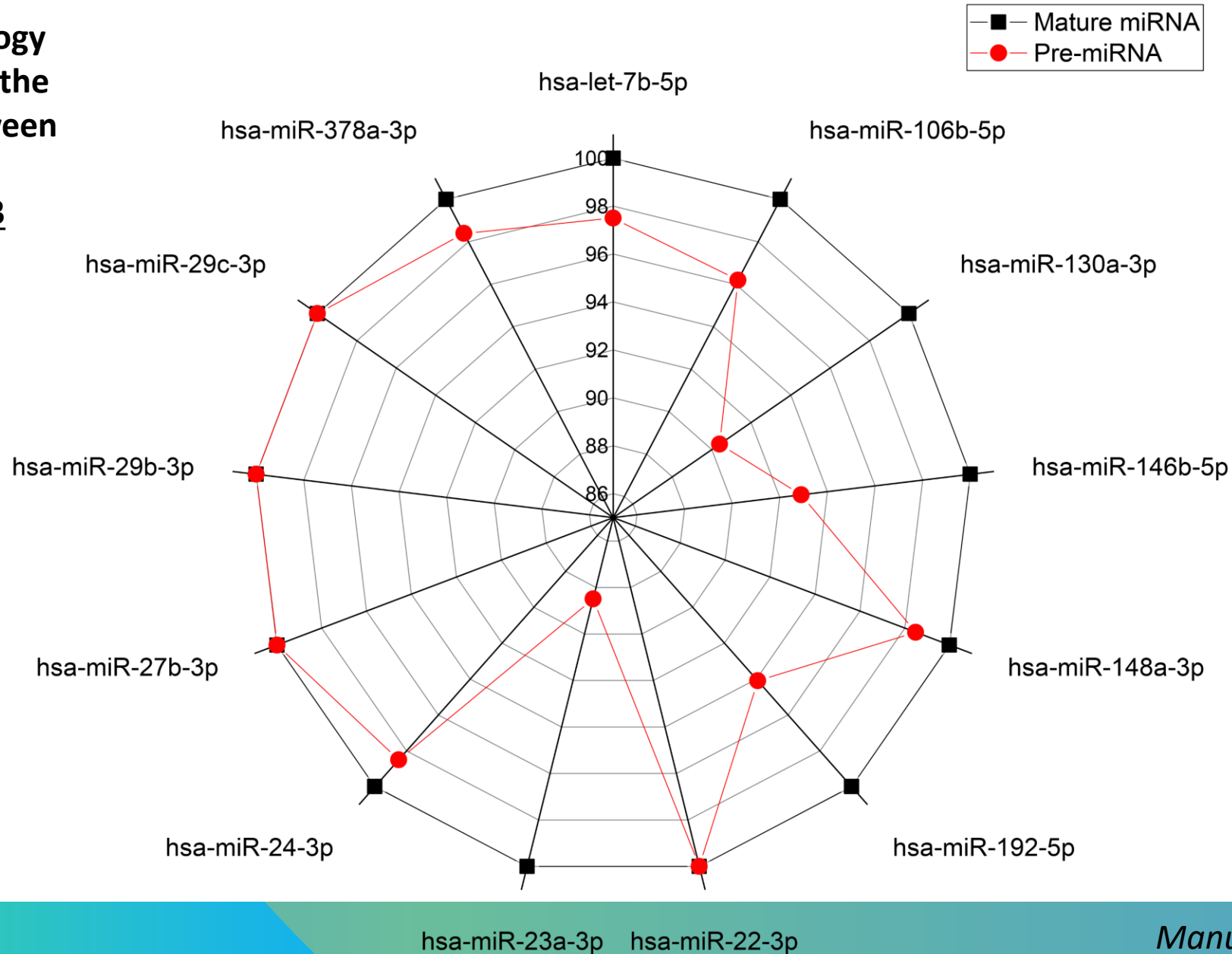


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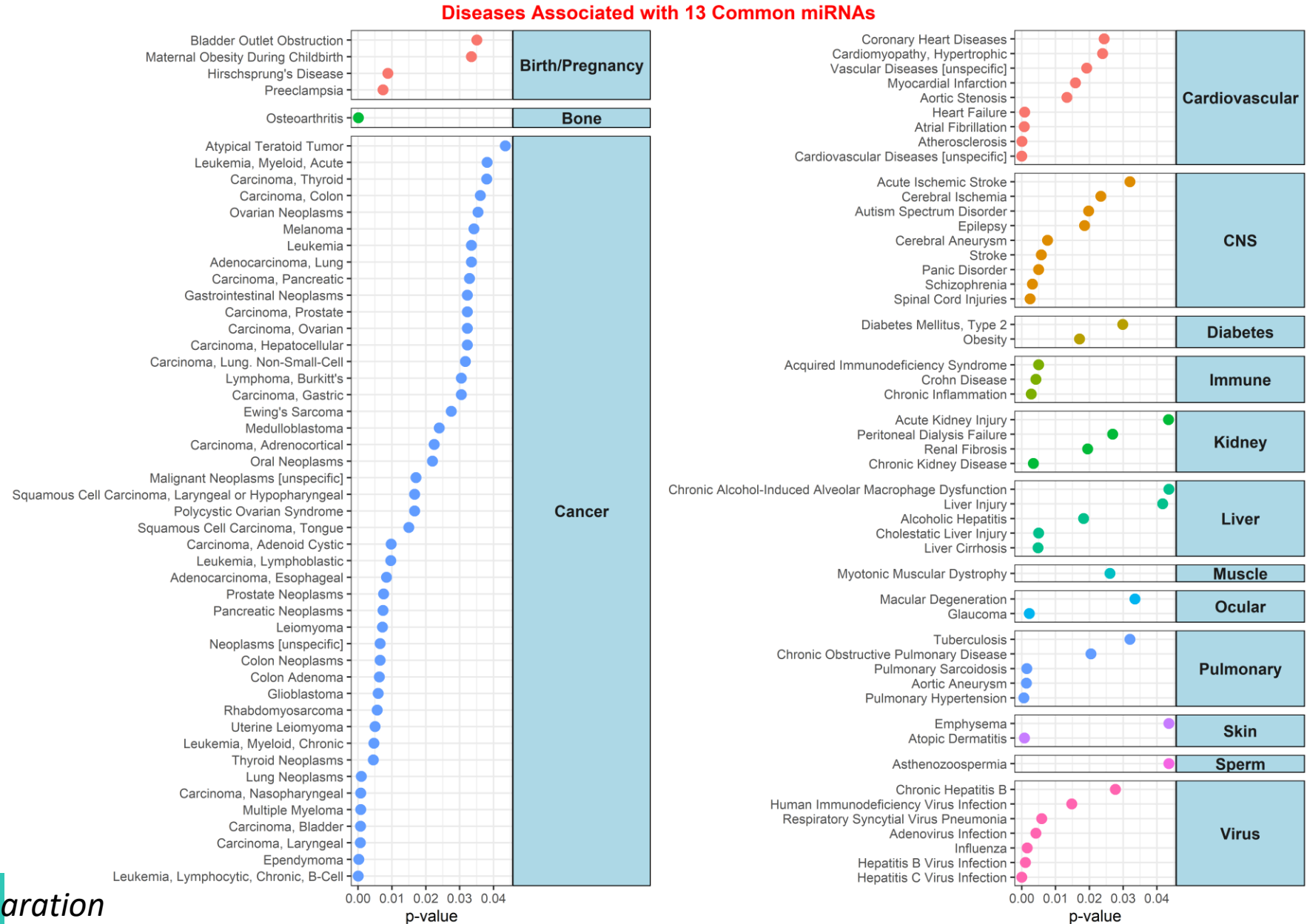
# Conserved miRNAs Between Mice and Humans

Percentage of homology  
(same nucleotides in the  
same positions) between  
mouse and human  
miRNAs shows the 13  
mature miRNAs are  
100% conserved  
between the two  
species!!



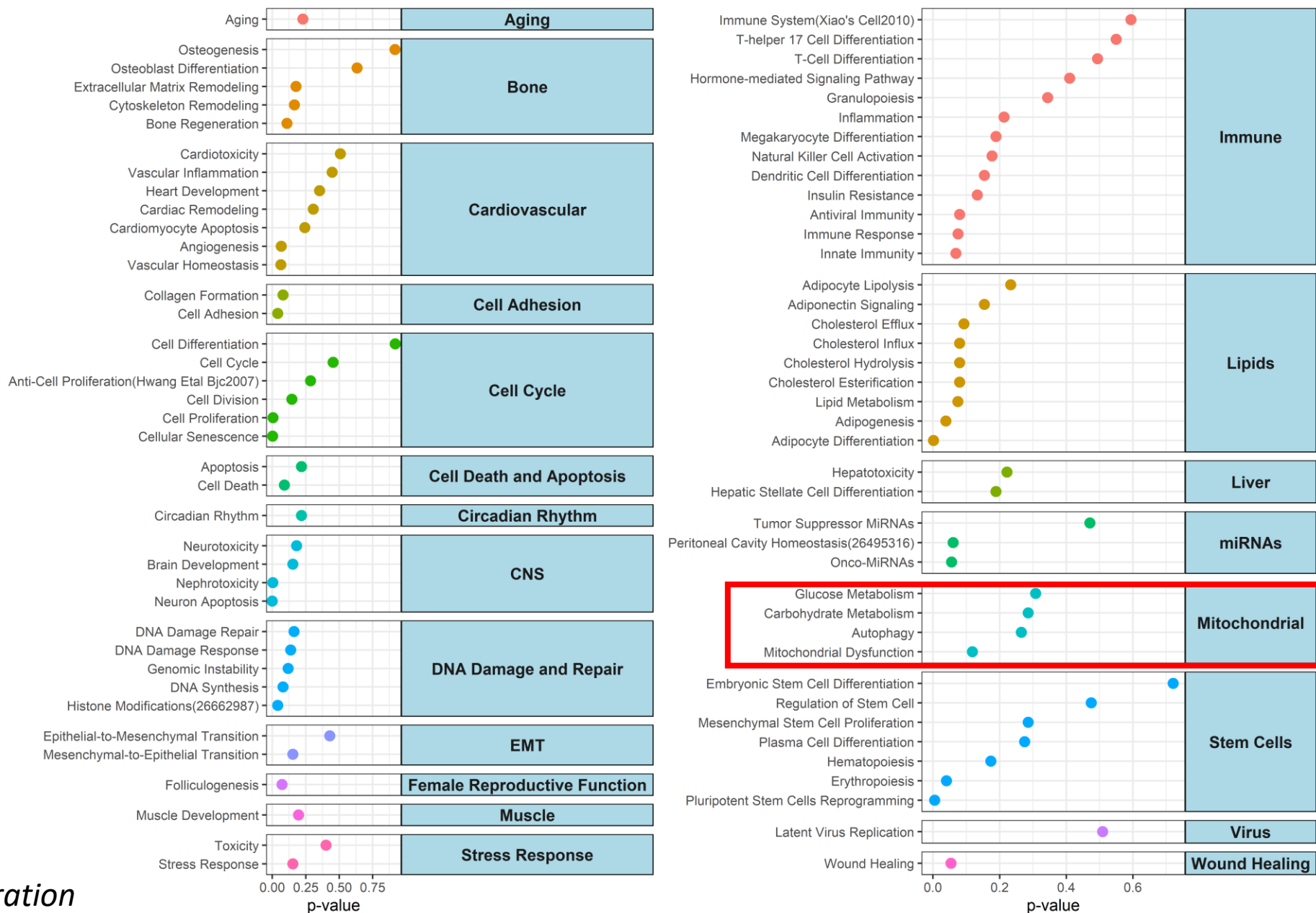
Francisco "Paco"  
Enguita, PhD

# Health Risks Associated with the Common miRNAs



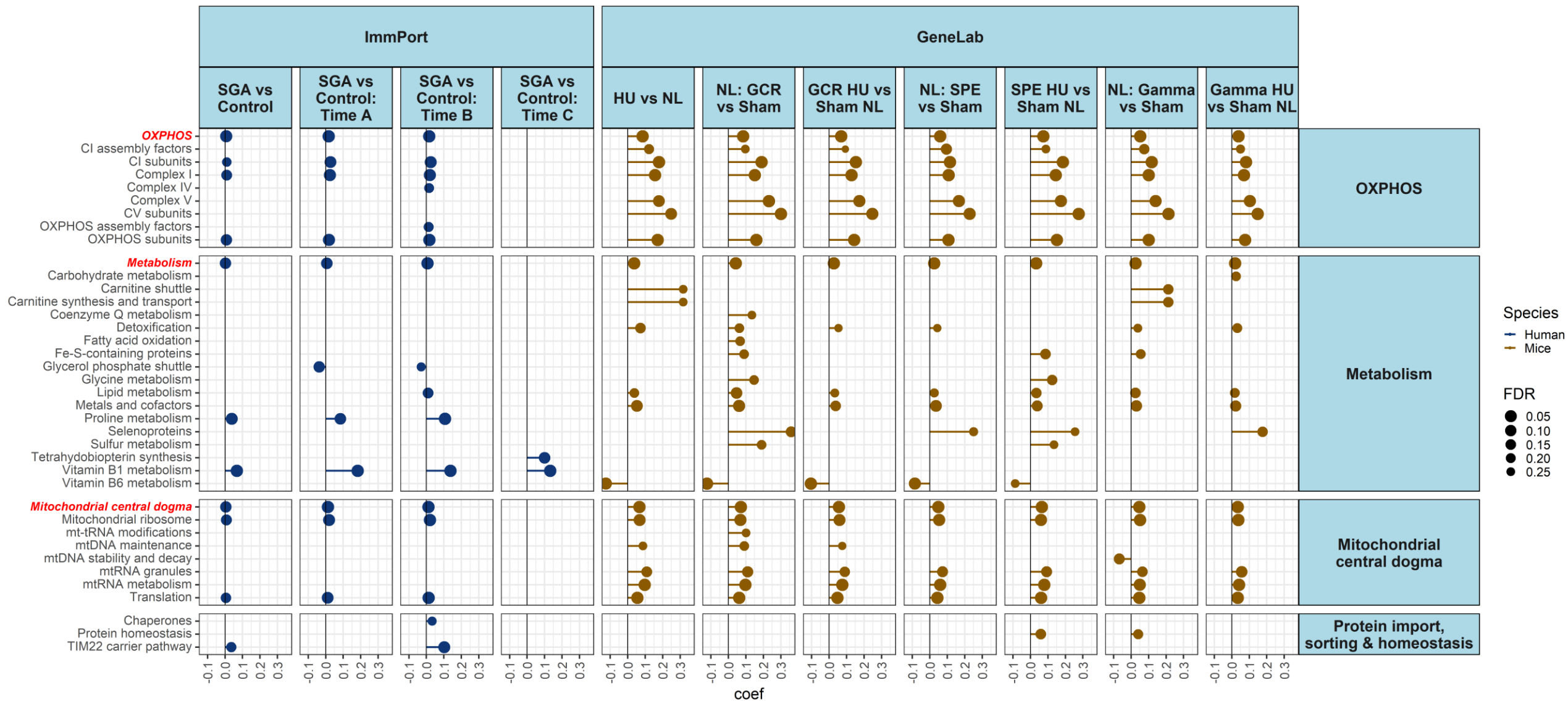
# Biological Functions Associated with the Common miRNAs

Functions Associated with 13 Common miRNAs

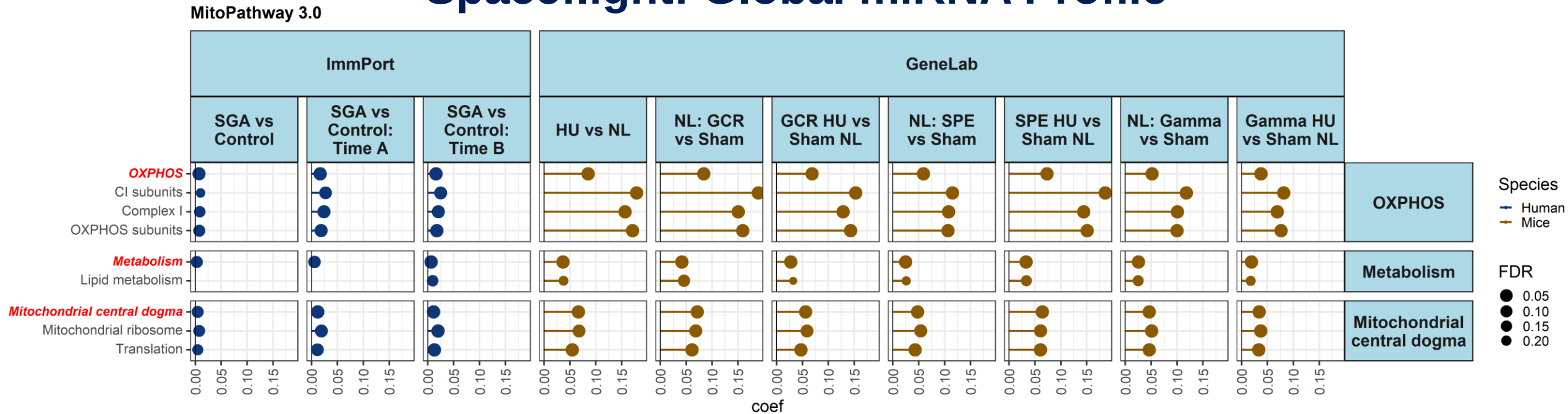


# Mitochondrial Related Pathways Impacted: Global miRNA Profile

MitoPathway 3.0



# Similar Mitochondrial Related Pathways Impacted between SGA and Spaceflight: Global miRNA Profile

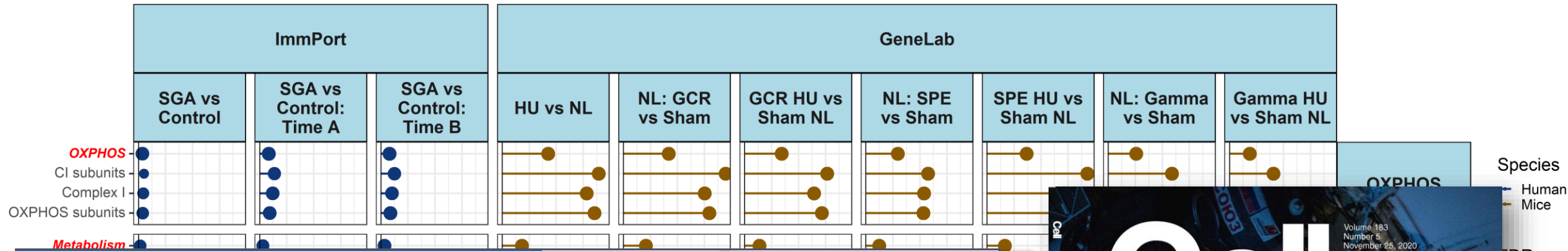


## What is the function of Mitochondria?

- “Batteries” of the cells
- Provides the energy your cells need to survive
- Produce more than 90% of the body’s energy

# Similar Mitochondrial Related Pathways Impacted between SGA and Spaceflight: Global miRNA Profile

MitoPathway 3.0



ARTICLE | VOLUME 183, ISSUE 5, P1185-1201 E20, NOVEMBER 25, 2020

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

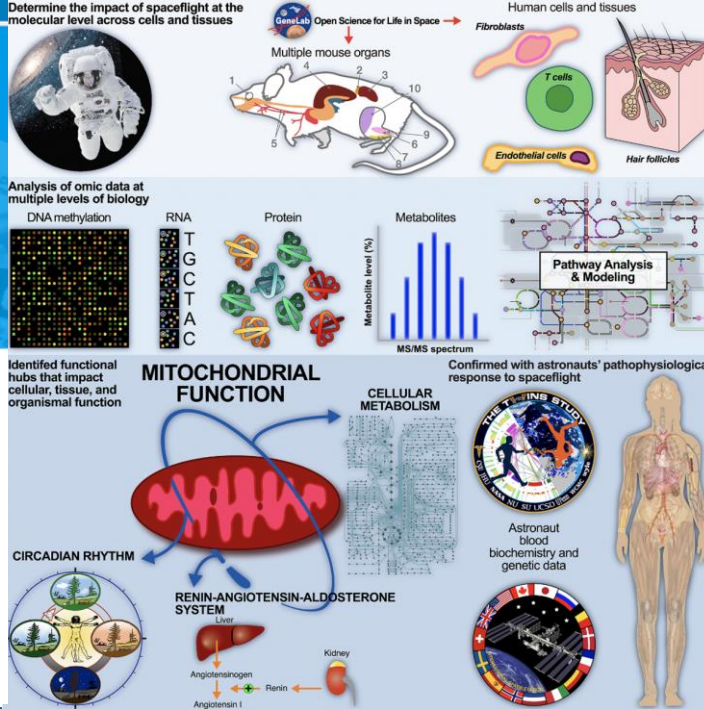
William A. da Silva<sup>23</sup> • Hossein Fazelinia<sup>23</sup> • Sara Brin Rosenthal<sup>23</sup> • ...  
 Christopher E. Mason<sup>24</sup> • Sylvain V. Costes<sup>24</sup> • Afshin Beheshti<sup>24, 25</sup> • Show all authors •

Show footnotesDOI: <https://doi.org/10.1016/j.cell.2020.11.002> • Check for updates

PlumX Metrics

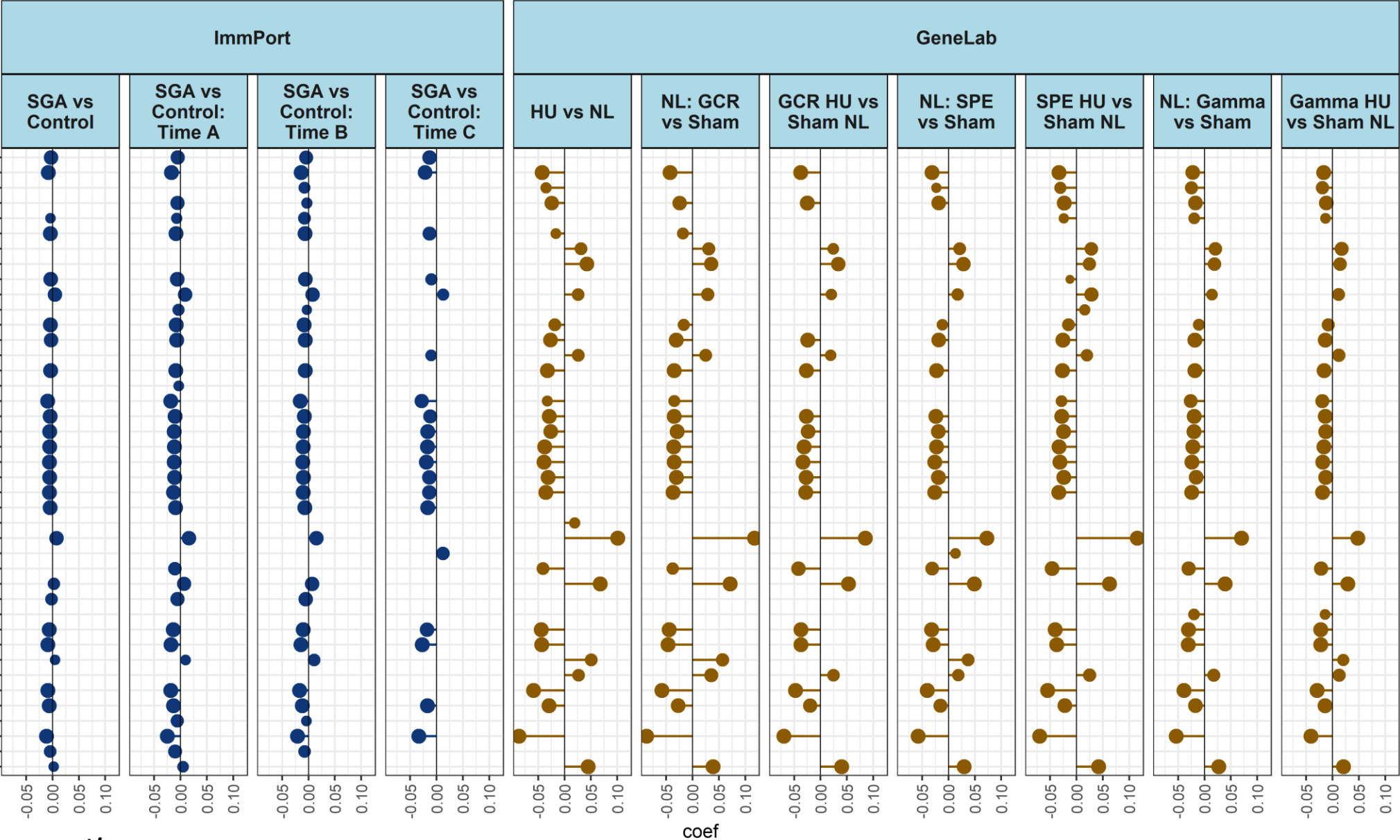
### Highlights

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

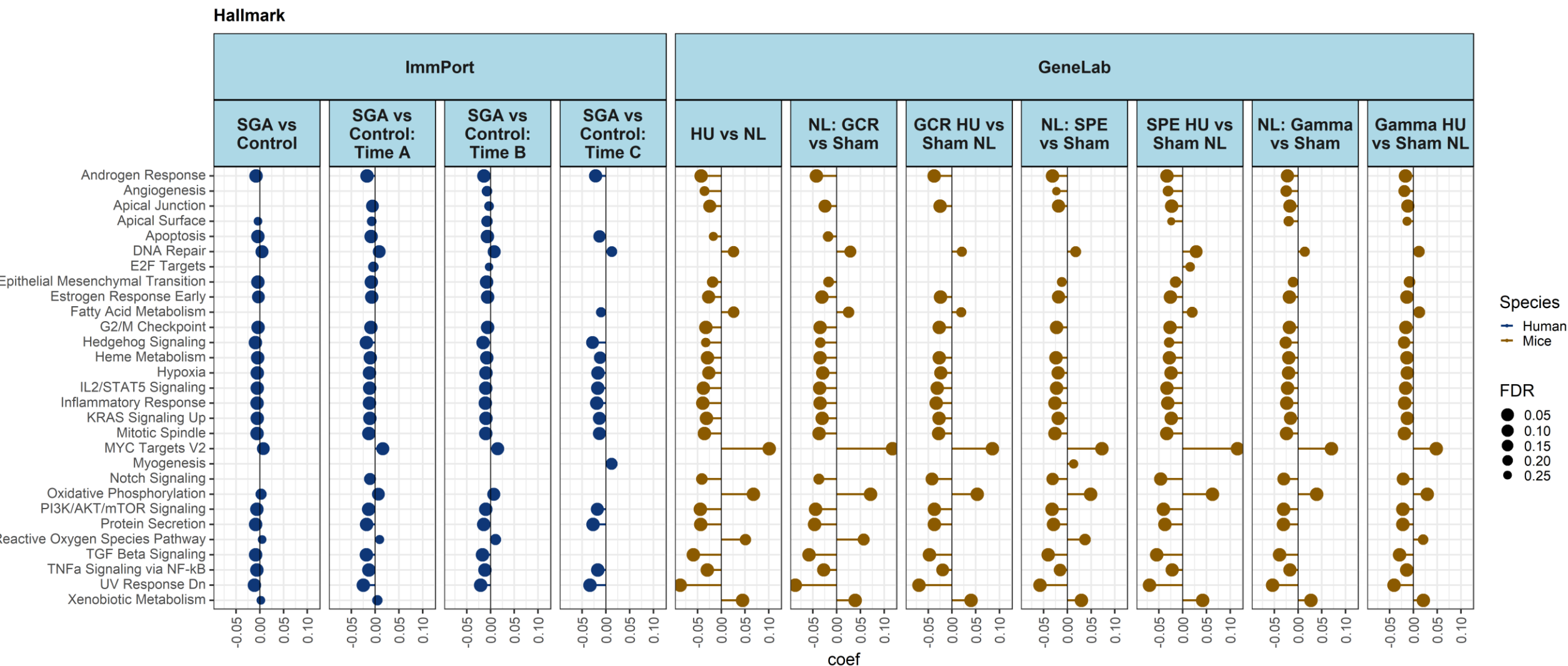


# General Pathways Impacted: Global miRNA Profile

Hallmark



# Similar General Related Pathways Impacted between SGA and Spaceflight: Global miRNA Profile

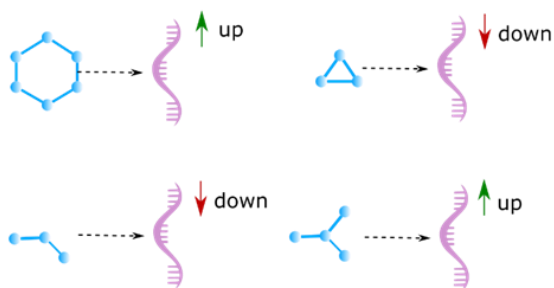


**Can we determine potential countermeasures to  
mitigate the impact of SGA in females during  
spaceflight and the clinic???**

# sChemNET: A deep learning framework for predicting miRNA targets of small molecules based on chemical structure (*manuscript in review*)

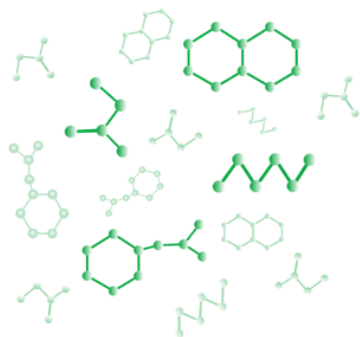
SM2miR database

small set of active small molecules on miRNA A (labeled)

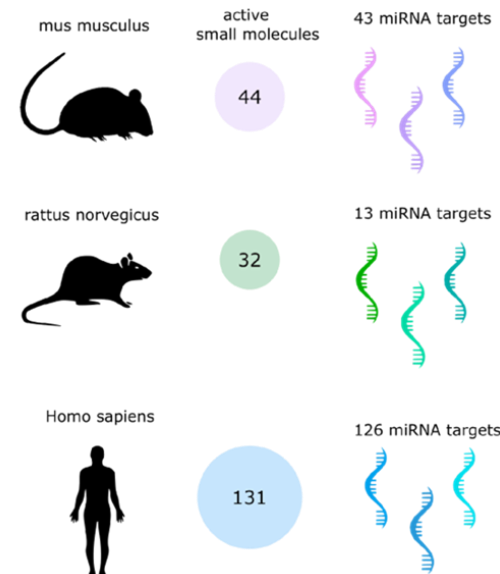


Drug Repositioning Hub database

Thousands of small molecules as-yet-unknown to affect miRNA A (unlabeled)



- Given a small molecule's chemical structure, sChemNET predicts whether it will affect miRNA targets
- We tested sChemNET for chemical data from homo sapiens and other model organisms
- sChemNET can be used in any chemical library for an *in-silico* screening against miRNA targets



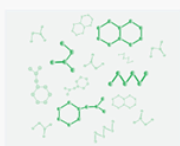
Training set

Labeled small molecules (multiple miRNAs)



+

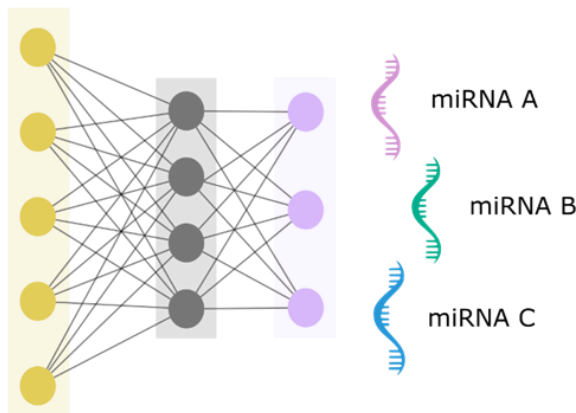
Unlabeled small molecules



chemical feature (input)

hidden layer

Probability of affecting a miRNA expression level

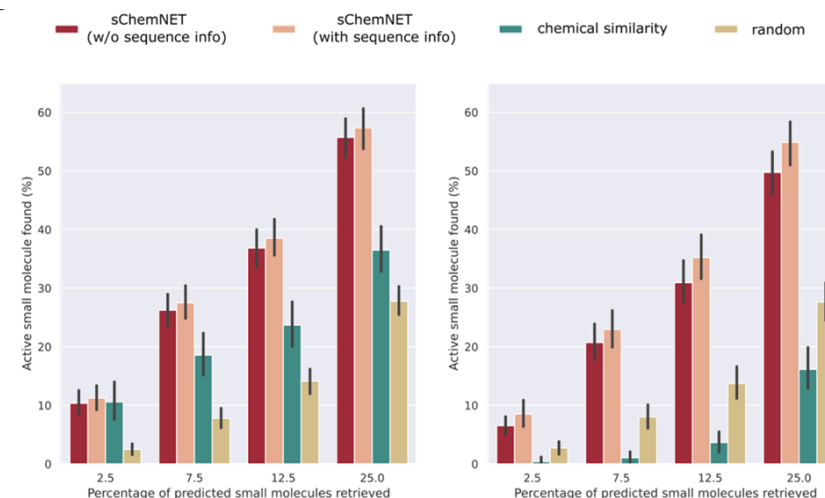


sChemNET minimizes the following loss function

$$\mathcal{L} = \frac{1}{2} \sum_{(i,v) \text{ is labelled}} s_{uv} (\hat{y}_{iv} - y_{iv})^2 + \frac{\alpha}{2} \sum_{(i,v) \text{ is unlabelled}} \hat{y}_{iv}^2$$



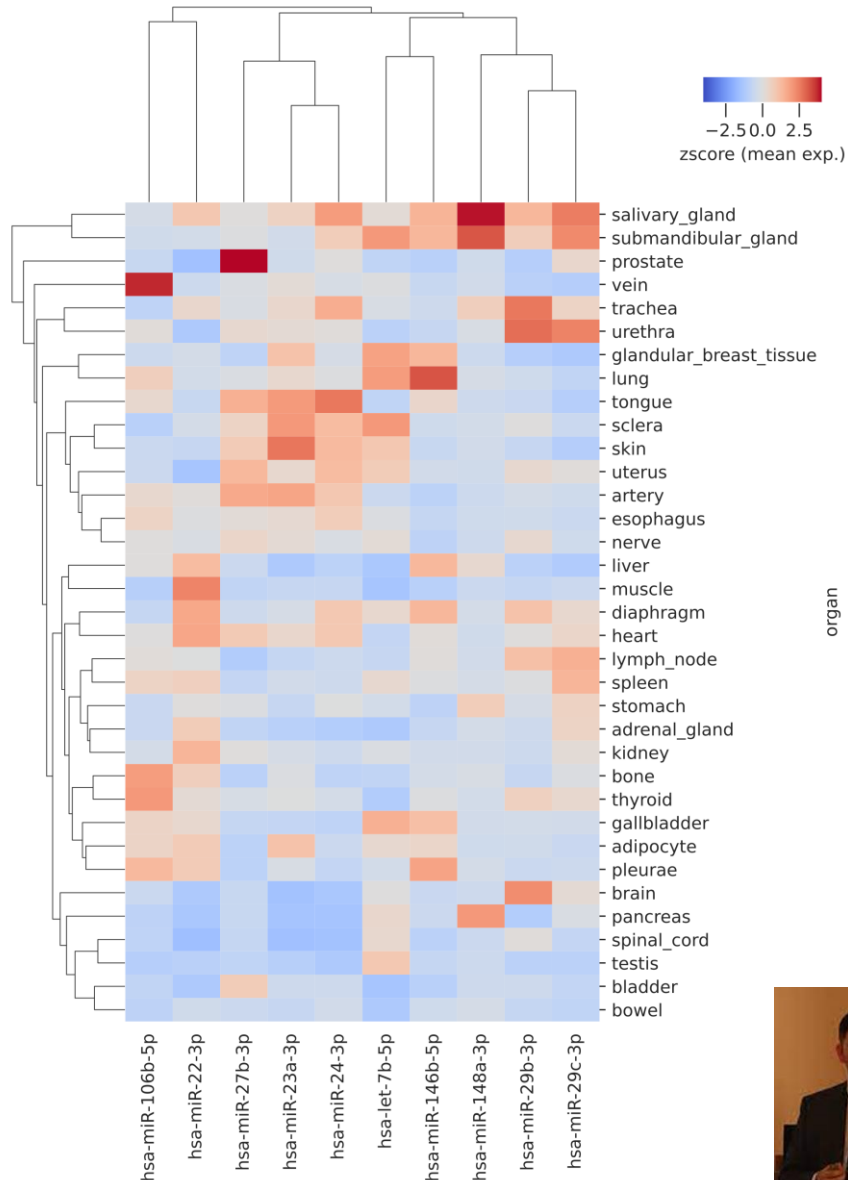
Diego Galeano,  
PhD



Manuscript Under Review

# sChemNET's predictions for our miRNA signature

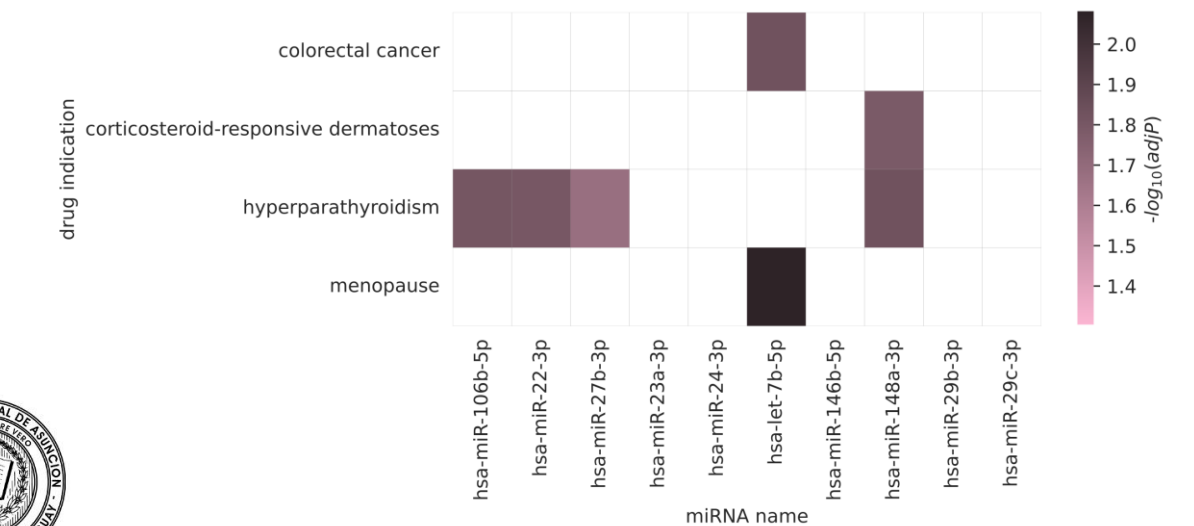
miRNA Tissue Atlas database



Enriched drug Mode of Action

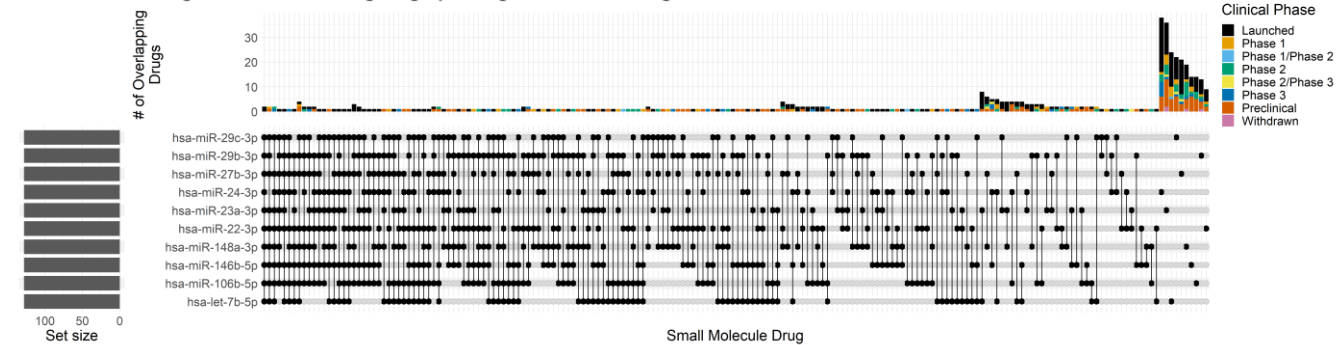


Enriched drug indications

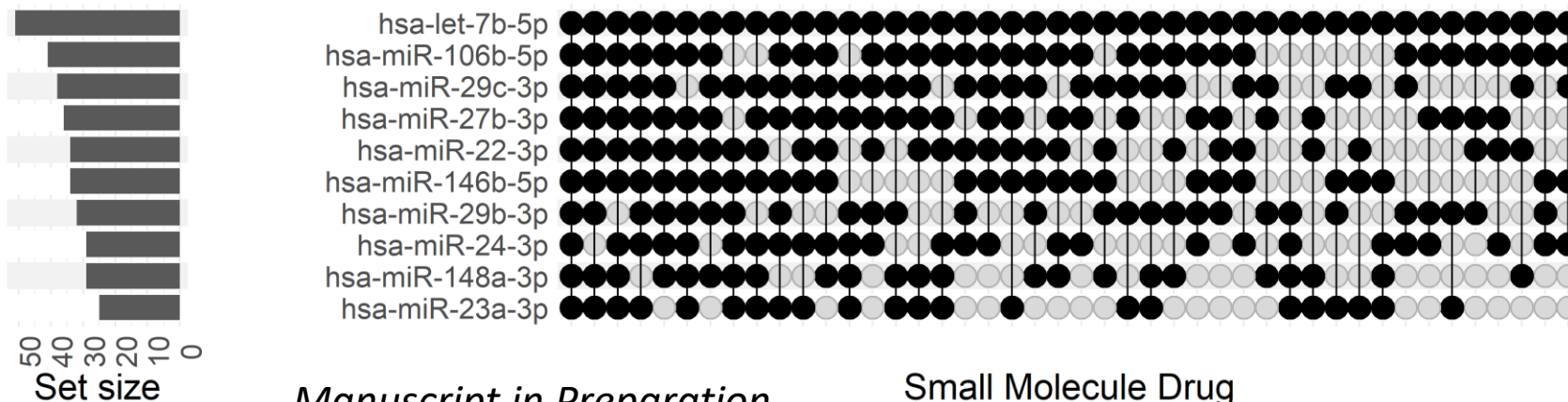
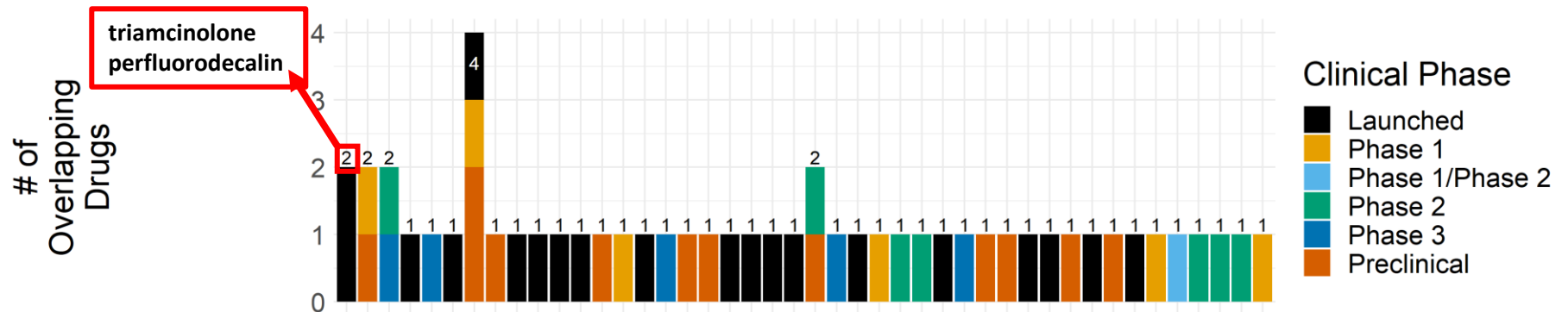


# sChemNET's Predicted Common Small Molecule Drugs

Small Molecule Drug Predictions for Targeting Spaceflight/SGA miRNA Signature



## Small Molecule Drug Predictions for Targeting Spaceflight/SGA miRNA Signature 5 or more miRNAs in common



Manuscript in Preparation



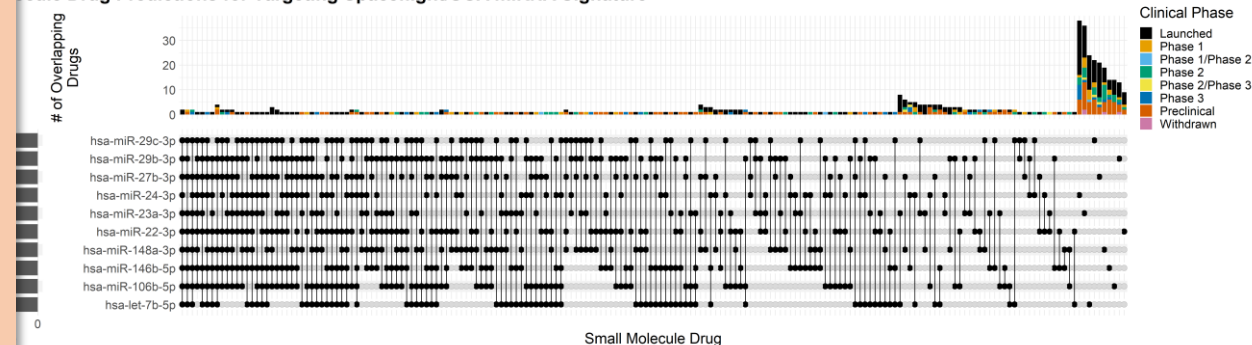
Diego Galeano,  
PhD



# sChemNET's Predicted Common Small Molecule Drugs

**Triamcinolone** is a glucocorticoid used to treat a number of different medical conditions, such as eczema, alopecia areata, lichen sclerosus, psoriasis, arthritis, allergies, ulcerative colitis, lupus, sympathetic ophthalmia, temporal arteritis, uveitis, ocular inflammation, keloids, urushiol-induced contact dermatitis, aphthous ulcers (usually as triamcinolone acetonide), central retinal vein occlusion, visualization during vitrectomy and the prevention of asthma attacks.

Small Molecule Drug Predictions for Targeting Spaceflight/SGA miRNA Signature



## Targeting Spaceflight/SGA miRNA Signature

[nature](#) > [pediatric research](#) > [translational investigation](#) > [article](#)

Published: 13 July 2012

**Aerosolized perfluorocarbon improves gas exchange and pulmonary mechanics in preterm lambs with severe respiratory distress syndrome**

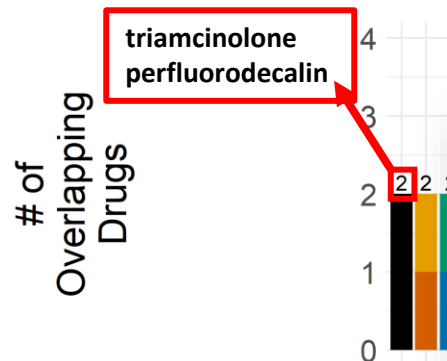
[Xabier Murgia](#) , [Victoria Mielgo](#), [Adolf Valls-i-Soler](#), [Estibaliz Ruiz-del-Yerro](#) & [Carmen Rey-Santano](#)

[Pediatric Research](#) **72**, 393–399 (2012) | [Cite this article](#)

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**Perfluorodecalin** was an ingredient in a product developed by Green Cross

...designed for use in liposomes, to provide a barrier to prevent wound healing. Organs and tissues can be submerged in oxygenated perfluorodecalin; the "two-phase" solution of perfluorodecalin and UW solution to



Manuscript in Pre

### Experimental and Numerical Modeling of Aerosol Delivery for Preterm Infants

by [Iñigo Aramendia](#) <sup>1,\*</sup>, [Unai Fernandez-Gamiz](#) <sup>1</sup>, [Alberto Lopez-Arraiza](#) <sup>2</sup>, [Carmen Rey-Santano](#) <sup>3</sup>, [Victoria Mielgo](#) <sup>3</sup>, [Francisco Jose Basterretxea](#) <sup>4</sup>, [Javier Sancho](#) <sup>1</sup> and [Miguel Angel Gomez-Solaetxe](#) <sup>2</sup>

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**Abstract** Respiratory distress syndrome (RDS) represents one of the major causes of mortality among preterm infants, and the best approach to treat it is an open research issue. The use of perfluorocarbons (PFC) along with non-invasive respiratory support techniques has proven the usefulness of PFC as a complementary substance to achieve a more homogeneous surfactant distribution. The aim of this work was to study the inhaled particles generated by means of an intracorporeal inhalation catheter, evaluating the size and mass distribution of different PFC aerosols. In this article, we discuss different experiments with the PFC perfluorodecalin (PFD) and FC75 with a driving pressure of 4–5 bar, evaluating properties such as the aerodynamic diameter ( $D_{p,50}$ ). Its value is directly linked to particle deposition in the lung. Furthermore, we develop a numerical model of the airflow axial velocity at different downstream positions when compared with the data gathered from the experiments. The numerical validation of the cumulative mass distribution for PFD particles also confirmed a closer match with the experimental data measured at the optimal distance of 60 mm from the catheter tip. In the case of FC75, the cumulative mass fraction for particles above 10  $\mu$ m was considerable higher with a driving pressure of 5 bar. These numerical models could be a helpful tool to assist parametric studies of new non-invasive devices for the treatment of RDS in preterm infants.

**Keywords:** aerosol; CFD; inhalation catheter; perfluorocarbons; respiratory distress syndrome

RESEARCH ARTICLE | VOLUME 38, ISSUE 1, P17–20, JANUARY 2003

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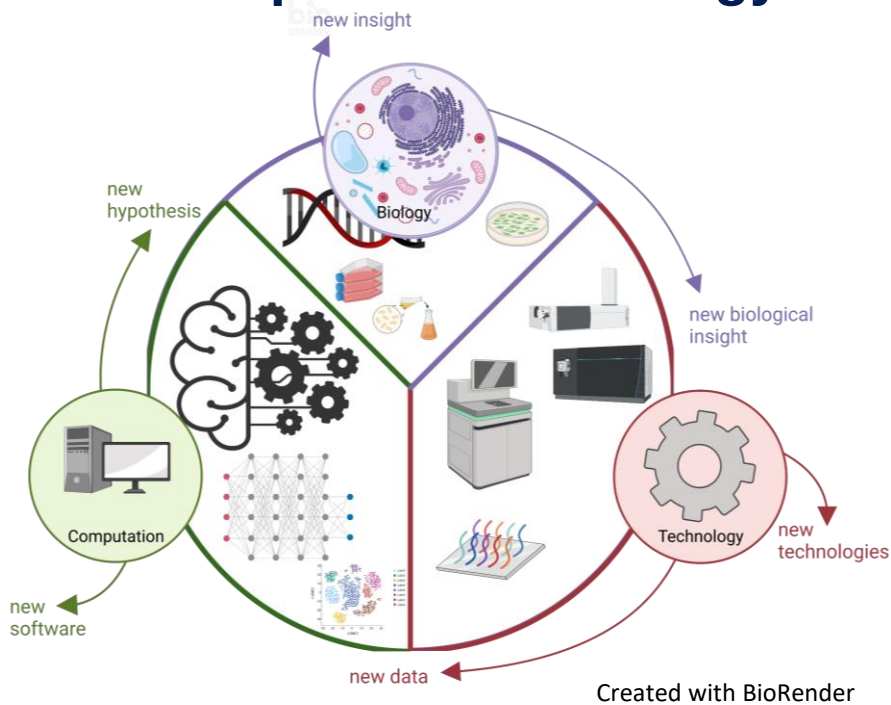
### Early perfluorodecalin lung distension in infants with congenital diaphragmatic hernia

[G.M. Walker](#) • [K.F. Kasem](#) • [S.J. O'Toole](#) • [A. Watt](#) • [C.H. Skeoch](#) • [C.F. Davis](#)

DOI: <https://doi.org/10.1053/jpsu.2003.50002>

PlumX Metrics

# Computational Biology is Key in Advancement of Therapy and Countermeasure Development

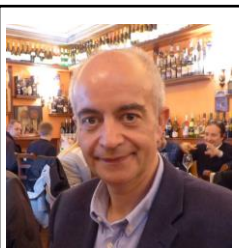


- The need for integrated computational biology in all research is the way of the future to push the boundaries of biology.
- ***Using Creativity to combine different publicly available platforms from both NIAID and NASA can benefit for space biology and the clinic!!!***
- ML techniques can be easily used as a “plug and play” method to apply to many experimental conditions and disease models.
- The combination of Systems Biology and AI/ML approaches will drive future research

## Acknowledgements



Diego  
Galeano



Francisco  
Enguita

