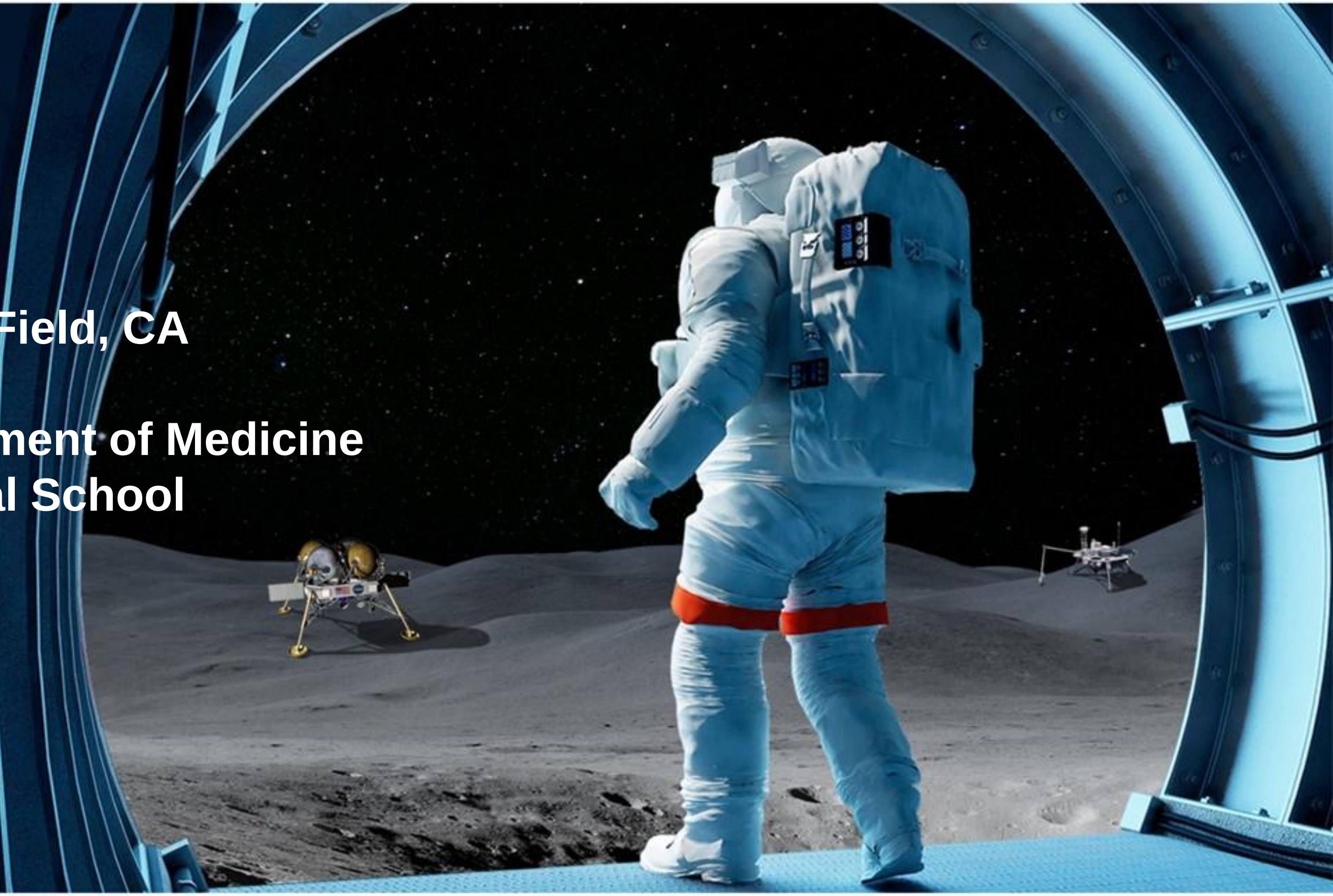
Circulating miRNA Signature Predicts Health Risks Associated with Radiation and Microgravity

National Aeronautics and Space Administration



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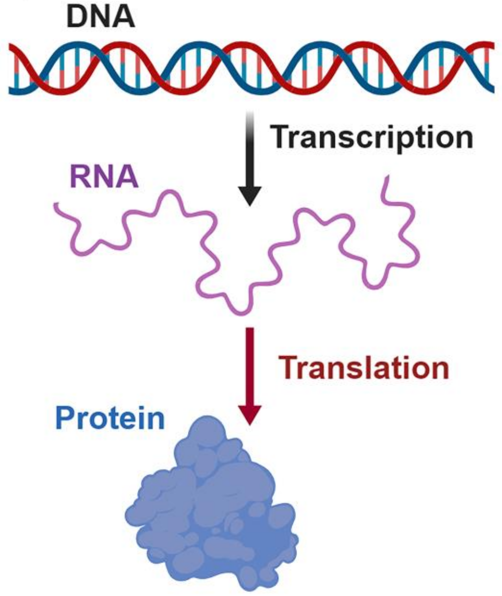
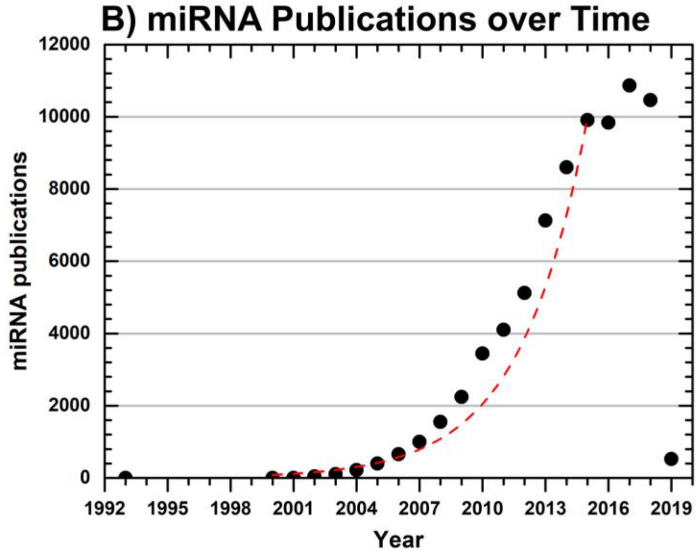
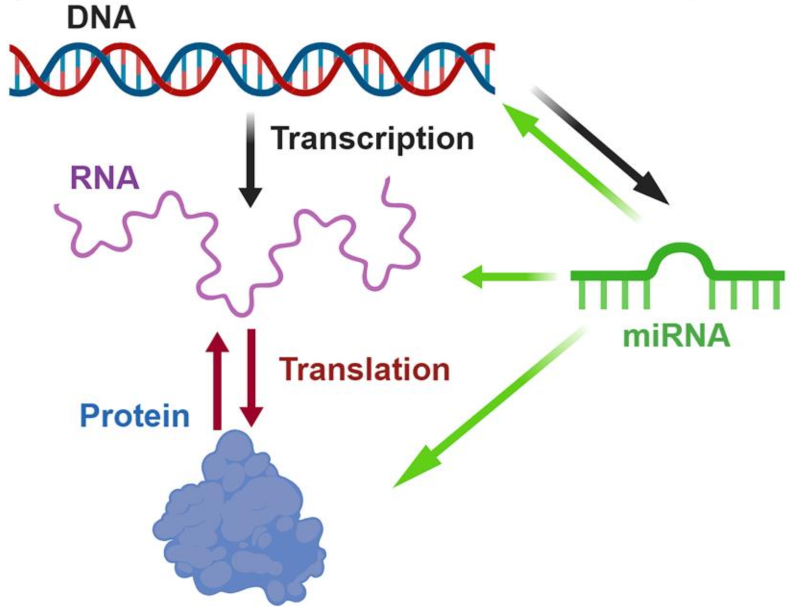
What are miRNAs and why study miRNAs

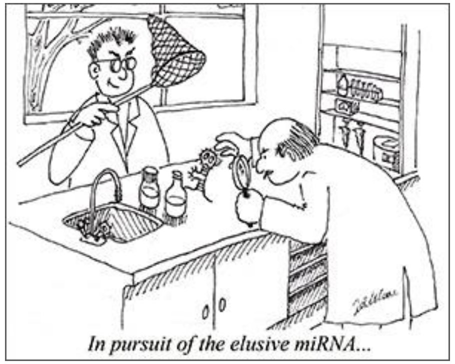
A) Classical View of Molecular Biology



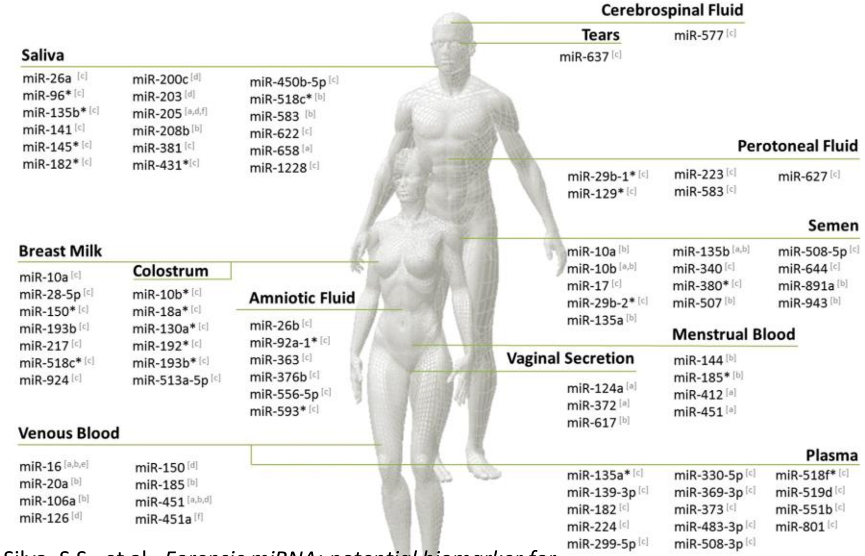


C) New Understanding of Molecular Biology



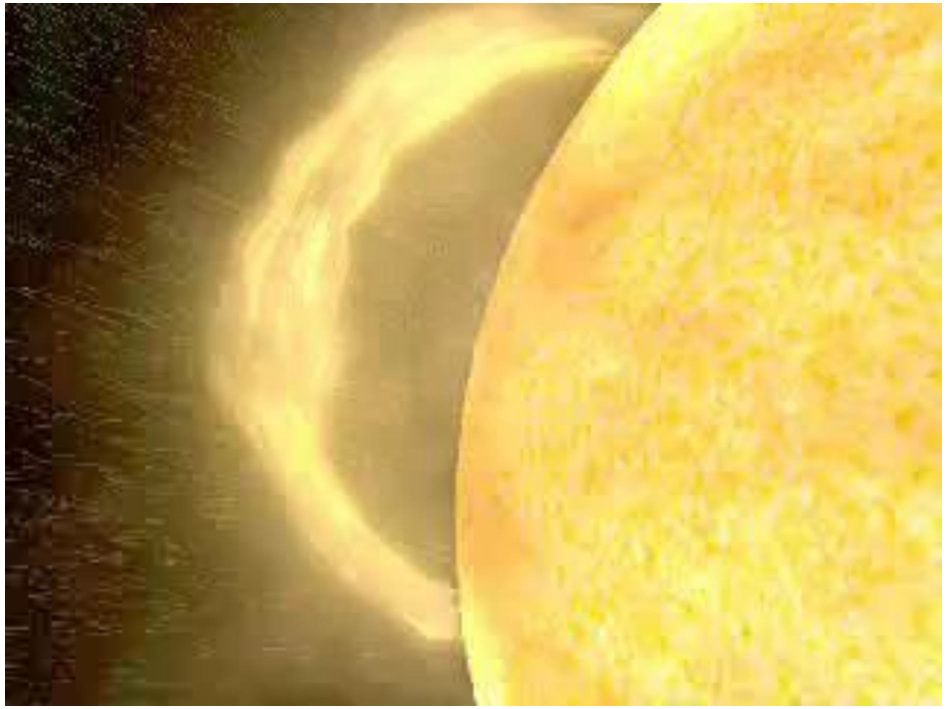


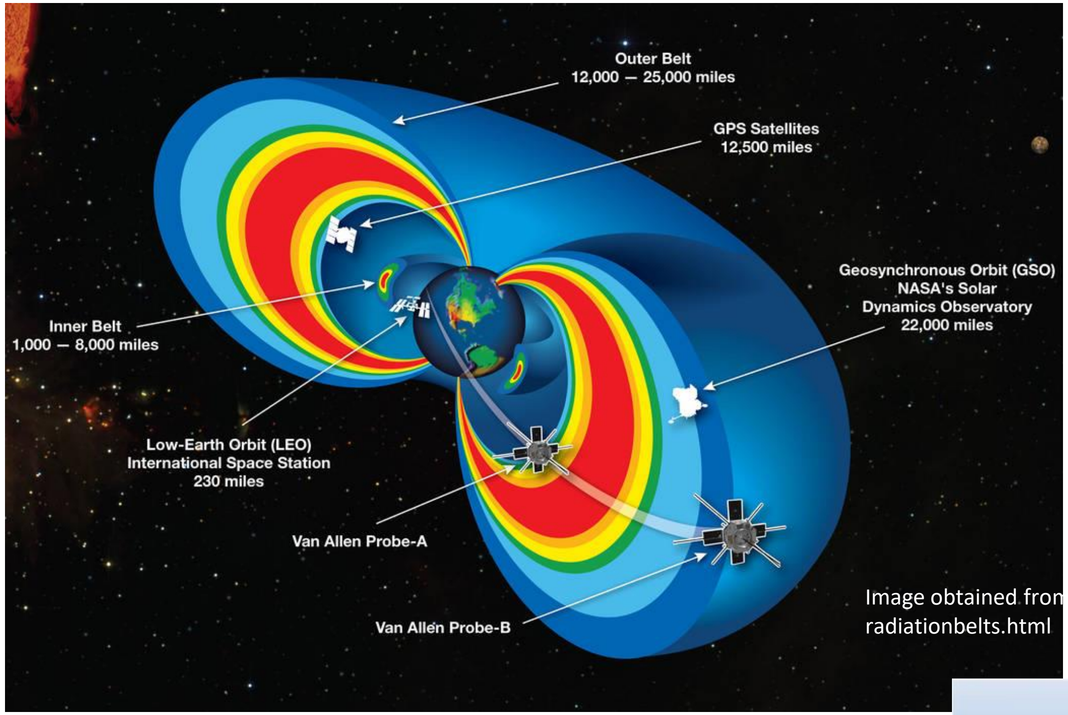
- **A single miRNA has been estimated to regulate up to 500 mRNAs.**
- **miRNAs are ~22nt**
- **Due to the size and stability of the miRNAs, it can float freely in the blood.** →
- **miRNAs are now known to be involved in all aspects of diseases.**
- **miRNA are not only found in mammals, but everything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



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

Space Environment





	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

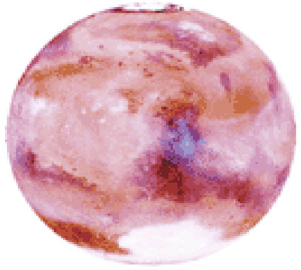
TRIP TO AND FROM MARS (1 YEAR): 80,000 — ON MARS (1.5 YEARS): 30,000 — FROM SOLAR FLARE: 20,000

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

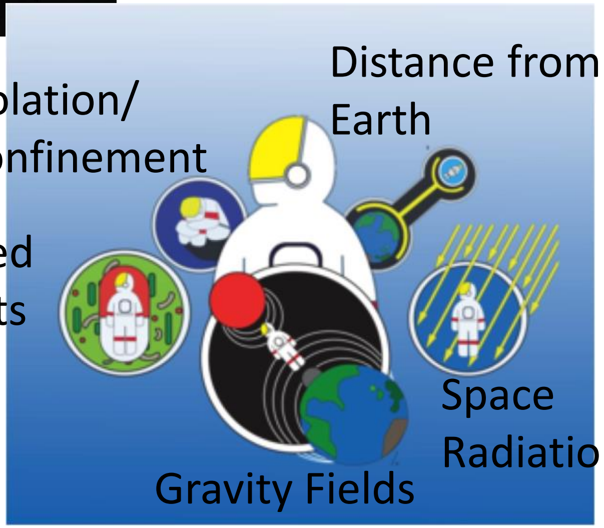
2½ Years, 2,600 X-Rays

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.

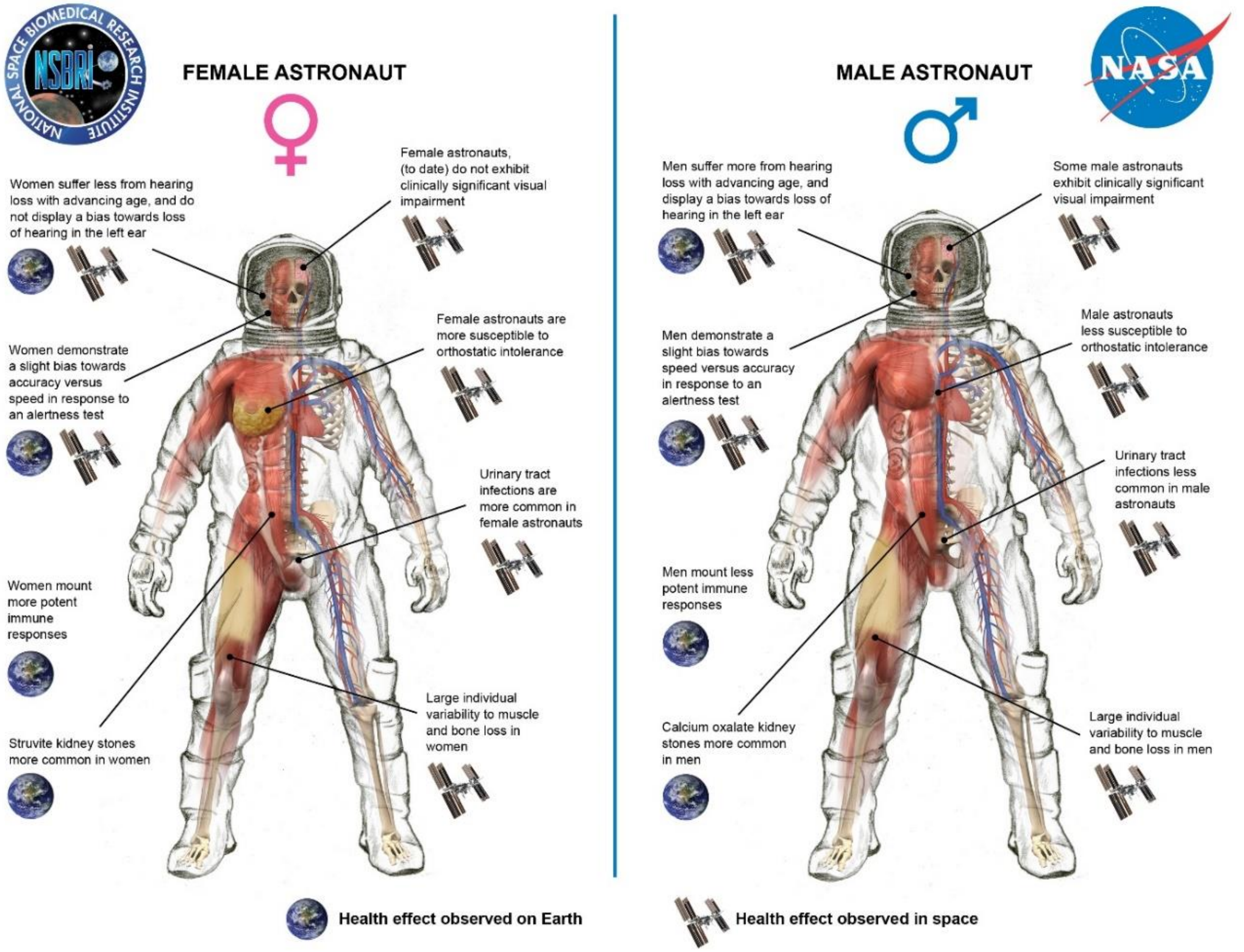


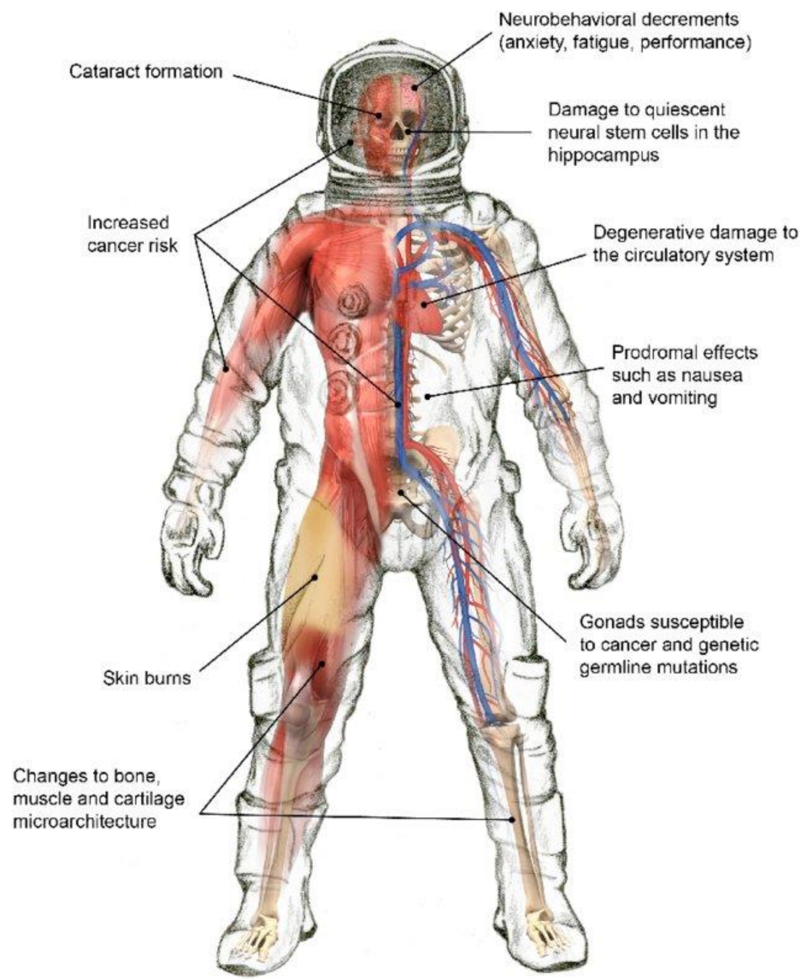
NASA



Credits: NASA

Space Health Risks On Astronauts

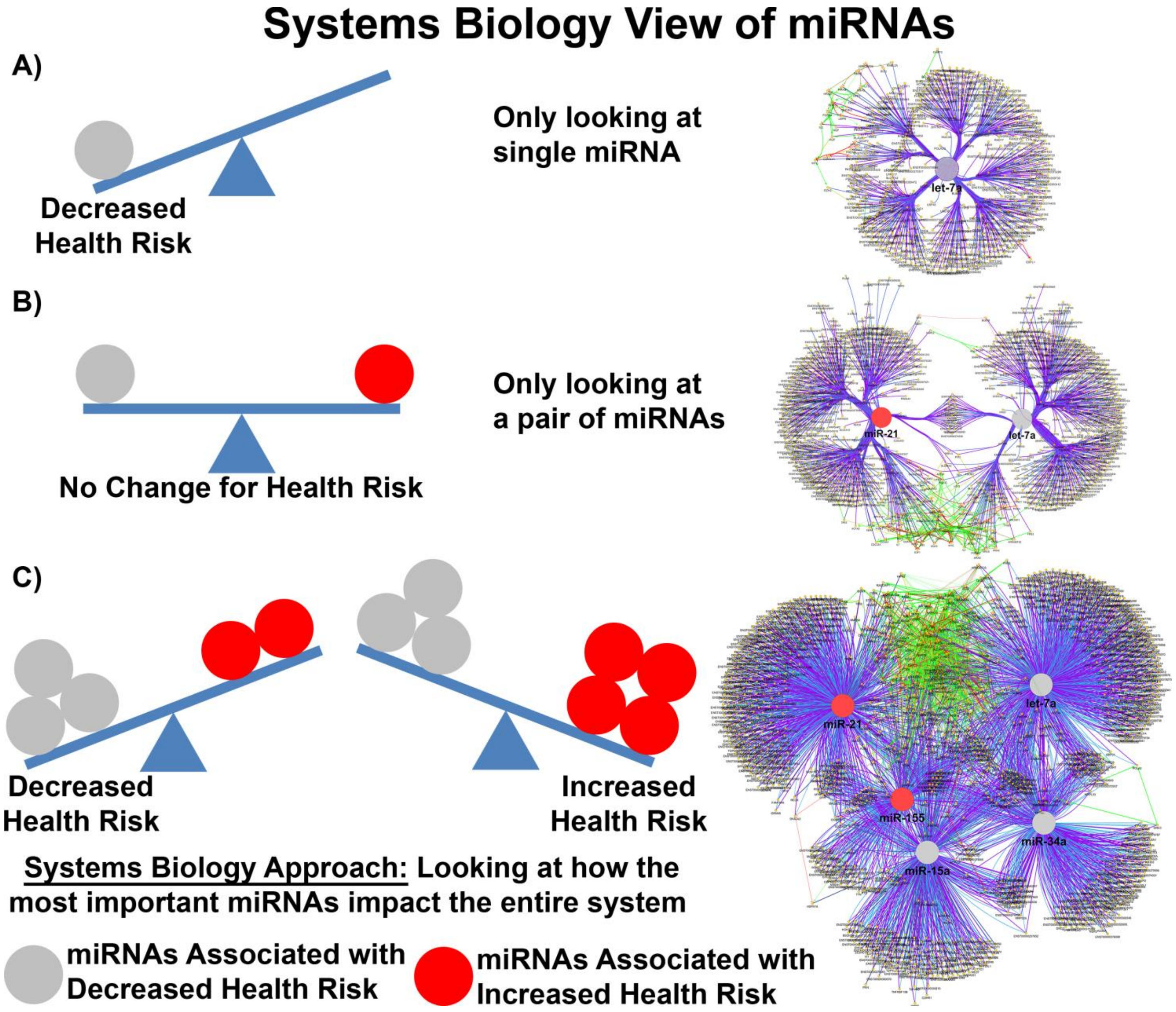




Select health effects due to space radiation exposures.

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

Systems Biology View of miRNAs



PLOS | ONE

RESEARCH ARTICLE

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

Afshin Beheshti[1]☯*, Shayoni Ray[2]☯, Homer Fogle[1], Daniel Berrios[2], Sylvain V. Costes[3]*

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

☯ These authors contributed equally to this work.
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Citation: Beheshti A, Ray S, Fogle H, Berrios D, Costes SV (2018) A microRNA signature and TGF-β1 response were identified as the key master regulators for spaceflight response. PLoS ONE 13 (7): e0199621. https://doi.org/10.1371/journal.pone.0199621

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

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Abstract

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International Journal of *Molecular Sciences* MDPI

Article

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

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

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2 Department of Physics, Hampton University, Hampton, VA 23668 USA; john.mcdonald@hamptonu.edu
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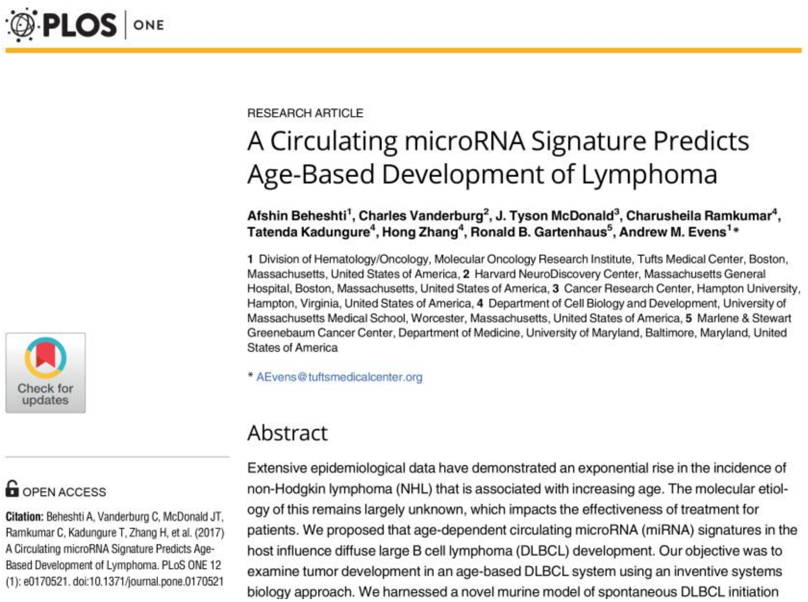
Determining miRNA signature associated with diseases: Lymphoma



PLOS | ONE

RESEARCH ARTICLE

A Circulating microRNA Signature Predicts Age-Based Development of Lymphoma

Afshin Beheshti[1], Charles Vanderburg[2], J. Tyson McDonald[3], Charusheila Ramkumar[4], Tatenda Kadungure[4], Hong Zhang[4], Ronald B. Gartenhaus[5], Andrew M. Evens[1]*

1 Division of Hematology/Oncology, Molecular Oncology Research Institute, Tufts Medical Center, Boston, Massachusetts, United States of America, 2 Harvard NeuroDiscovery Center, Massachusetts General Hospital, Boston, Massachusetts, United States of America, 3 Cancer Research Center, Hampton University, Hampton, Virginia, United States of America, 4 Department of Cell Biology and Development, University of Massachusetts Medical School, Worcester, Massachusetts, United States of America, 5 Marlene & Stewart Greenebaum Cancer Center, Department of Medicine, University of Maryland, Baltimore, Maryland, United States of America

* AEvens@tuftsmedicalcenter.org

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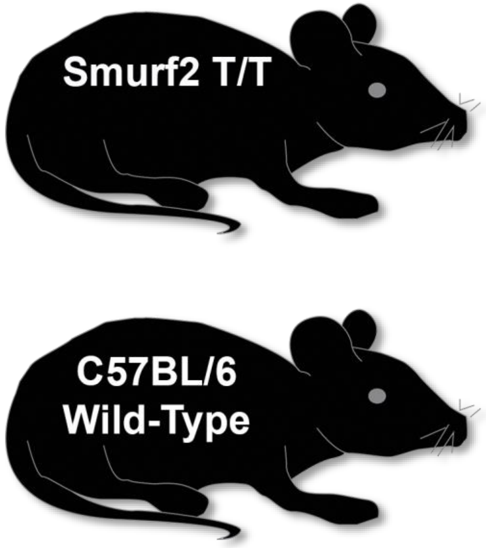
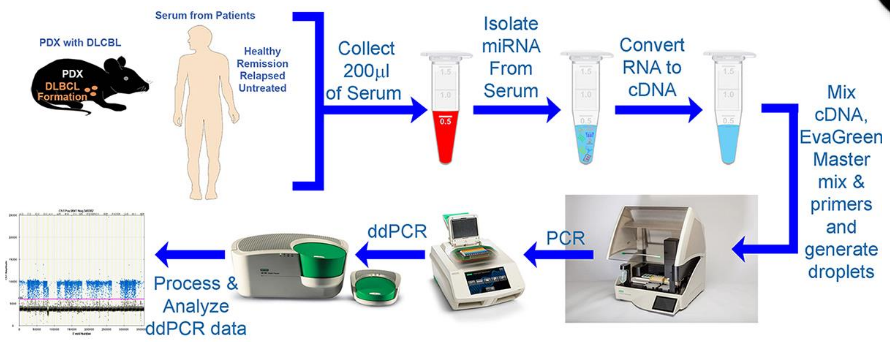
Citation: Beheshti A, Vanderburg C, McDonald JT, Ramkumar C, Kadungure T, Zhang H, et al. (2017) A Circulating microRNA Signature Predicts Age-Based Development of Lymphoma. PLoS ONE 12 (1): e0170521. doi:10.1371/journal.pone.0170521

Abstract

Extensive epidemiological data have demonstrated an exponential rise in the incidence of non-Hodgkin lymphoma (NHL) that is associated with increasing age. The molecular etiology of this remains largely unknown, which impacts the effectiveness of treatment for patients. We proposed that age-dependent circulating microRNA (miRNA) signatures in the host influence diffuse large B cell lymphoma (DLBCL) development. Our objective was to examine tumor development in an age-based DLBCL system using an inventive systems biology approach. We harnessed a novel murine model of spontaneous DLBCL initiation

Young Mice (2 months old)





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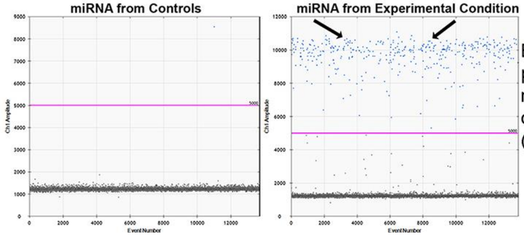
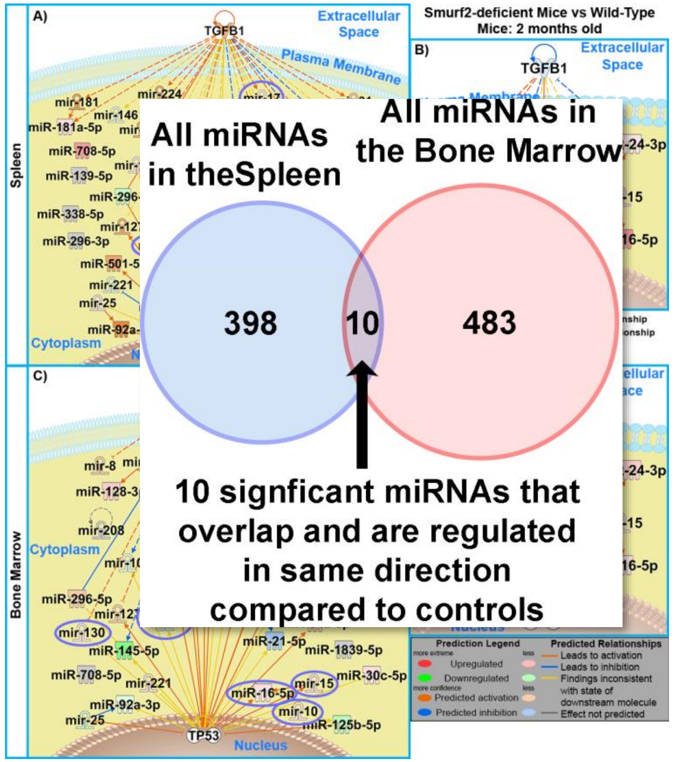
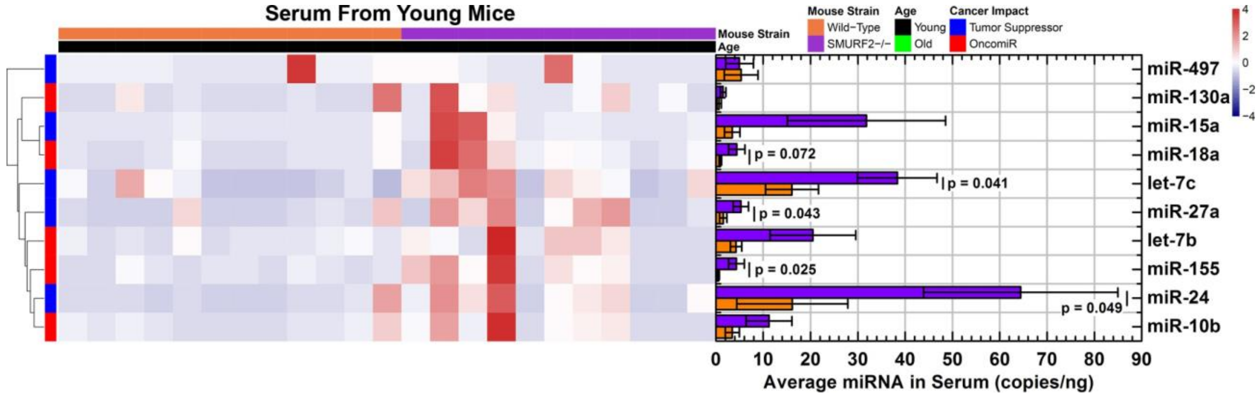
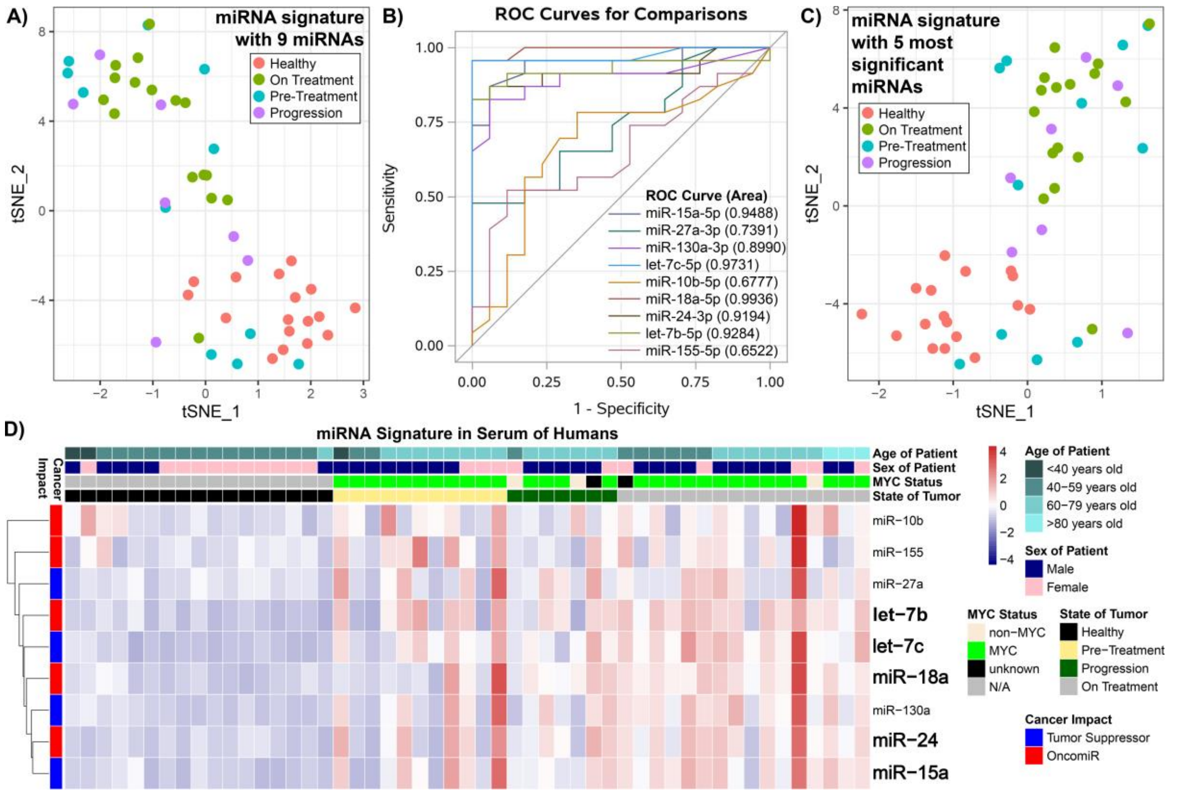


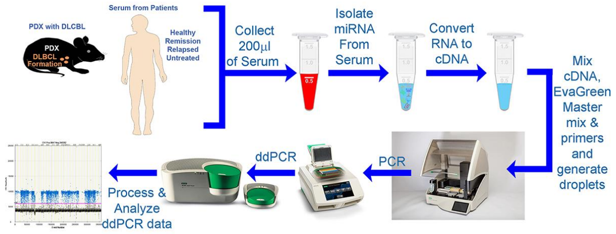
Every single blue point on the plots represents one copy of miRNA (see arrows).





miRNAs Associated with DLBCL Development: in Humans





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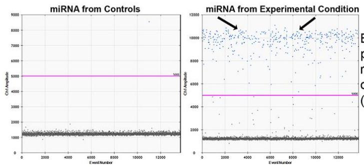

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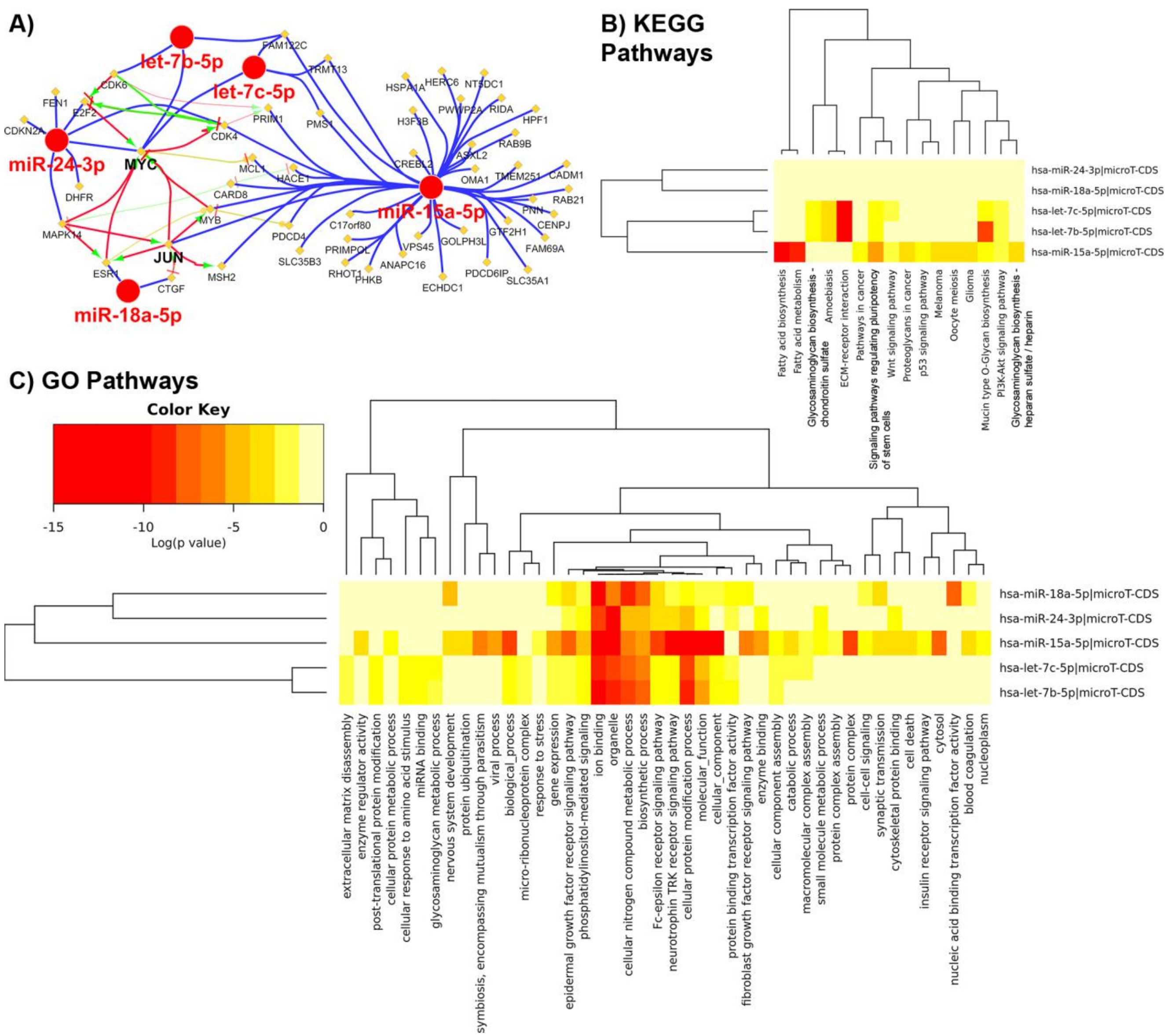
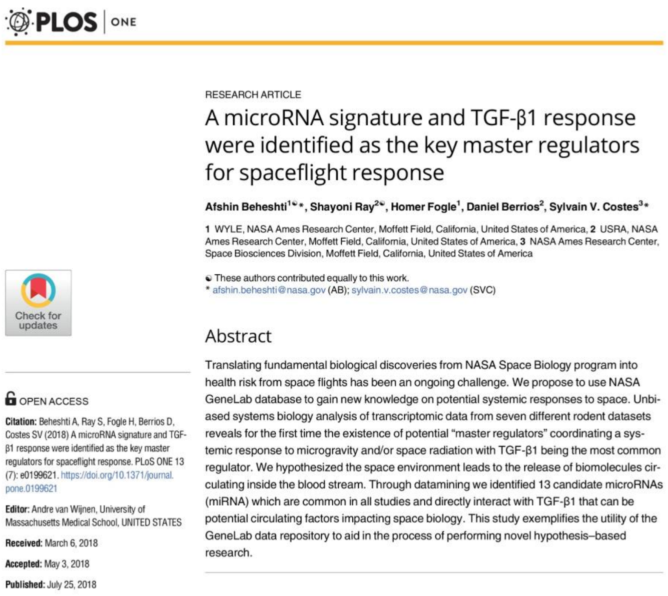


Manuscript Accepted

miRNA Signature Prediction Associated with Space Flight



PLOS | ONE

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☯ These authors contributed equally to this work.
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Citation: Beheshti A, Ray S, Fogle H, Berrios D, Costes SV (2018) A microRNA signature and TGF-β1 response were identified as the key master regulators for spaceflight response. PLoS ONE 13 (7): e0199621. https://doi.org/10.1371/journal.pone.0199621

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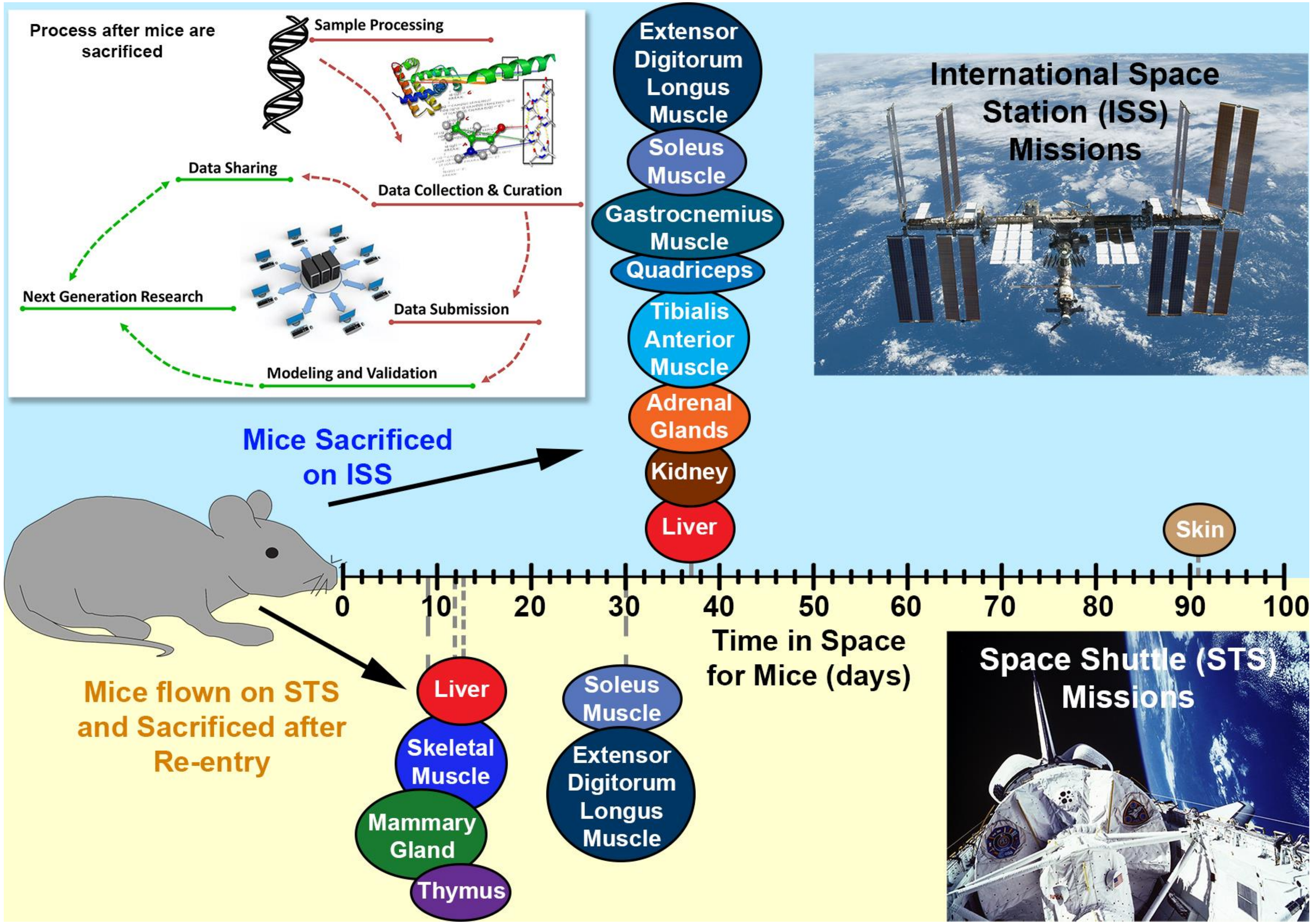
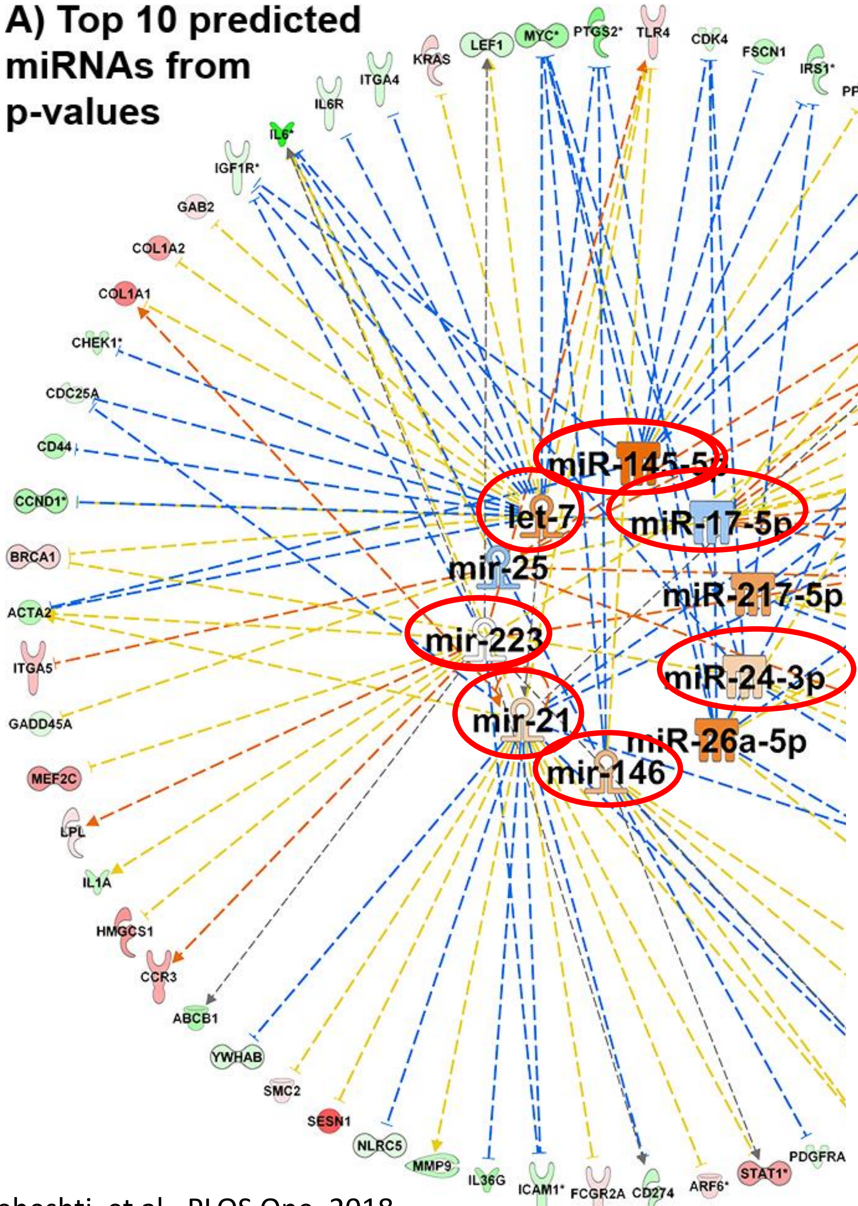
https://genelab.nasa.gov/

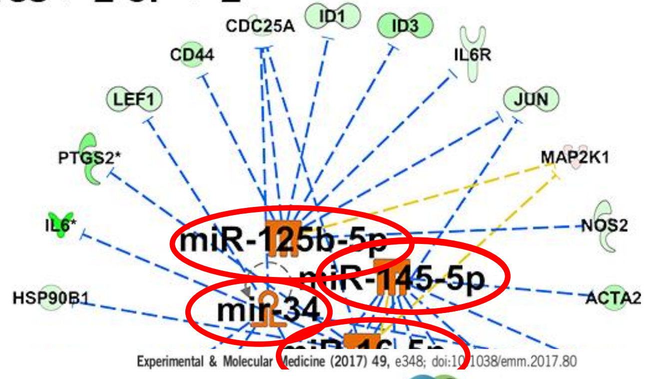


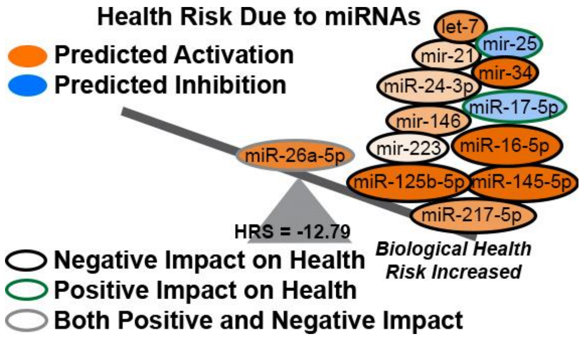
Predicted miRNAs Involved with Spaceflight

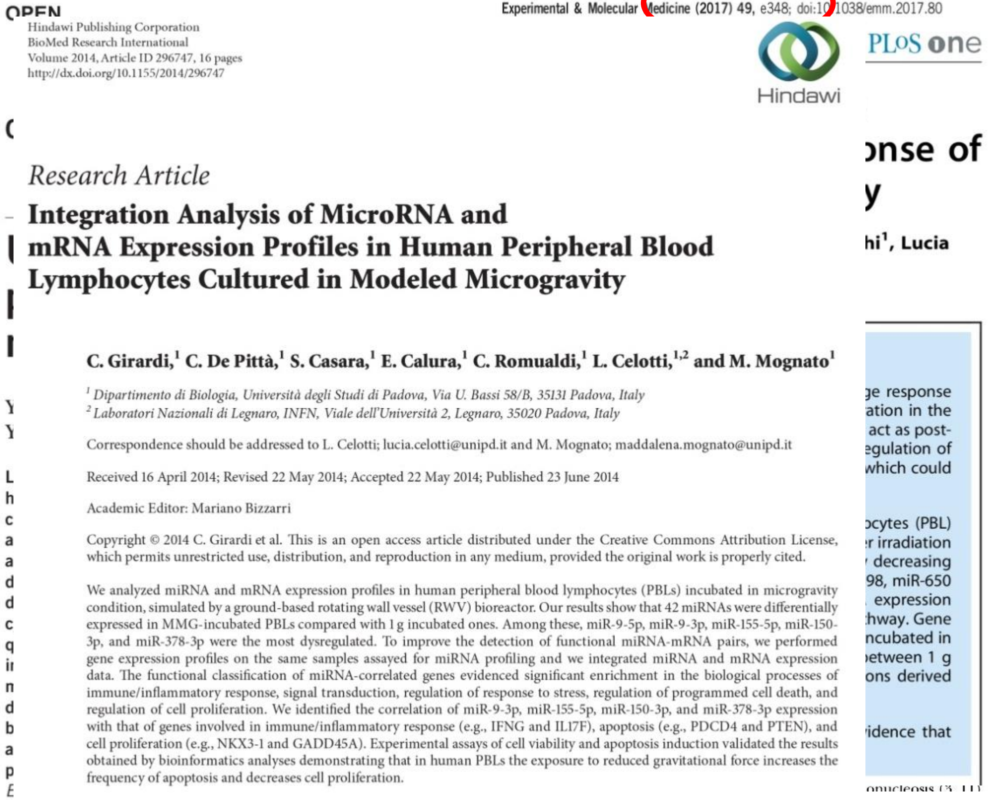
A) Top 10 predicted miRNAs from p-values



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






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

Hindawi PLOS one

Research Article

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

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

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

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Academic Editor: Mariano Bizzarri

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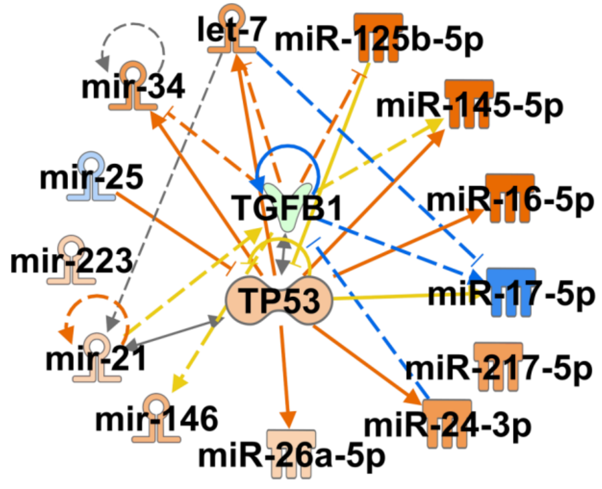
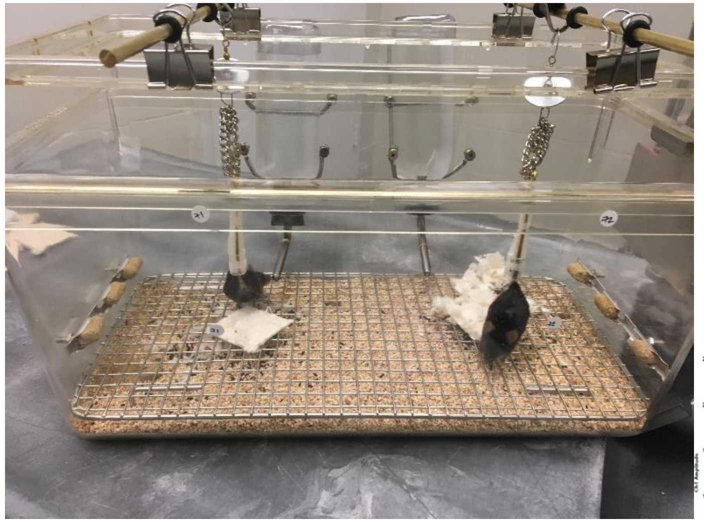
We analyzed miRNA and mRNA expression profiles in human peripheral blood lymphocytes (PBLs) incubated in microgravity condition, simulated by a ground-based rotating wall vessel (RWV) bioreactor. Our results show that 42 miRNAs were differentially expressed in MMG-incubated PBLs compared with 1 g incubated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

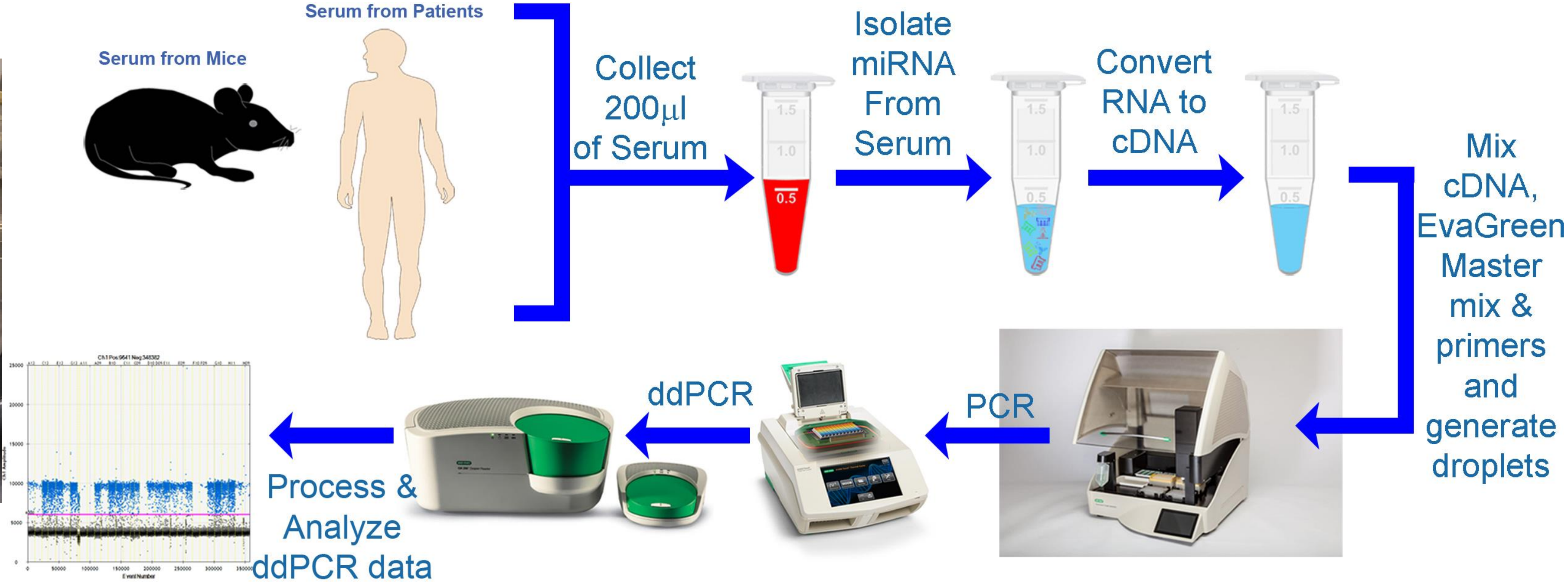


Beheshti, et al., PLOS One, 2018

Technique to Quantify miRNAs

Hindlimb Unloading





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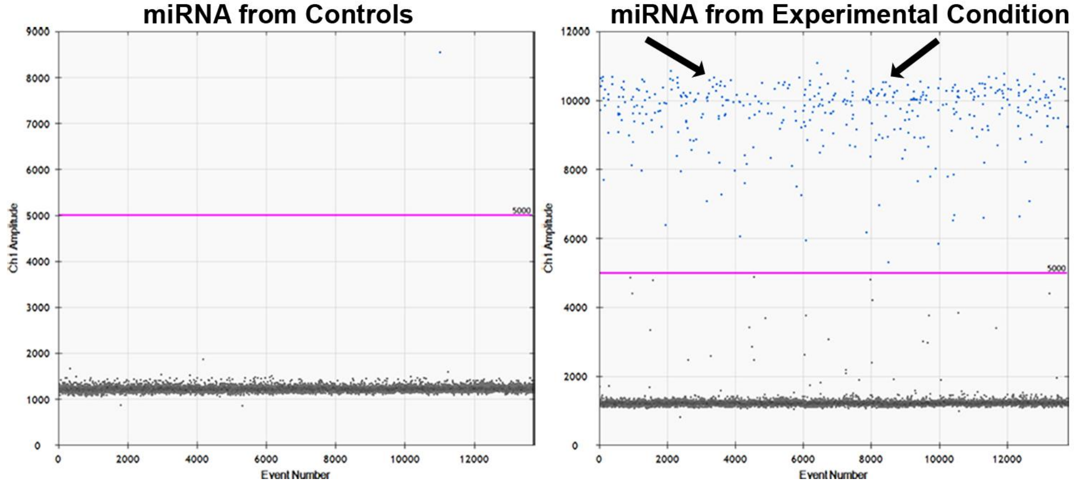
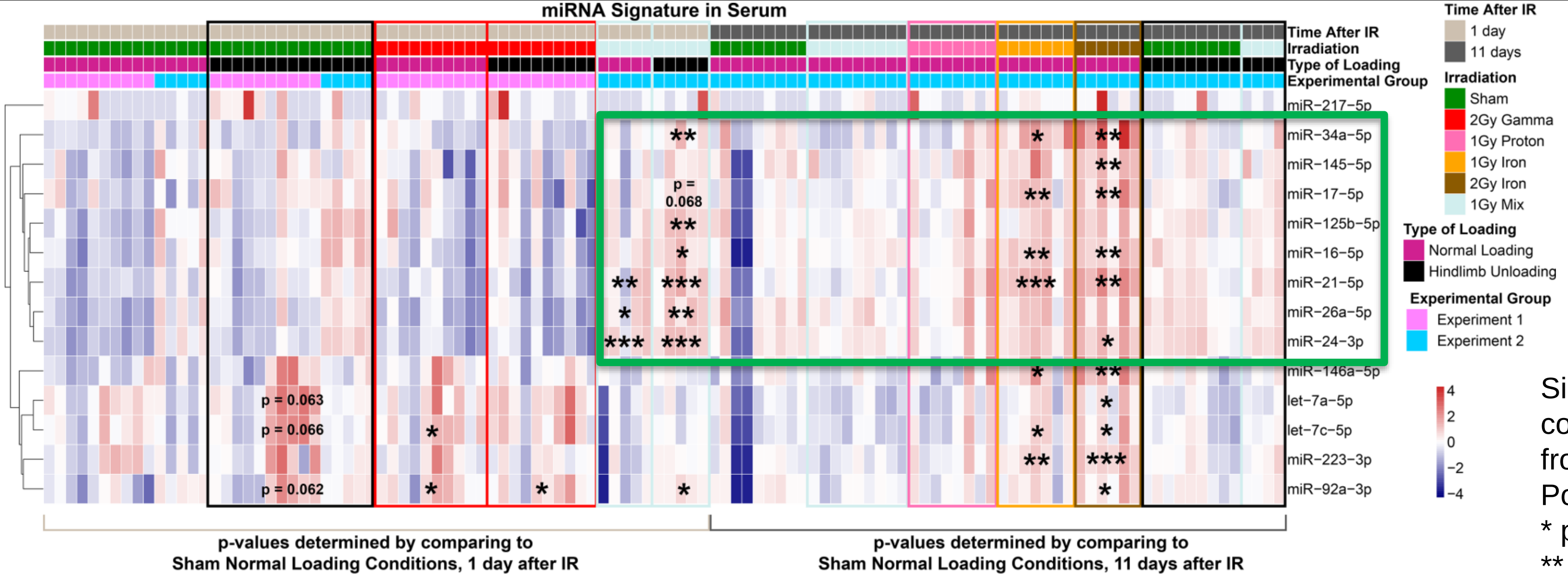


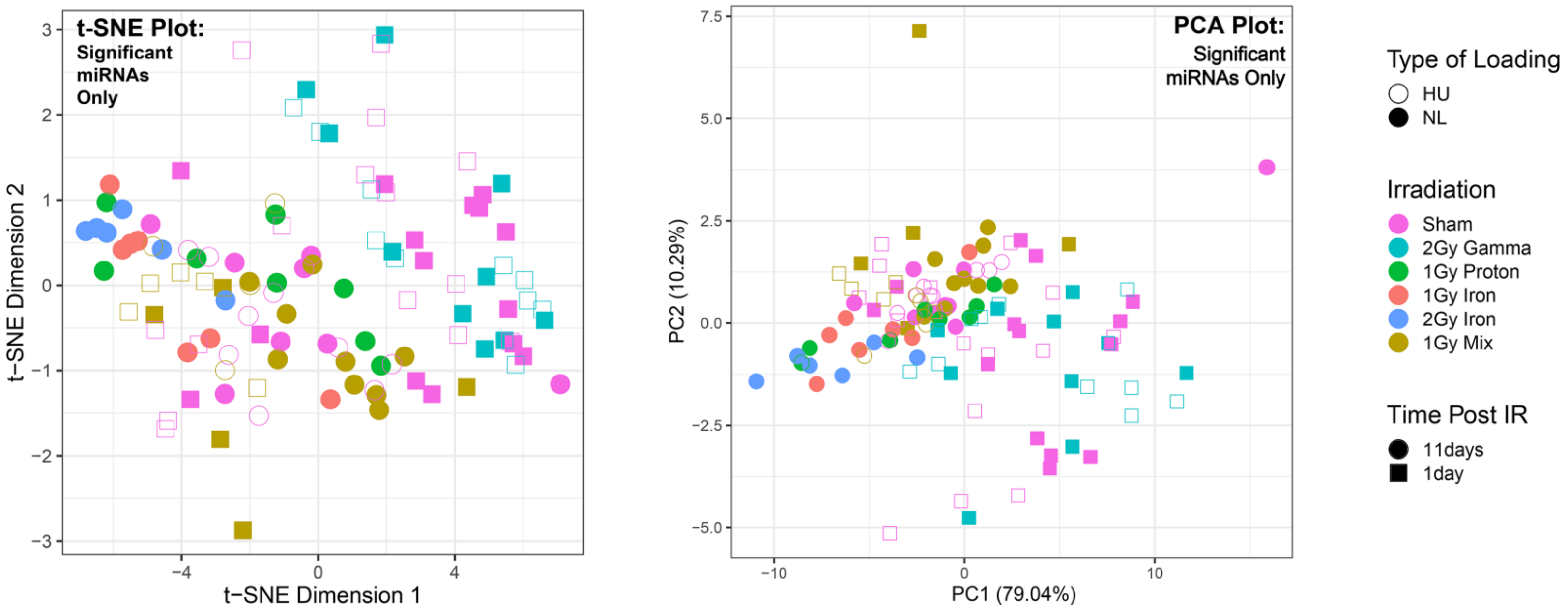
Every single blue point on the plots represents one copy of miRNA (see arrows).

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

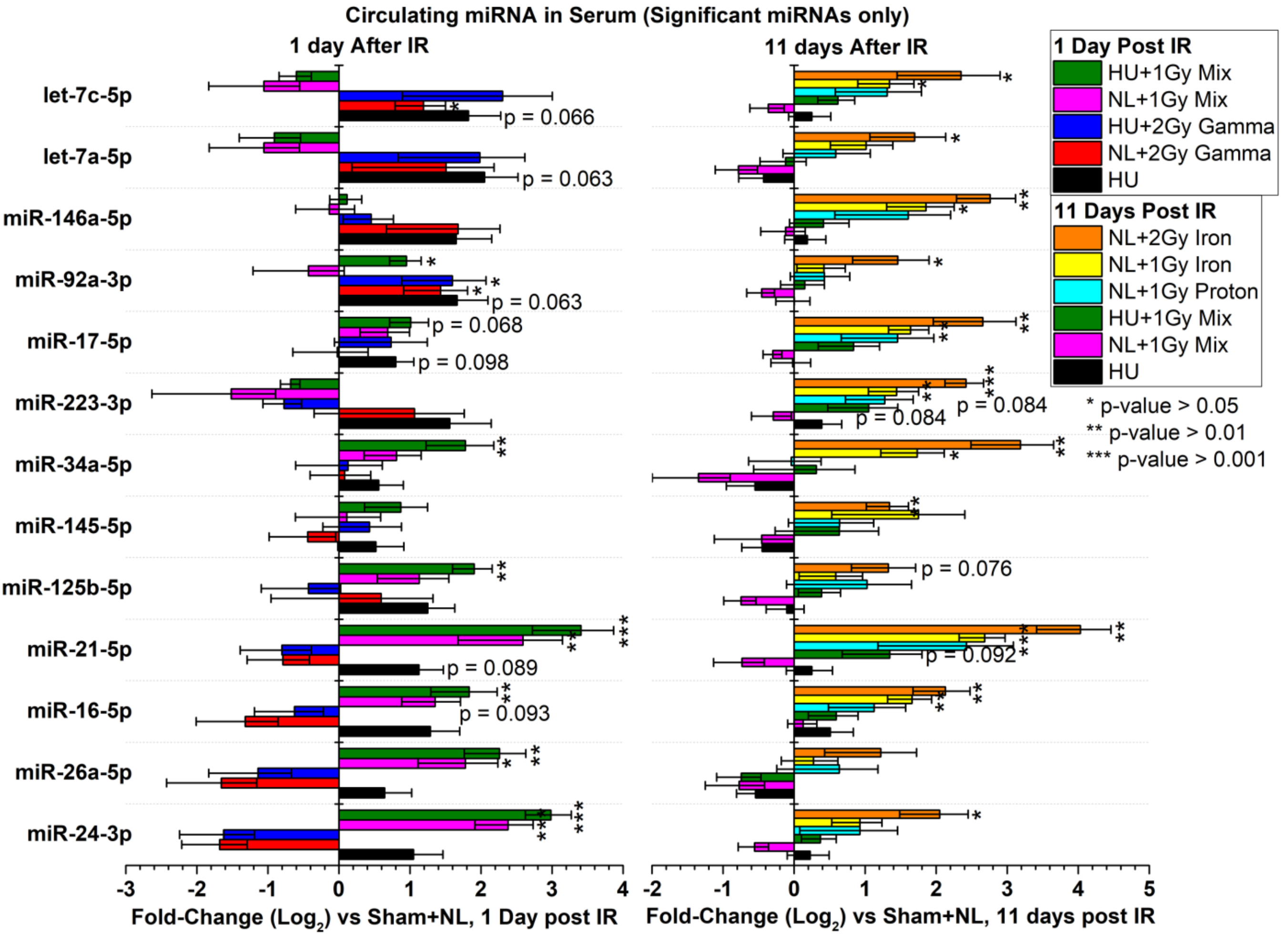
- HU for an initial three days followed by IR and continuation of HU for another 1 or 11 days
- Radiation exposure: Total body irradiation on conscious mice
  - 2Gy Gamma
  - 600 MeV/n ^{56}Fe (1 Gy and 2 Gy)
  - 150 MeV Proton (1Gy)
  - '1Gy Mix' (0.5Gy ^{56}Fe and 0.5Gy Proton)

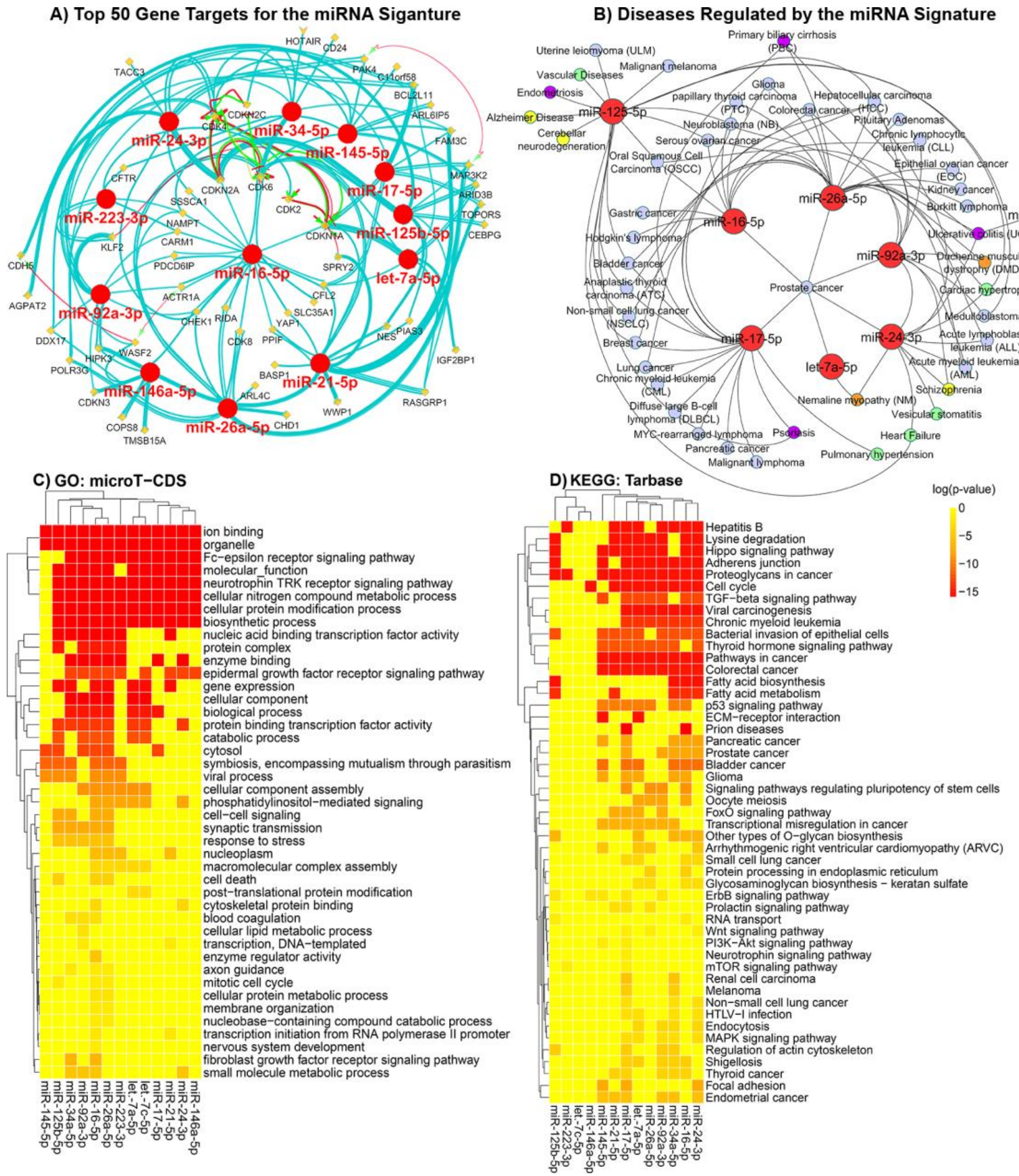


Significance compared to serum from Sham NL (Time Post IR)
* p-value < 0.05
** p-value < 0.01
*** p-value < 0.001



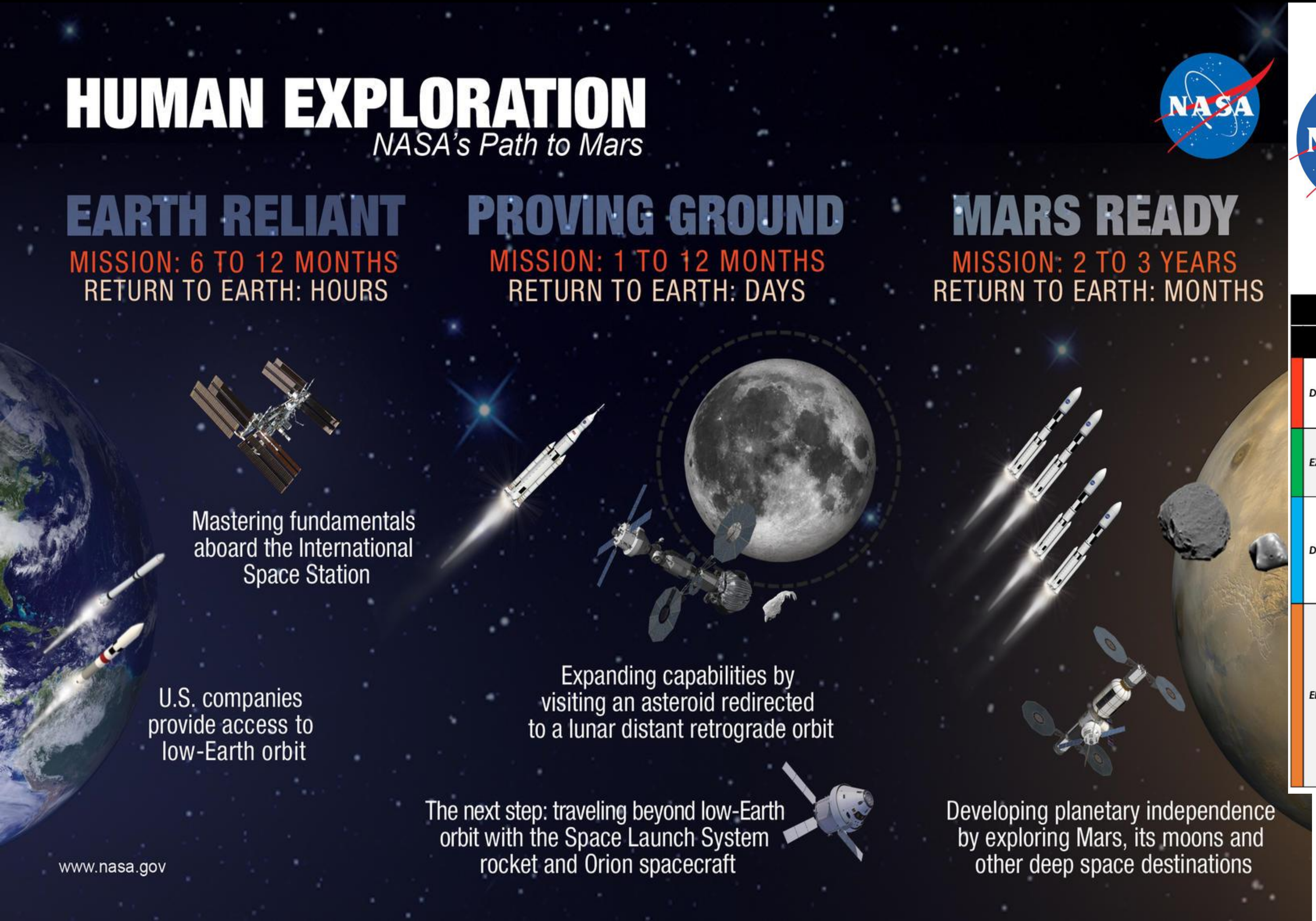
Predicted Targets for the Space Environment miRNA Signature

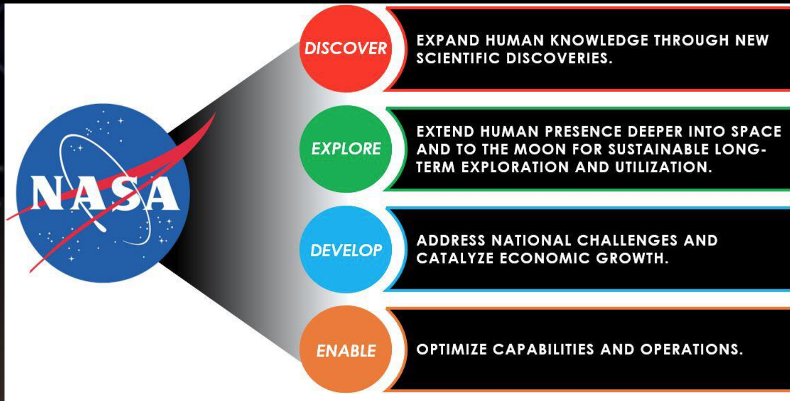




Confirmation exists in the miRNAs from the NASA Twin Study!!!

miRNA Research will Further Assist with NASA's Future Missions





NASA 2018 Strategic Plan Framework

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

Acknowledgments for miRNA Studies

SLPSRA

NASA


Sylvain Costes
Space Bio miRNAs

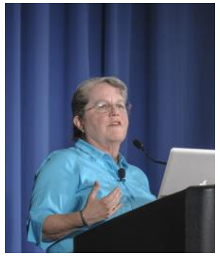

Egle Cekanaviciute
Quantifying miRNAs


Sherina Malkani
Quantifying miRNAs


Ann-Sofie Schreurs
Provided Archived Tissues


Margareth Cheng-Campbell
Quantifying miRNAs


Yasaman Shirazi
Provided Archived Tissues


Ruth Globus
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NASA

Ames Research Center

Space Biosciences
NASA AMES RESEARCH CENTER


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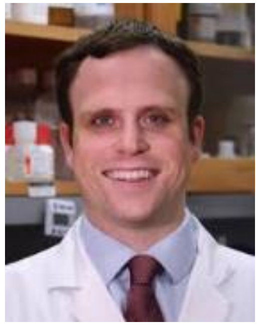
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