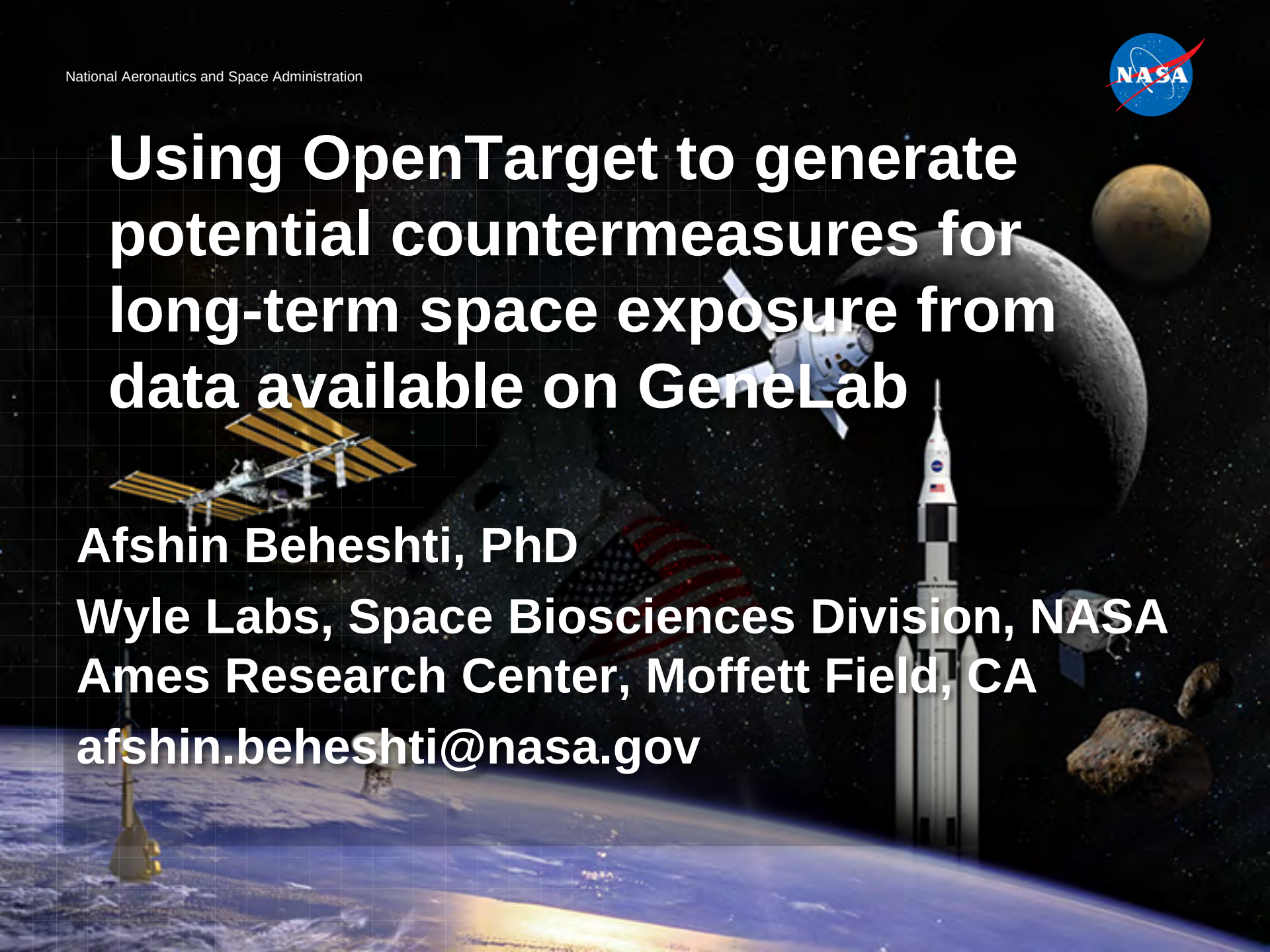
National Aeronautics and Space Administration



Using OpenTarget to generate potential countermeasures for long-term space exposure from data available on GeneLab

Afshin Beheshti, PhD

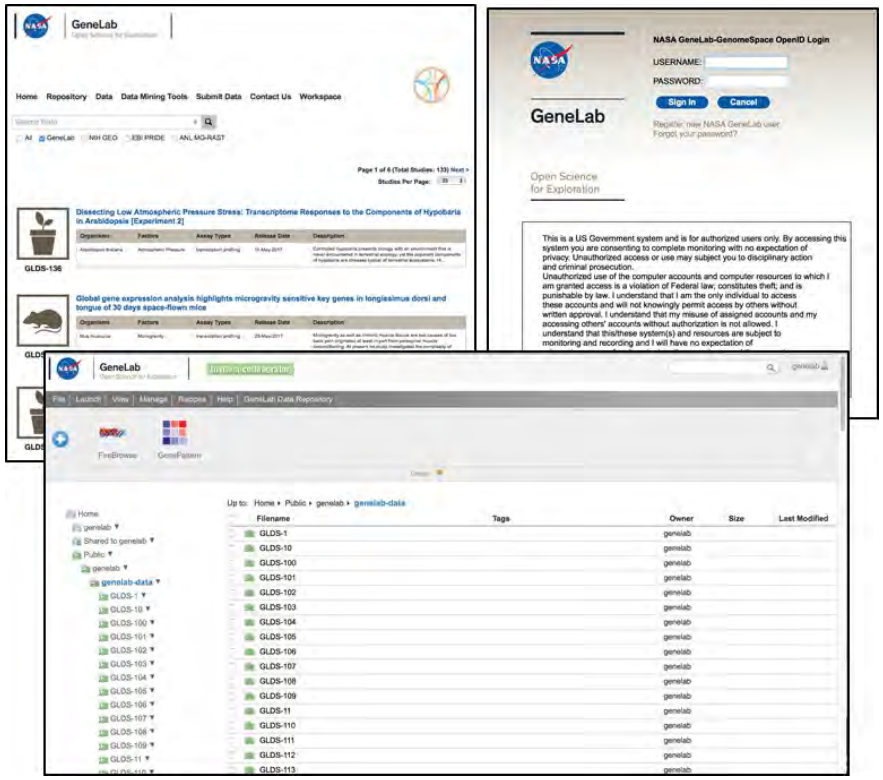
Wyle Labs, Space Biosciences Division, NASA Ames Research Center, Moffett Field, CA

afshin.beheshti@nasa.gov

GeneLab
Open Science for Exploration

What is GeneLab?

- Currently, GeneLab is a (1) data repository that hosts space biology datasets, (2) a collaborative workspace for users to share files and access data analysis tools, and (3) workspace to do metadata curation.



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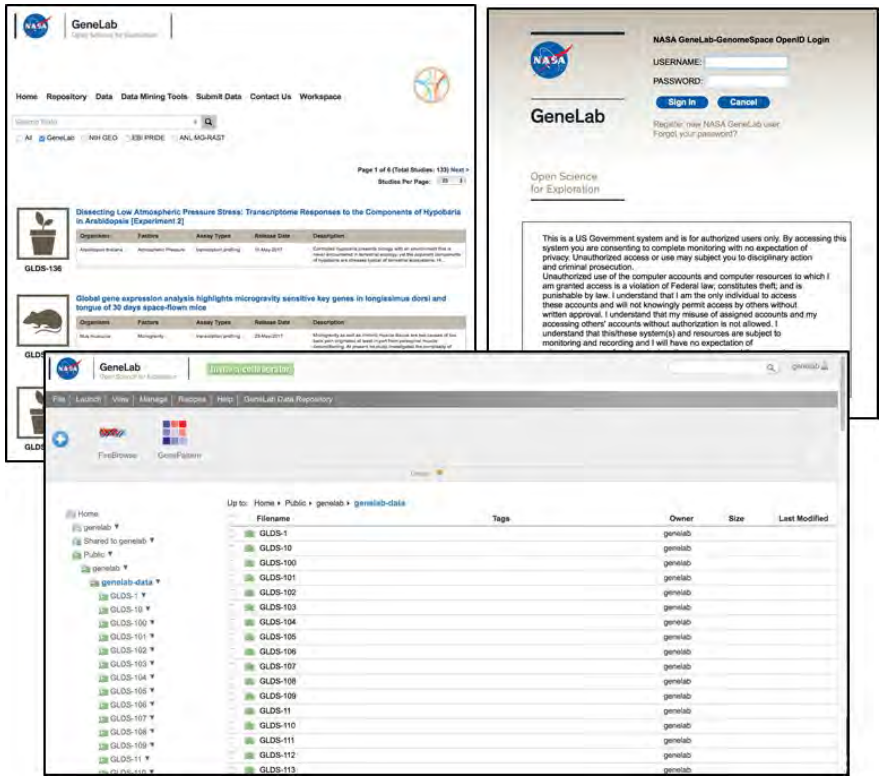

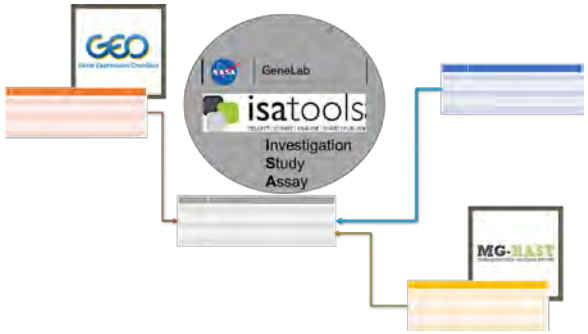

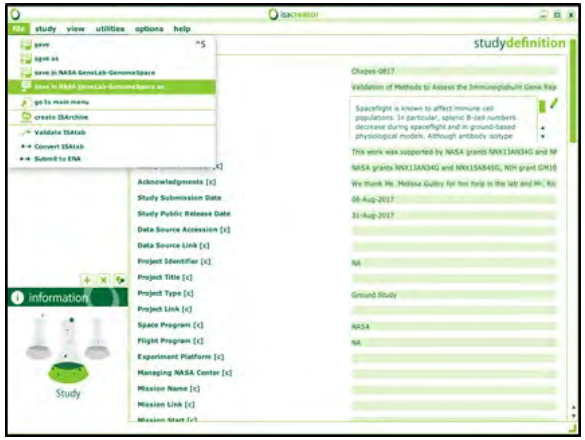

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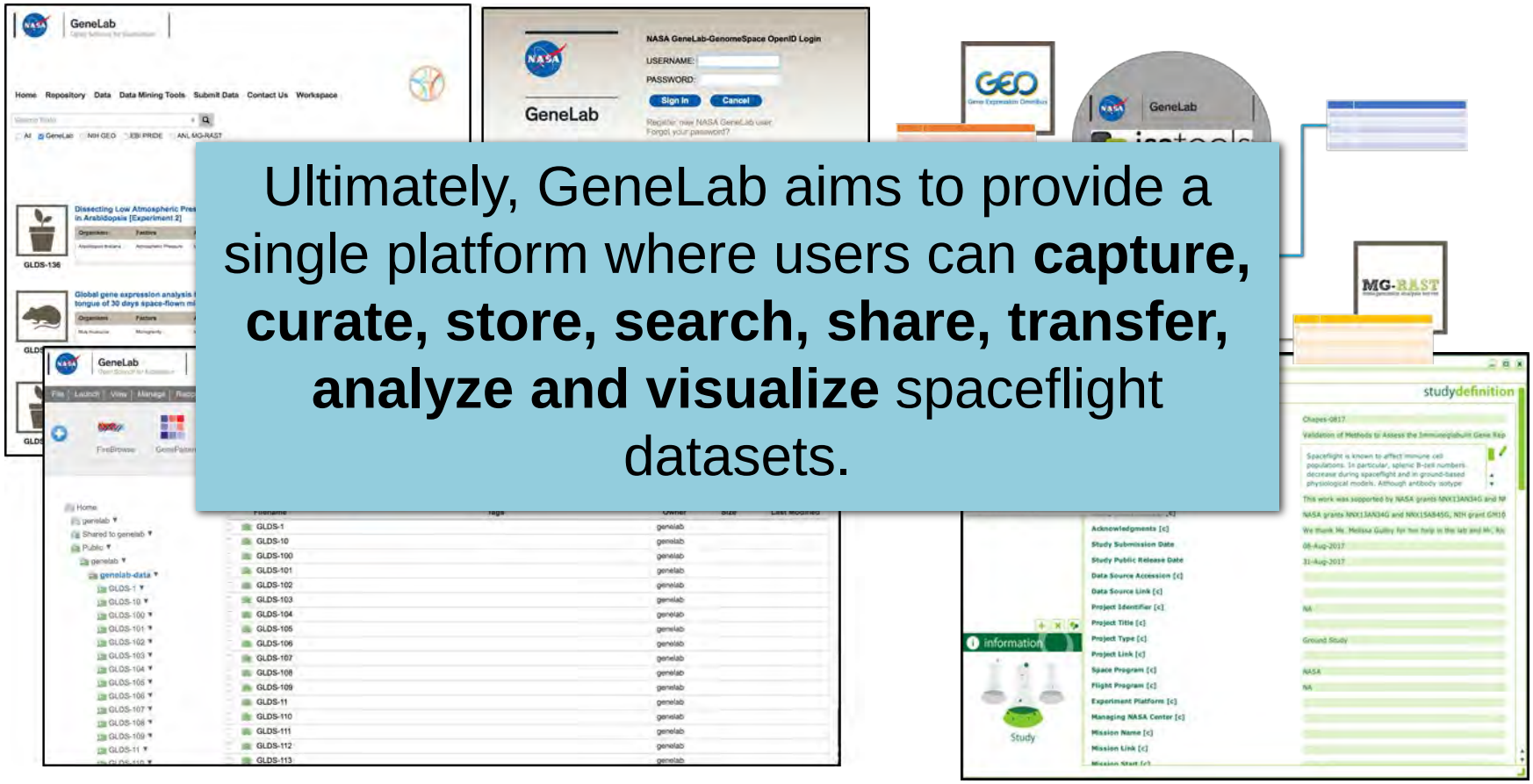
What is GeneLab?



Ultimately, GeneLab aims to provide a single platform where users can **capture, curate, store, search, share, transfer, analyze and visualize** spaceflight datasets.

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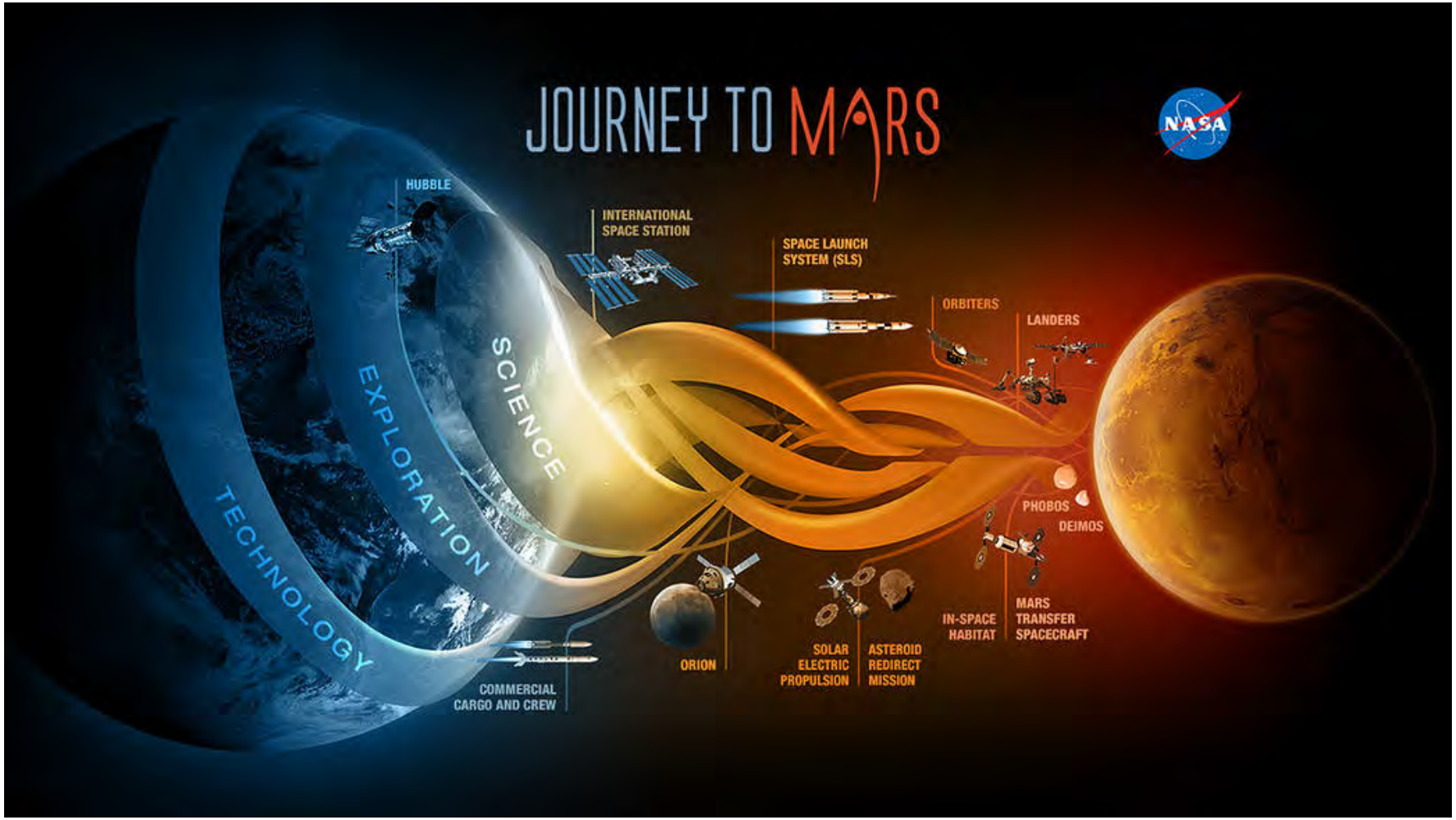
What is GeneLab?

Overall, the goal of GeneLab is to allow for better understanding of the impact of spaceflight on biology!



What Already Exists on GeneLab Database: 154 data sets

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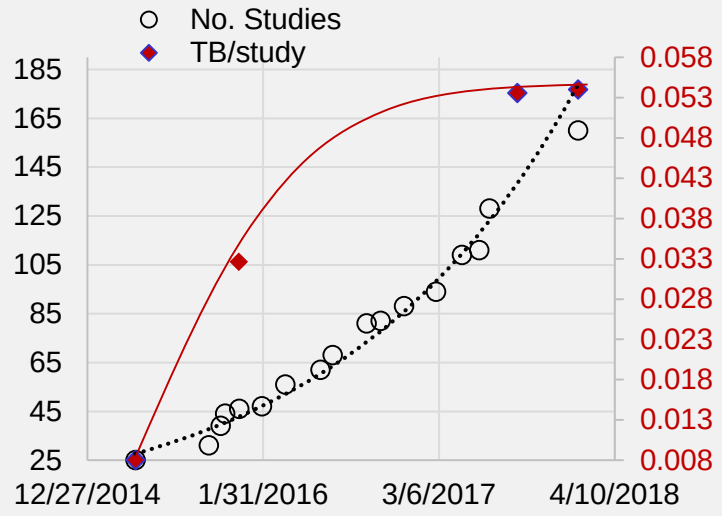
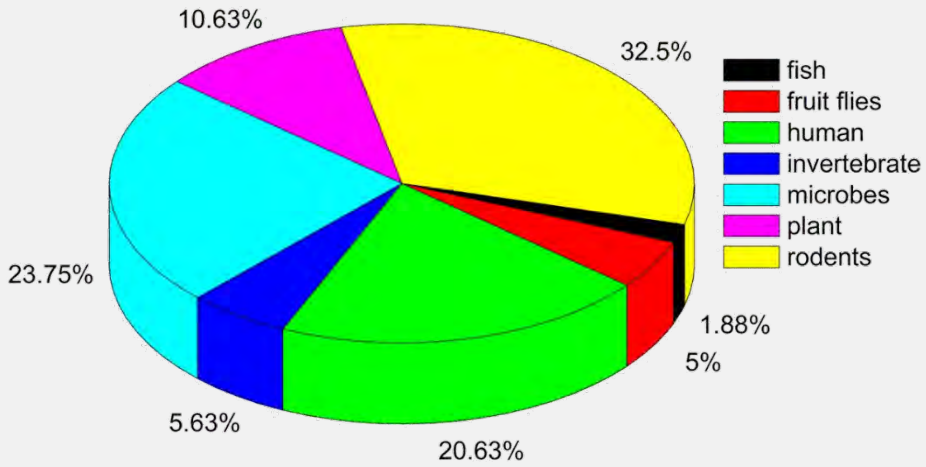
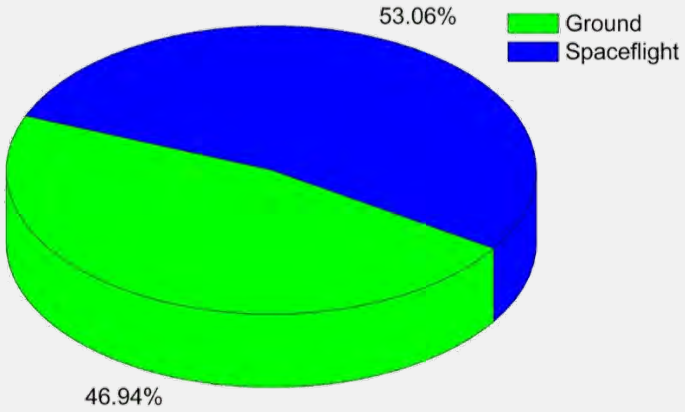


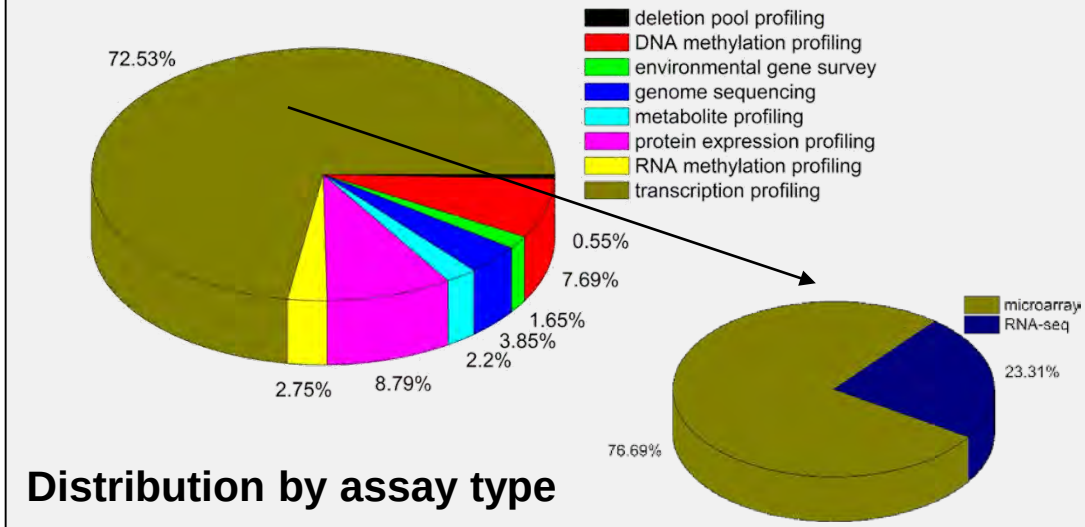
Data Growth Since 2014



Distribution by organism type



Majority is spaceflight samples



Distribution by assay type

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Overall Goal of GeneLab

- Overall goal is to allow for better understanding of the impact of spaceflight on biology using publicly available omics data
  - Generate **Hypothesis** to direct future experimental research
  - Determine acceptable health risks for long-term space missions
  - Develop potential countermeasures against
- A rich resource for both the scientific and non-scientific community to explore questions they have on space biology.
- A platform which can be used by both advanced and basic users to explore all omics data.

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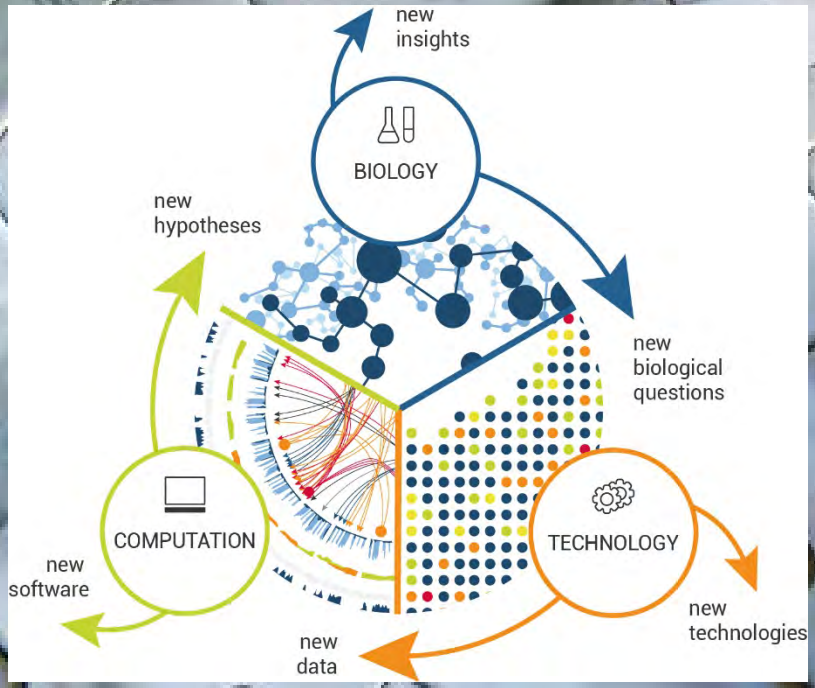
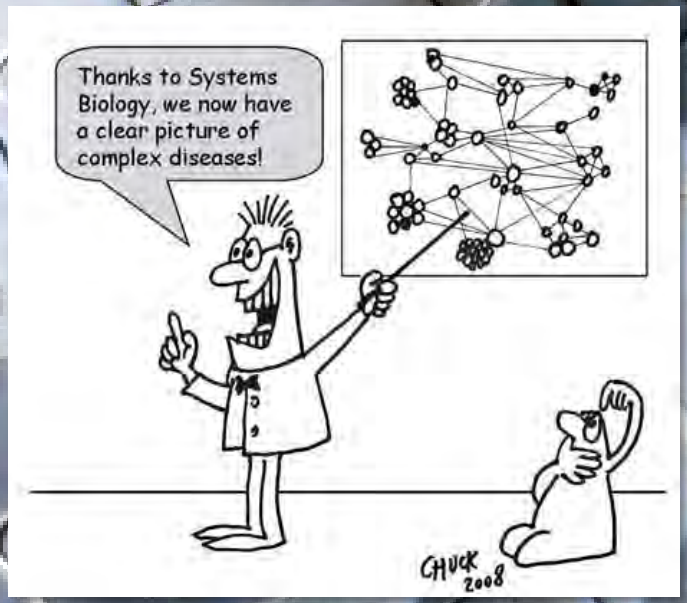
What is Systems Biology?

- 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."





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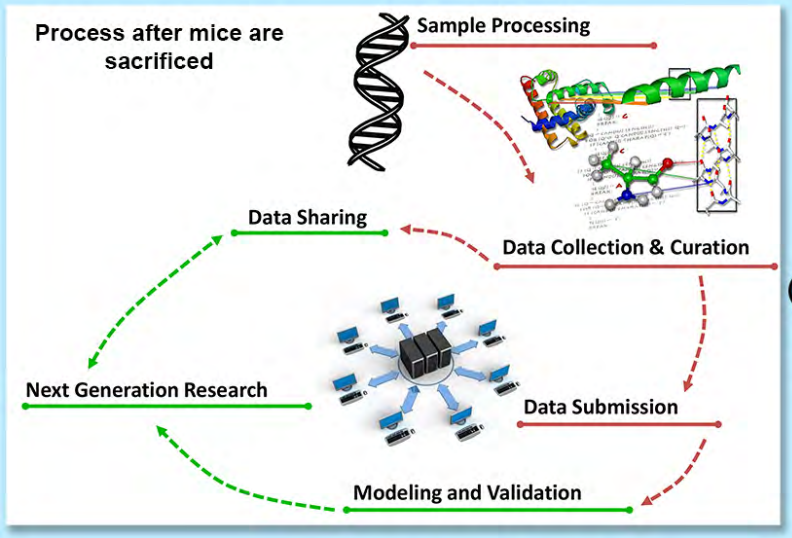
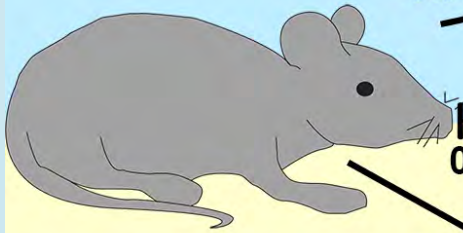
Hypothesis generation from GeneLab Data



Extensor Digitorum Longus Muscle
Soleus Muscle
Gastrocnemius Muscle
Quadriceps
Tibialis Anterior Muscle
Adrenal Glands
Kidney
Liver

Mice Sacrificed on ISS



Skin

0 10 20 30 40 50 60 70 80 90 100

Time in Space for Mice (days)

Mice flown on STS and Sacrificed after Re-entry

Liver
Skeletal Muscle
Mammary Gland
Thymus

Soleus Muscle
Extensor Digitorum Longus Muscle

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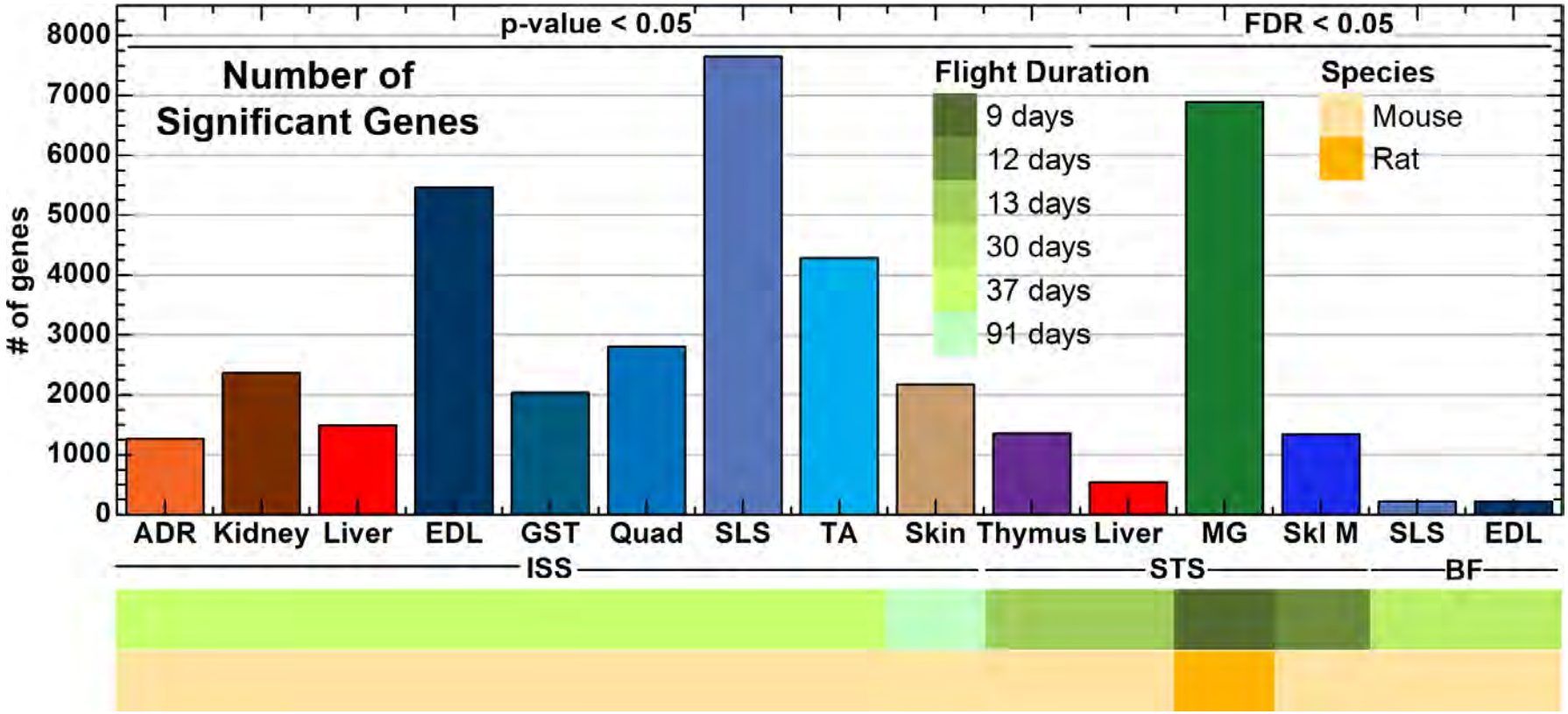
Number of Significant Genes from Multiple Datasets



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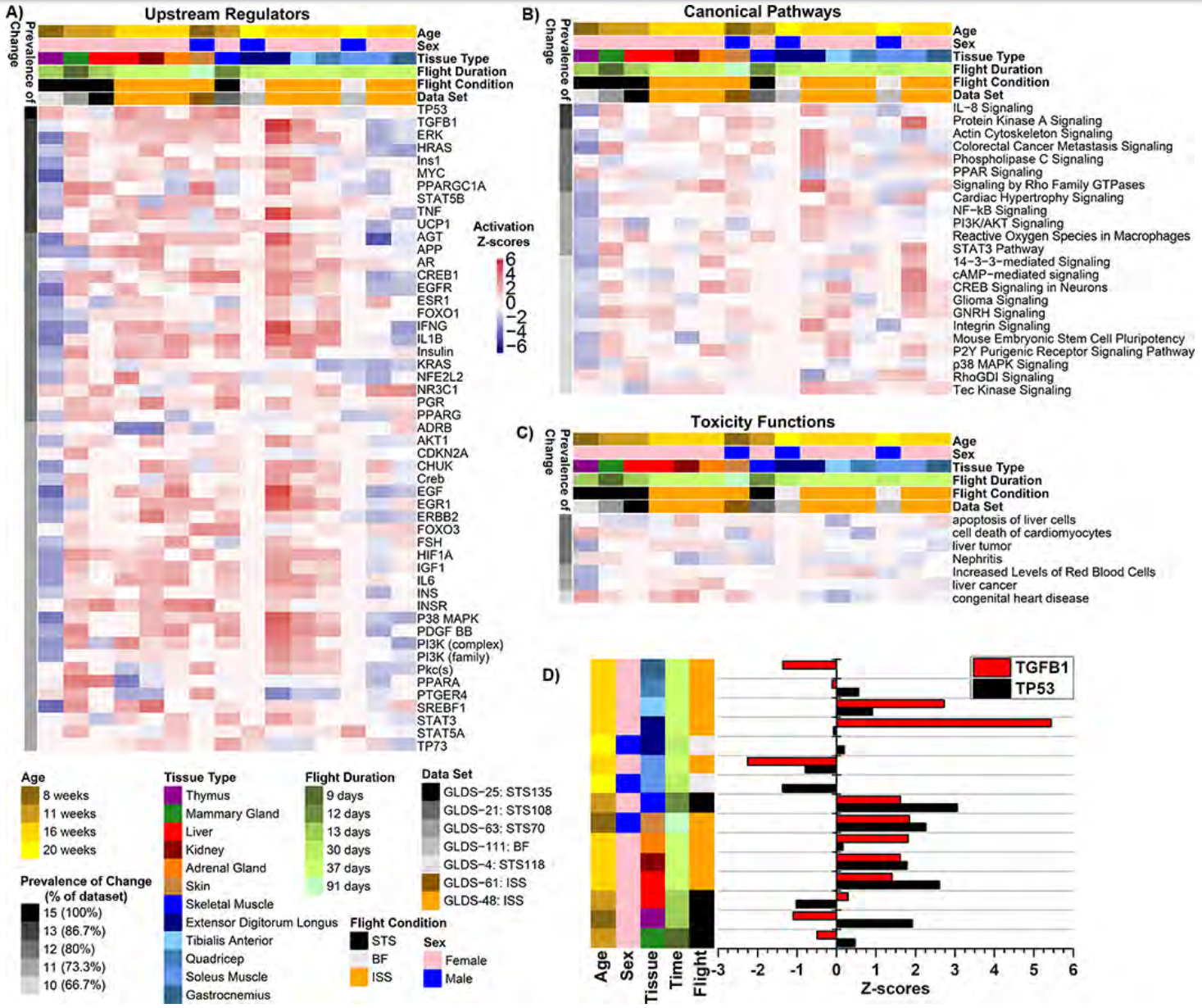
Predicted Master Regulators



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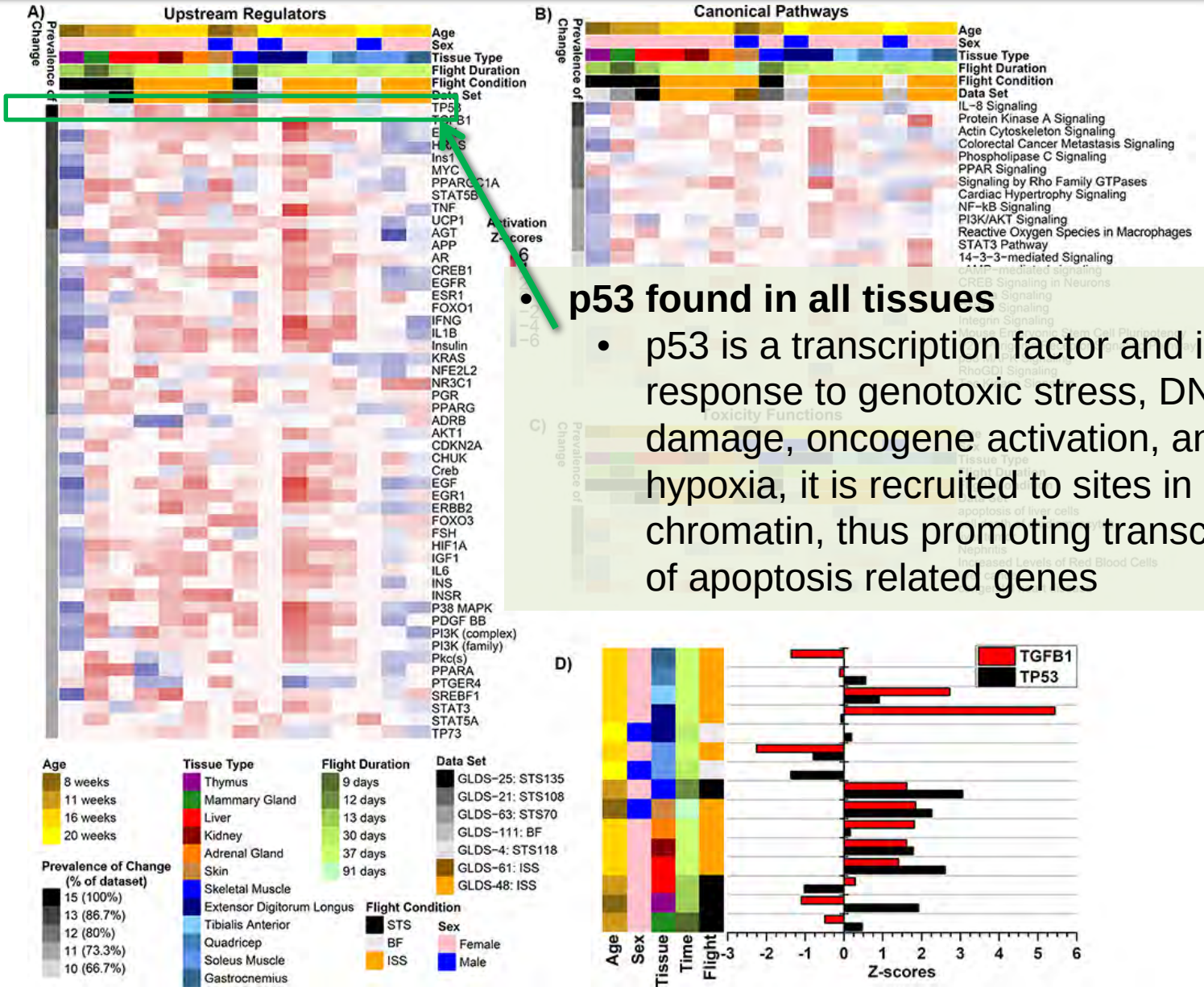
Predicted Master Regulators



- **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

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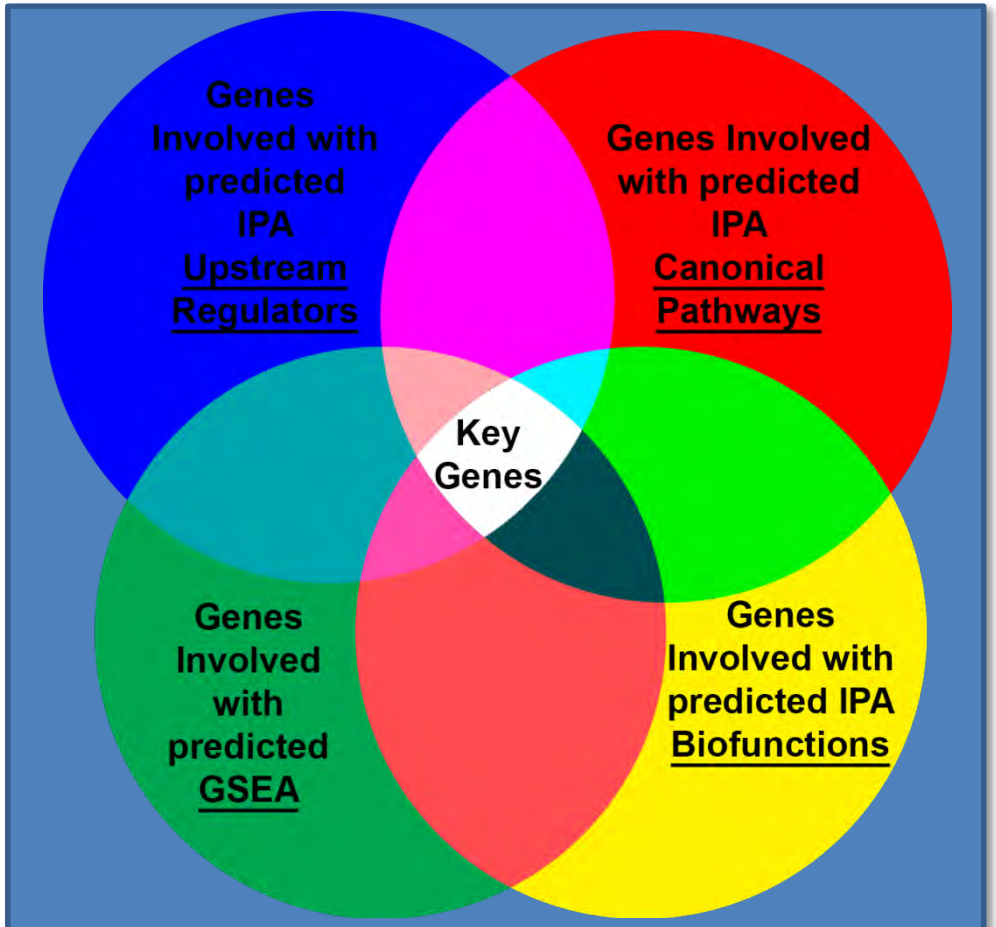
Determination of Key Genes/Drivers



Beheshti, et al. Cancer Research 2015
Beheshti, et al. Oncotarget 2015
Beheshti, et al. Cancer Informatics 2015
Beheshti, et al, Radiat Res. 2014 & J. Radiat Res. 2015.
Ravi, Beheshti, et al. Cancer Research 2016

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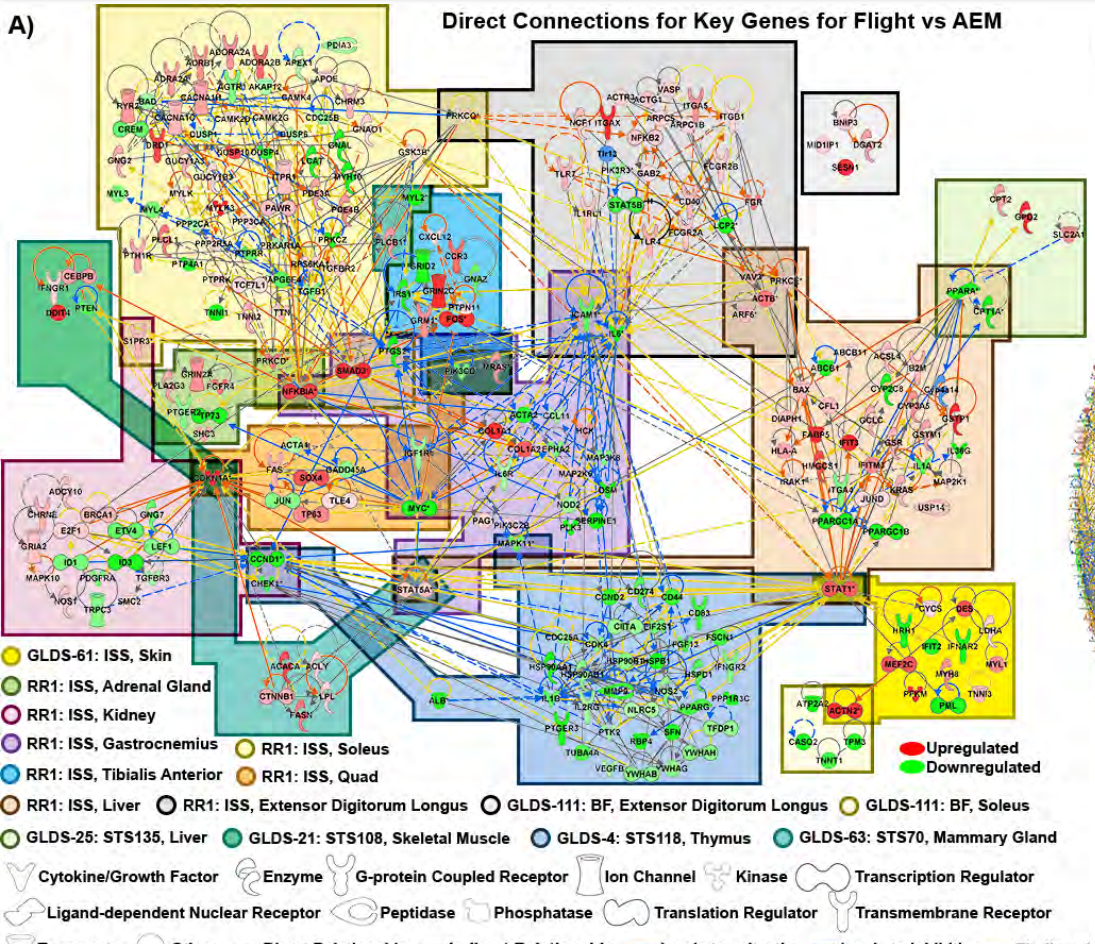
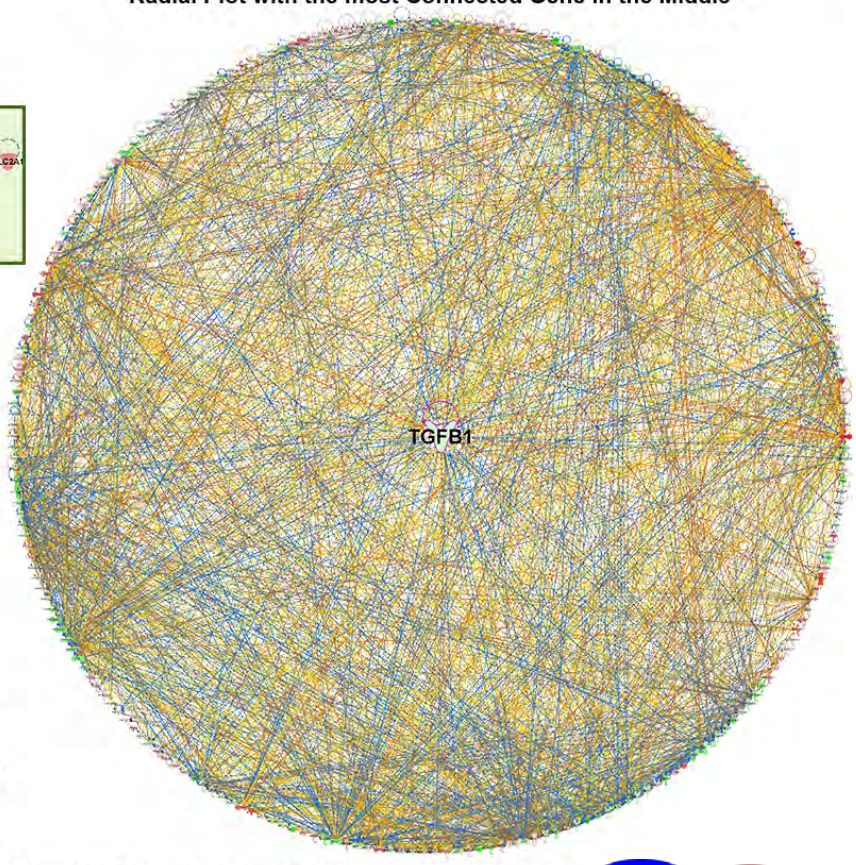
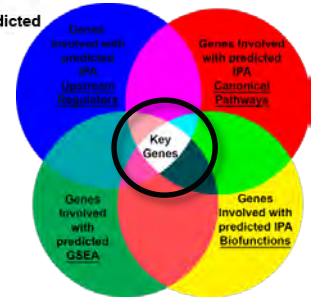
Key Genes and the Connections







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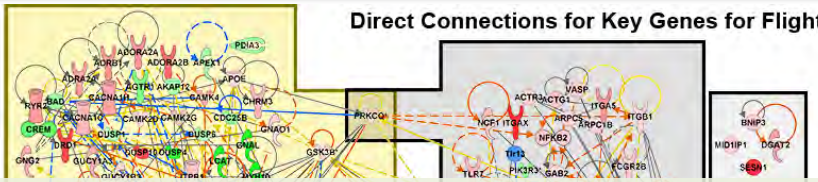
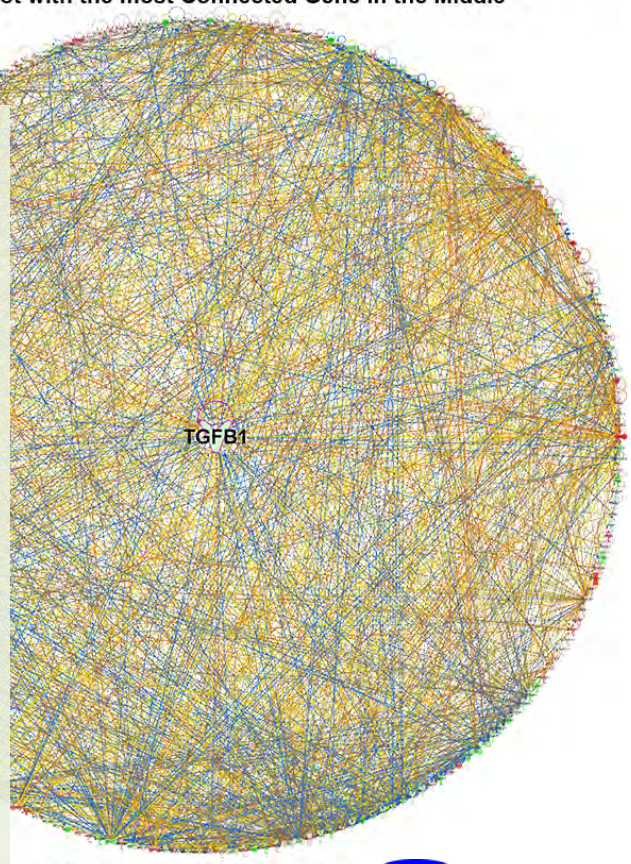
Key Genes and the Connections

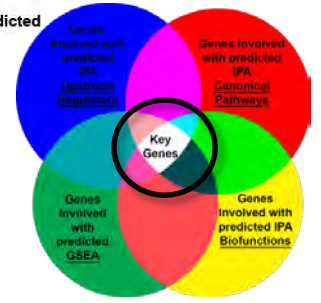
A)



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



- **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



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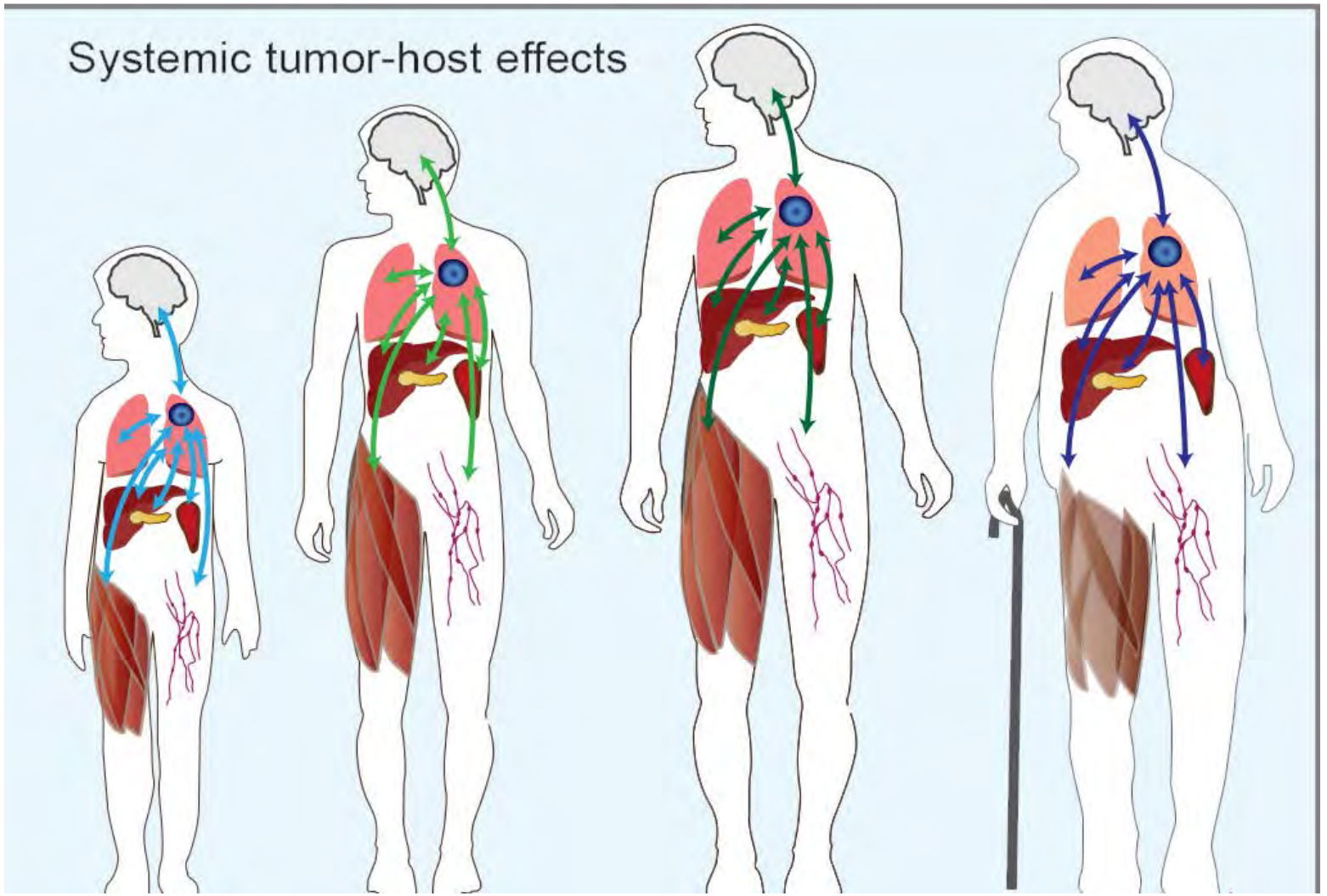
Generating a Hypothesis from GeneLab Analysis



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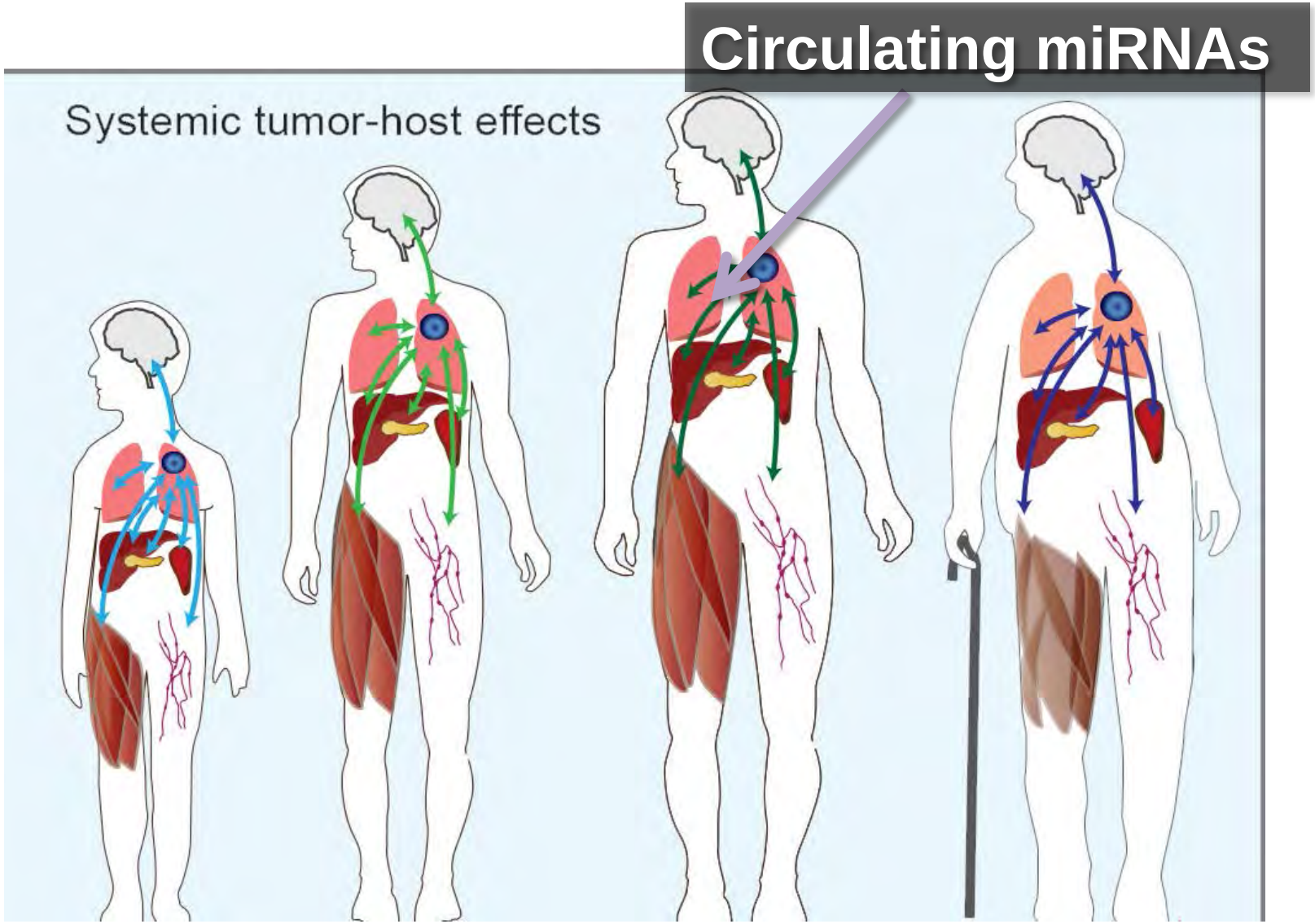

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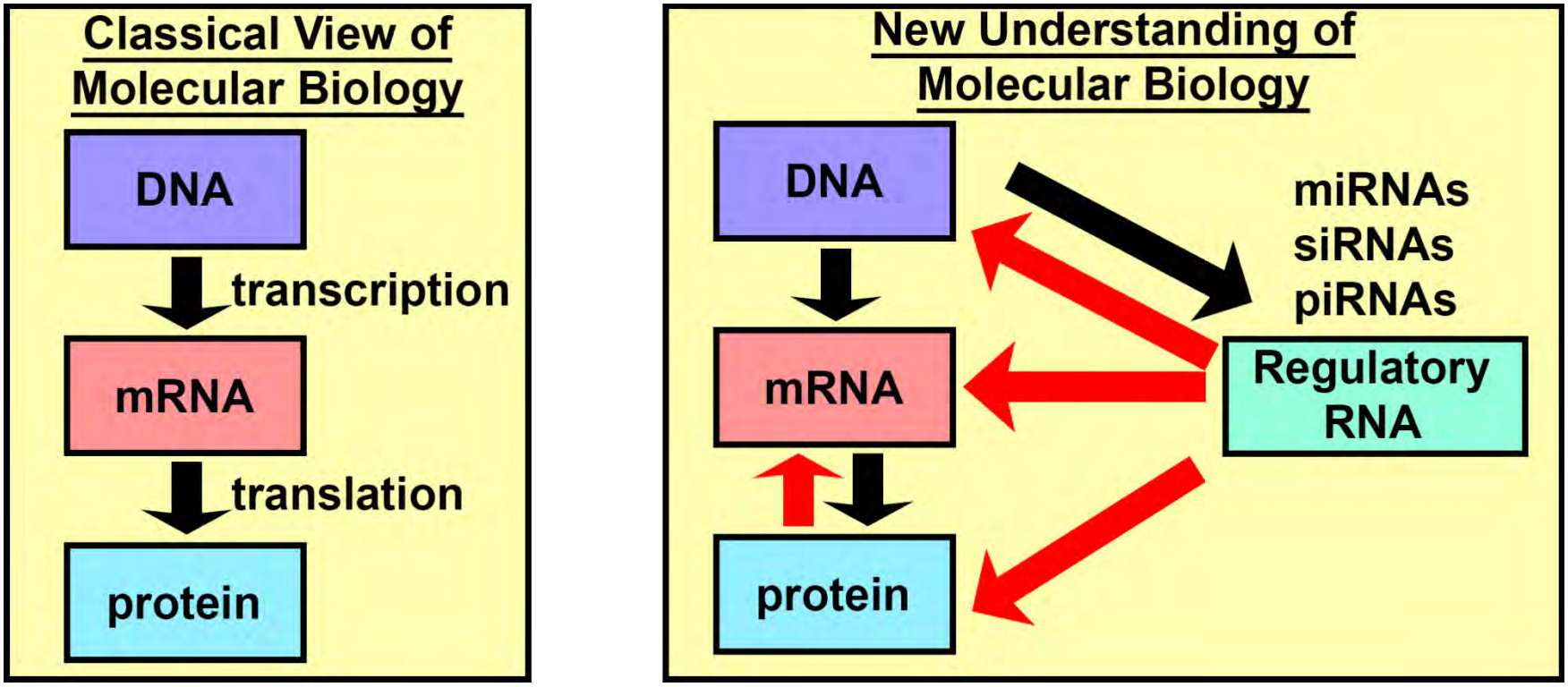
Revised View of Molecular Biology



- A single miRNA has been estimated to regulate up to 500 mRNAs
- miRNAs are single-stranded RNA sequences, of about 22 nucleotides in length, processed from longer transcripts.
- miRNAs are important regulators that repress the translation of mRNA transcripts

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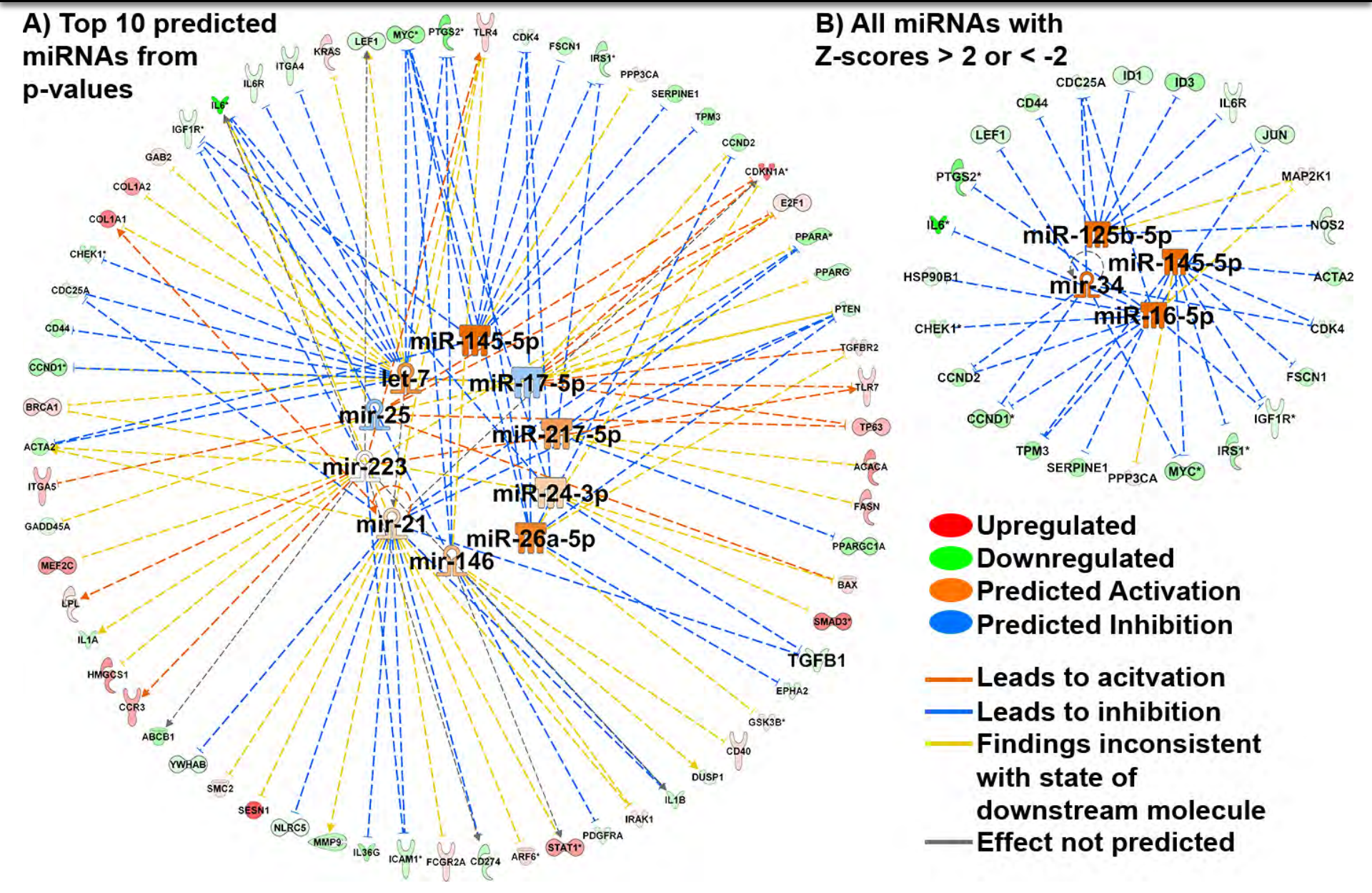
Predicted miRNAs Involved with Microgravity Effects



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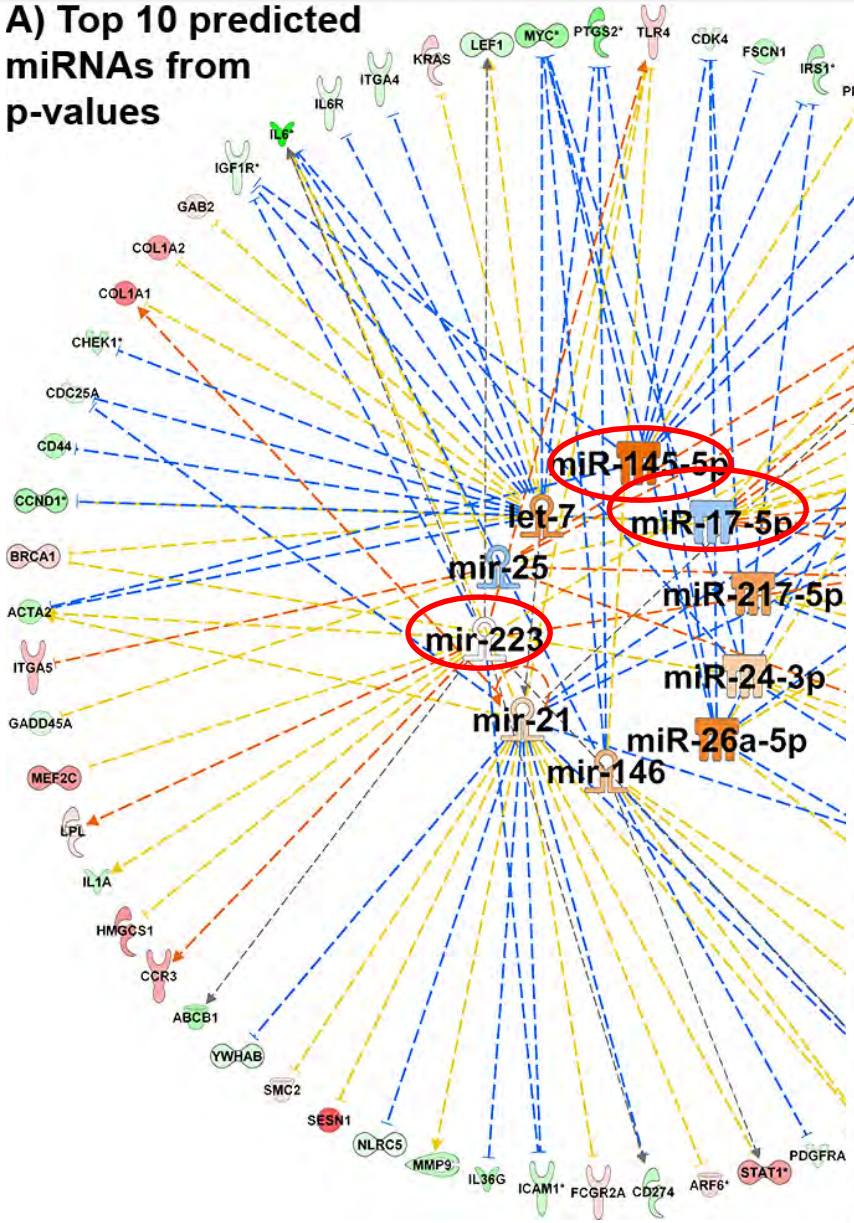
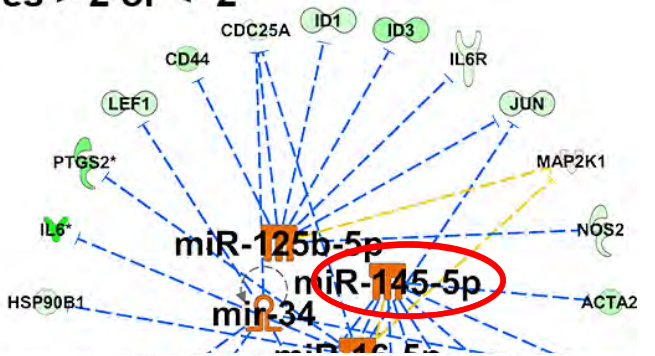
Predicted miRNAs Involved with Microgravity Effects

A) Top 10 predicted miRNAs from p-values



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



Experimental & Molecular Medicine (2017) 49, e348; doi:10.1038/emm.2017.80

www.nature.com/emm

OPEN

ORIGINAL ARTICLE

Upregulation of miR-223 in the rat liver inhibits proliferation of hepatocytes under simulated microgravity

Yongjie Chen[1,2,4], Ji Xu[2,3,4], Chao Yang[2], Hongyu Zhang[2], Feng Wu[2], Jian Chen[2], Kai Li[2], Hailong Wang[2], Yu Li[1,3], Yinghui Li[2,3] and Zhongquan Dai[2]

Long-term spaceflight affects numerous organ systems in the body, including metabolic dysfunction. Recently, ample evidence has demonstrated that the liver is a vulnerable organ during spaceflight. However, the changes in hepatocyte proliferation and cell cycle control under microgravity remain largely unexplored. In the present study, we first confirmed that the serum levels of aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase, biochemical markers of liver function, were altered in rats under tail suspension (TS) conditions to simulate microgravity, as shown in previous reports. Next, we demonstrated that the cell proliferation activity, determined by Ki67, PCNA and PH3, was significantly decreased at the different TS time points (TS for 14, 28 and 42 days) compared with that in the control group. Consistently, the positive cell cycle regulators *Ccna2*, *Ccnd1*, *Cdk1*, *Cdk2* and cyclin D3 were also significantly decreased in the TS groups as shown by quantitative real-time PCR and western blotting analysis. Subsequent analysis revealed that the aberrant hepatocyte proliferation inhibition under simulated microgravity was associated with the upregulation of miR-223 in the liver. We further found that miR-223 inhibited the proliferation of Hepa1-6 cells and identified CDK2 and CUL1 as its direct targets. In addition, the decreased expression of CDK2 and CUL1 was negatively correlated with the level of p27 *in vitro* and *in vivo*, which may have been responsible for retarding hepatocyte proliferation. Collectively, these data indicate that upregulation of miR-223 was associated with the inhibition of liver cell growth and reveal the role of miR-223 in rat hepatocyte proliferation disorders and the pathophysiological process under simulated microgravity.

Experimental & Molecular Medicine (2017) **49**, e348; doi:10.1038/emm.2017.80; published online 23 June 2017

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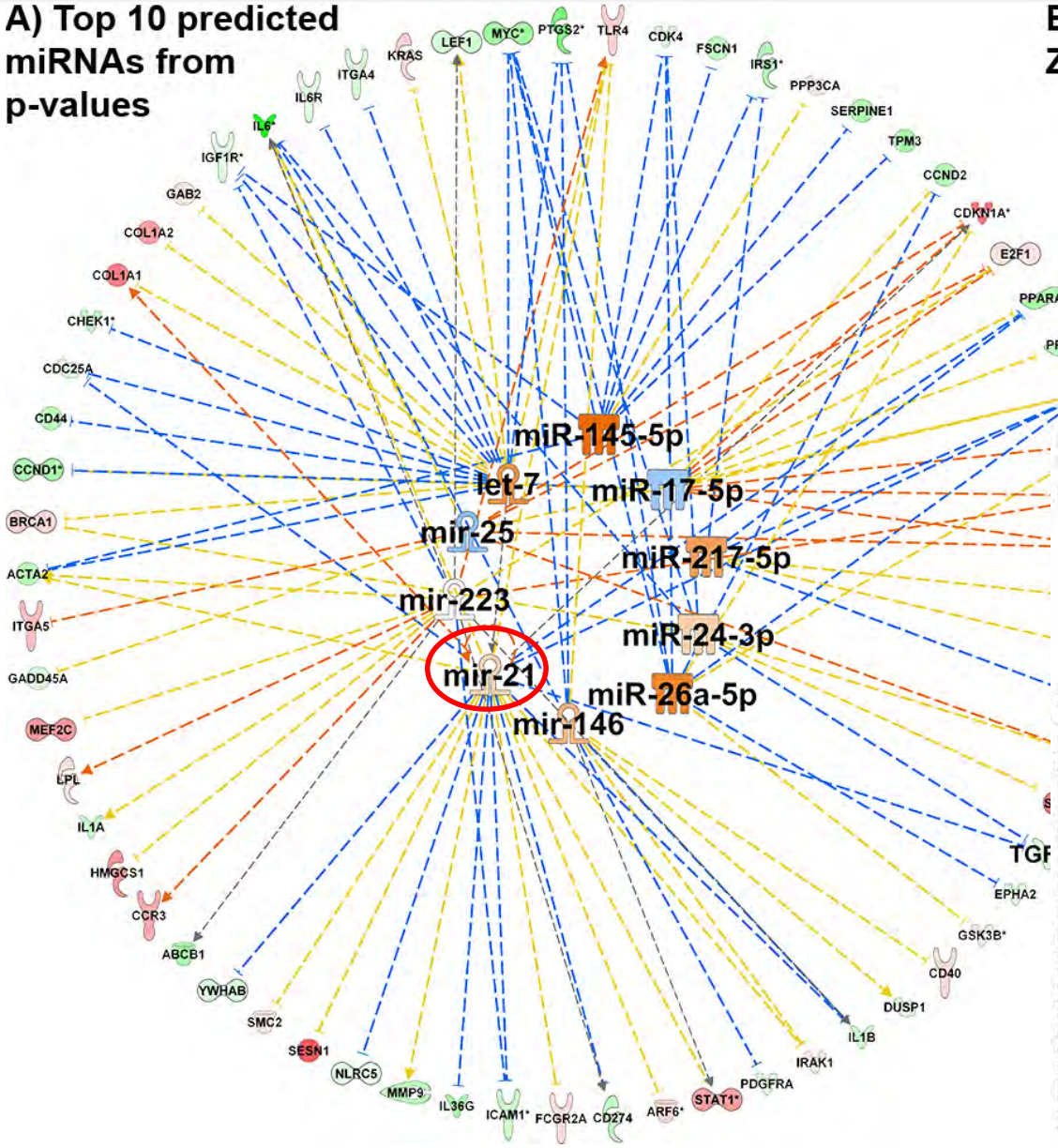
Predicted miRNAs Involved with Microgravity Effects

NASA

A) Top 10 predicted miRNAs from p-values



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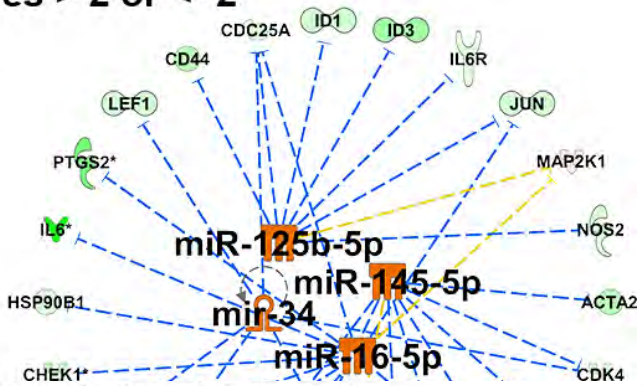

The FASEB Journal • Research Communication

Spaceflight alters expression of microRNA during T-cell activation

Millie Hughes-Fulford,[*,†,‡,1] Tammy T. Chang,[§] Emily M. Martinez,[†] and Chai-Fei Li[†]

[*]Hughes-Fulford Laboratory, Department of Medicine, Metabolism Division, San Francisco Department of Veterans Affairs Medical Center, San Francisco, California, USA; and [†]Northern California Institute for Research and Education, [‡]Department of Medicine, and [§]Department of Surgery, University of California, San Francisco, California, USA

ABSTRACT **Altered immune function has been demonstrated in astronauts during spaceflights dating back to Apollo and Skylab; this could be a major barrier to long-term space exploration. We tested the hypothesis that spaceflight causes changes in microRNA (miRNA) expression. Human leukocytes were stimulated with mitogens on board the International Space Station using an onboard normal gravity control. Bioinformatics showed that miR-21 was significantly up-regulated 2-fold during early T-cell activation in normal gravity, and gene expression was suppressed under microgravity. This was confirmed using quantitative real-time PCR ($n = 4$). This is the first report that spaceflight regulates miRNA expression. Global microarray analysis showed significant ($P < 0.05$) suppression of 85 genes under microgravity conditions compared to normal gravity samples. *EGR3*, *FASLG*, *BTG2*, *SPRY2*, and *TAGAP* are biologically confirmed targets and are co-up-regulated with miR-21. These genes share common promoter regions with pre-mir-21; as the miR-21 matures and accumulates, it most likely will inhibit translation of its target genes and limit the immune response. These data suggest that gravity regulates T-cell activation not only by transcription promotion but also by blocking translation via noncoding RNA mechanisms. Moreover, this study suggests that T-cell activation itself may induce a sequence of gene expressions that is self-limited by miR-21.—Hughes-Fulford, M., Chang, T. T., Martinez, E. M., Li, C.-F. Spaceflight alters expression of microRNA during T-cell activation. *FASEB J.* 29, 4893–4900 (2015). www.fasebj.org**

contracted *Pseudomonas aeruginosa* and experienced intense chills and fever (1). *P. aeruginosa* is an opportunistic pathogen that rarely causes disease unless the person is immunosuppressed. As a result, the U.S. National Aeronautics and Space Administration (NASA) implemented a preflight quarantine program that subsequently reduced the number of reported infections to a single Apollo astronaut (1). To this day, the preflight quarantine program is still actively used in both the U.S. and Russian programs. Even with the precautions, astronauts working on Skylab (2), Shuttle (3, 4), International Space Station (ISS) (3), and Soyuz (5) showed changes in immune function and depressed lymphocyte activation compared to levels before spaceflight. Experiments from Skylab and Shuttle have confirmed that T cells have a suppressed immune response (*in vivo* and *in vitro*) with lower T-cell proliferation/activation, lower IL-2 synthesis and severely reduced IL-2-Rα expression (RNA and protein) (6–9). More recently, our ISS experiments proved that microgravity of spaceflight was a major cause of decrease of T-cell activation and altered gene expression in microgravity compared to onboard normal gravity controls (10). Immunosuppression during spaceflight may increase the risk of opportunistic infections. Shuttle astronauts on short duration (11 d) spaceflights had significant increases in early viral gene transcription of the Epstein-Barr virus compared to healthy controls, while astronauts on board the ISS for long-duration spaceflight (180 d) had latent and lytic viral gene expression that resembled activation patterns observed during infectious mononucleosis (3, 11).

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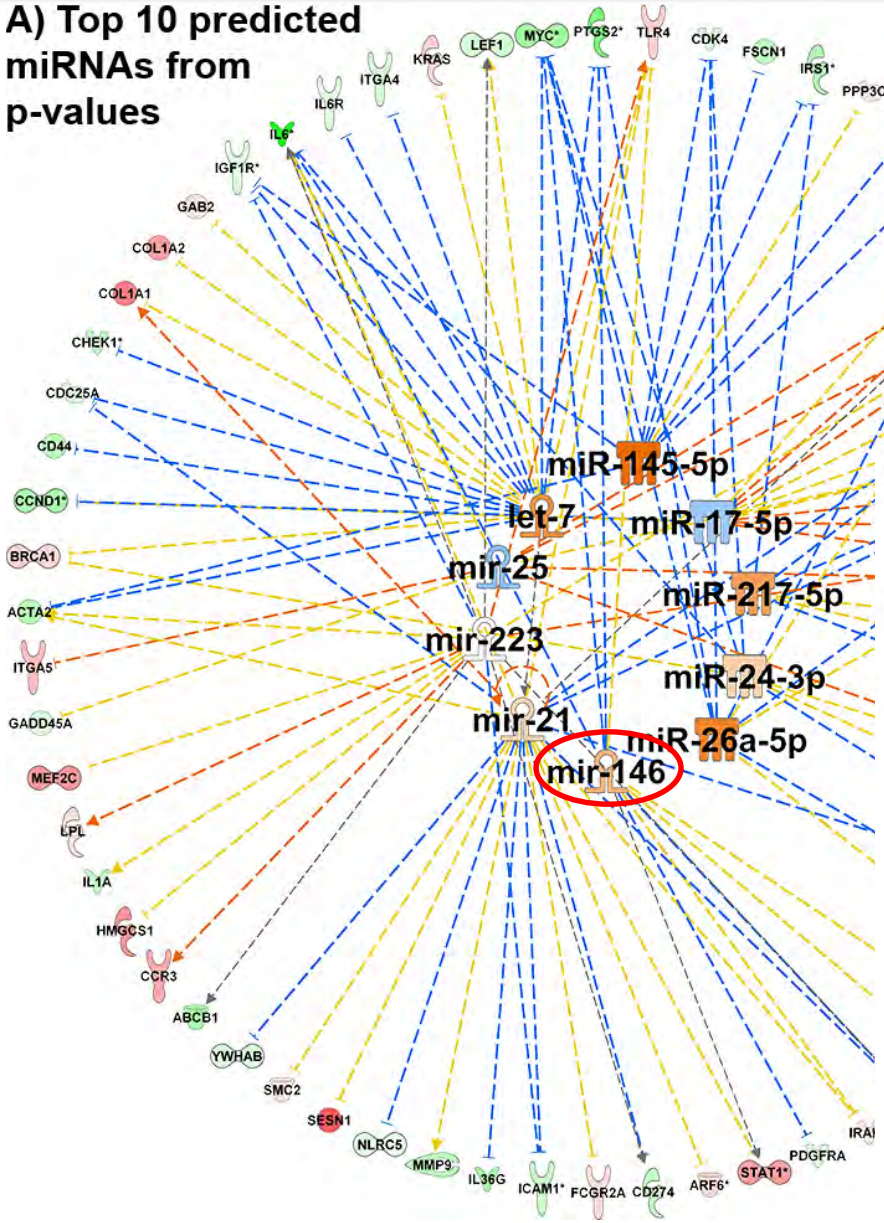
Predicted miRNAs Involved with Microgravity Effects

NASA

A) Top 10 predicted miRNAs from p-values



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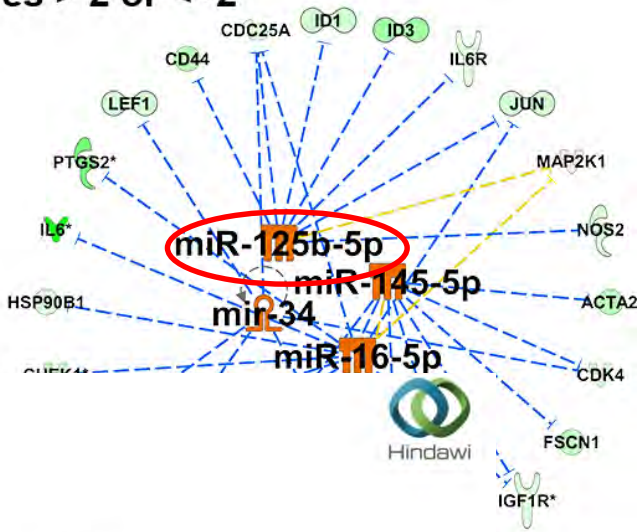

Hindawi Publishing Corporation
BioMed Research International
Volume 2014, Article ID 296747, 16 pages
http://dx.doi.org/10.1155/2014/296747

Hindawi

Research Article

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

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

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

Academic Editor: Mariano Bizzarri

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.

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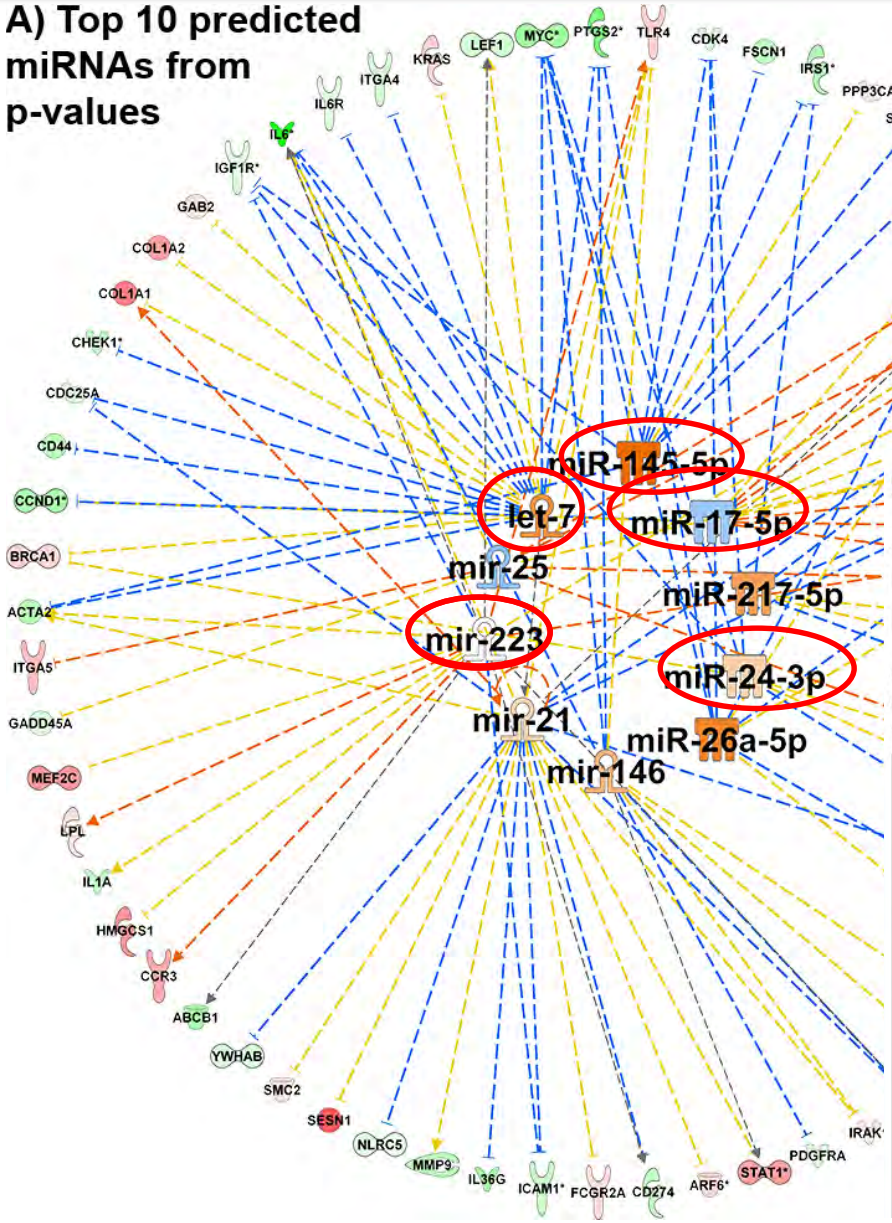
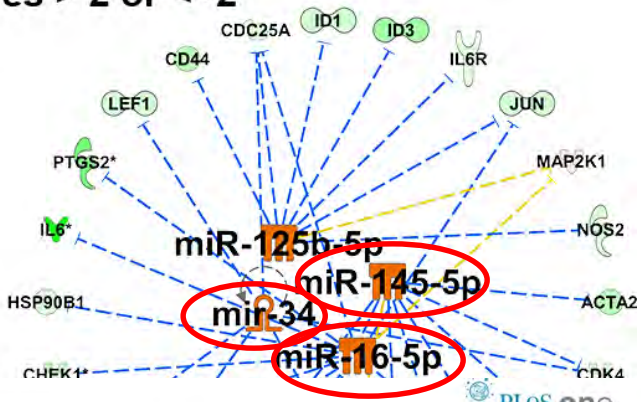
Predicted miRNAs Involved with Microgravity Effects

NASA

A) Top 10 predicted miRNAs from p-values



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



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PLoS one

Analysis of miRNA and mRNA Expression Profiles Highlights Alterations in Ionizing Radiation Response of Human Lymphocytes under Modeled Microgravity

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Abstract

Background: Ionizing radiation (IR) can be extremely harmful for human cells since an improper DNA-damage response (DDR) to IR can contribute to carcinogenesis initiation. Perturbations in DDR pathway can originate from alteration in the functionality of the microRNA-mediated gene regulation, being microRNAs (miRNAs) small noncoding RNA that act as post-transcriptional regulators of gene expression. In this study we gained insight into the role of miRNAs in the regulation of DDR to IR under microgravity, a condition of weightlessness experienced by astronauts during space missions, which could have a synergistic action on cells, increasing the risk of radiation exposure.

Methodology/Principal Findings: We analyzed miRNA expression profile of human peripheral blood lymphocytes (PBL) incubated for 4 and 24 h in normal gravity (1 g) and in modeled microgravity (MMG) during the repair time after irradiation with 0.2 and 2Gy of γ-rays. Our results show that MMG alters miRNA expression signature of irradiated PBL by decreasing the number of radio-responsive miRNAs. Moreover, let-7i*, miR-7, miR-7-1*, miR-27a, miR-144, miR-200a, miR-598, miR-650 are deregulated by the combined action of radiation and MMG. Integrated analyses of miRNA and mRNA expression profiles, carried out on PBL of the same donors, identified significant miRNA-mRNA anti-correlations of DDR pathway. Gene Ontology analysis reports that the biological category of "Response to DNA damage" is enriched when PBL are incubated in 1 g but not in MMG. Moreover, some anti-correlated genes of p53-pathway show a different expression level between 1 g and MMG. Functional validation assays using luciferase reporter constructs confirmed miRNA-mRNA interactions derived from target prediction analyses.

Conclusions/Significance: On the whole, by integrating the transcriptome and microRNome, we provide evidence that modeled microgravity can affects the DNA-damage response to IR in human PBL.

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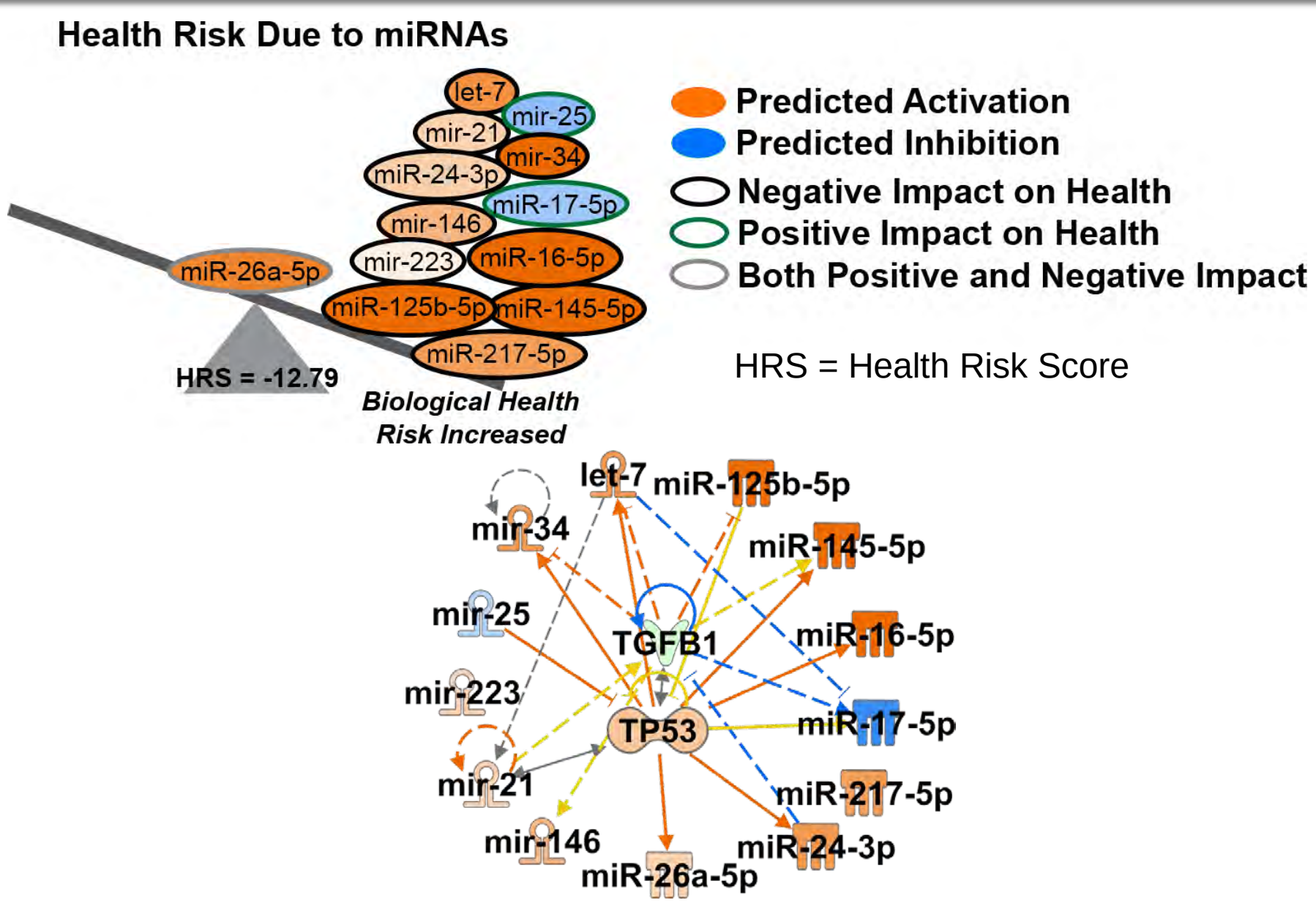
Predicted miRNAs Involved with Microgravity Effects



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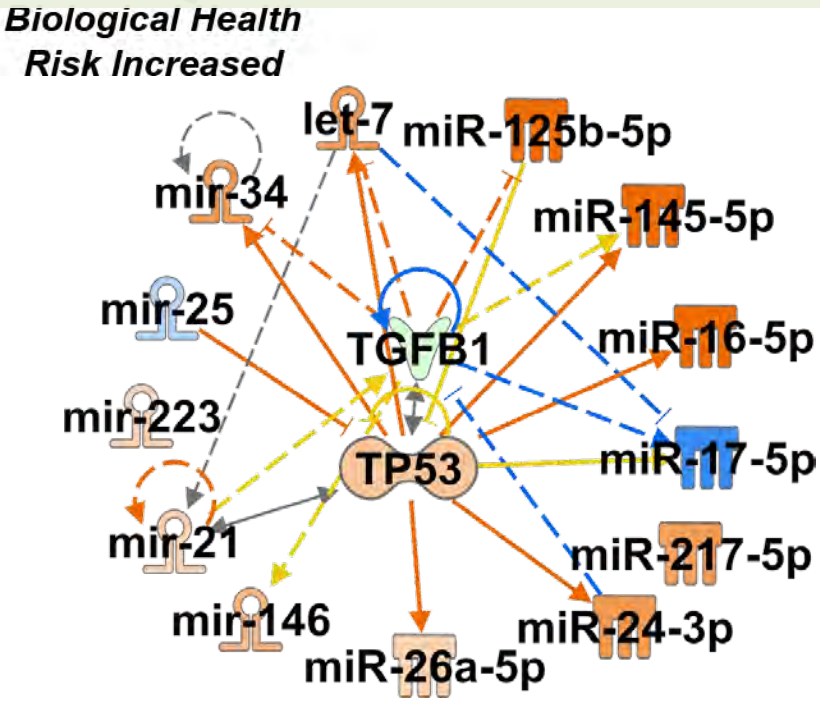
Predicted miRNAs Involved with Microgravity Effects

Health Risk Due to miRNAs

Predicted Activation
Predicted Inhibition

- 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



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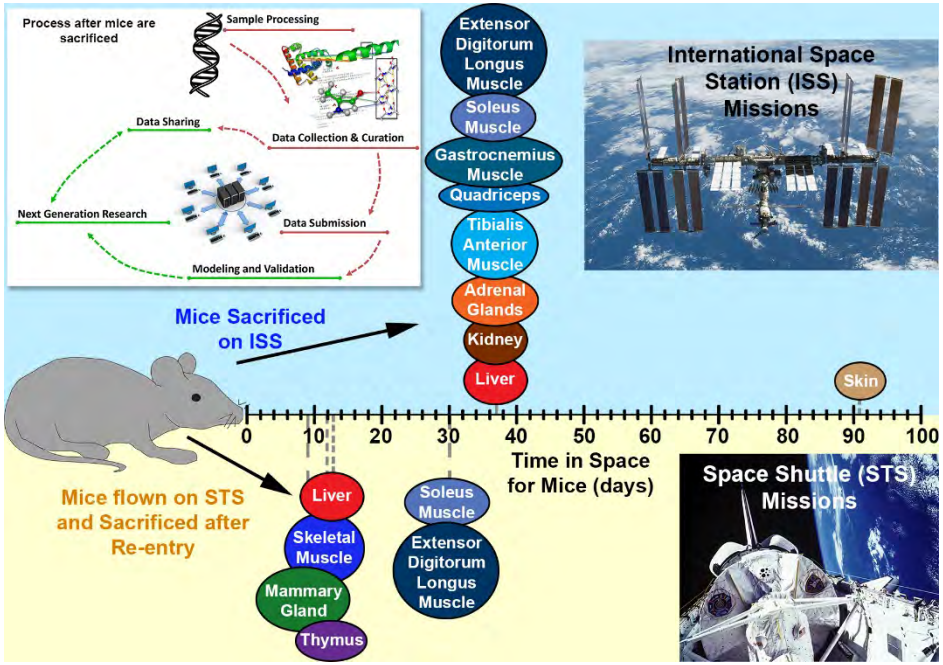
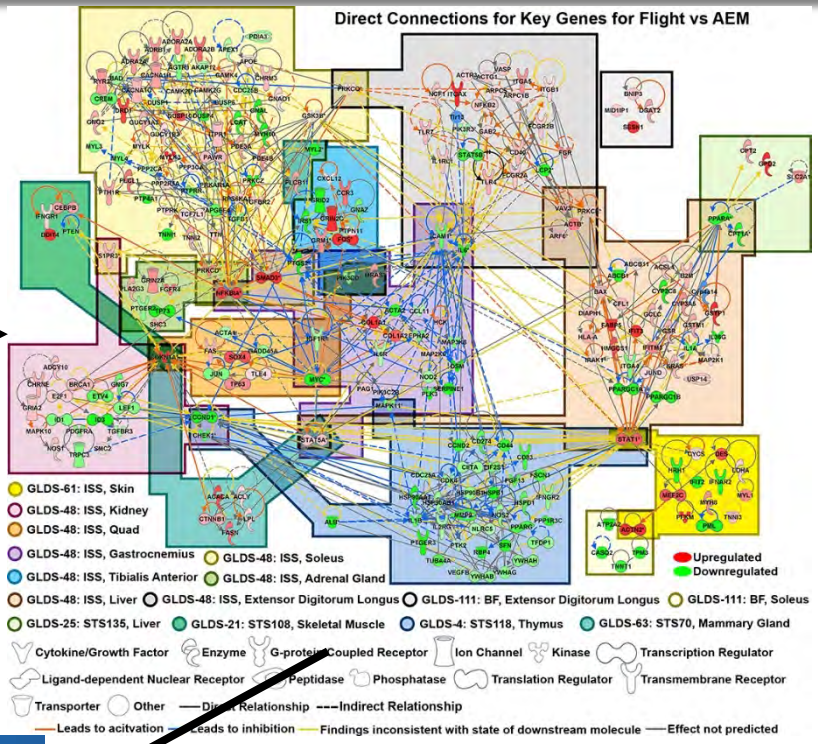
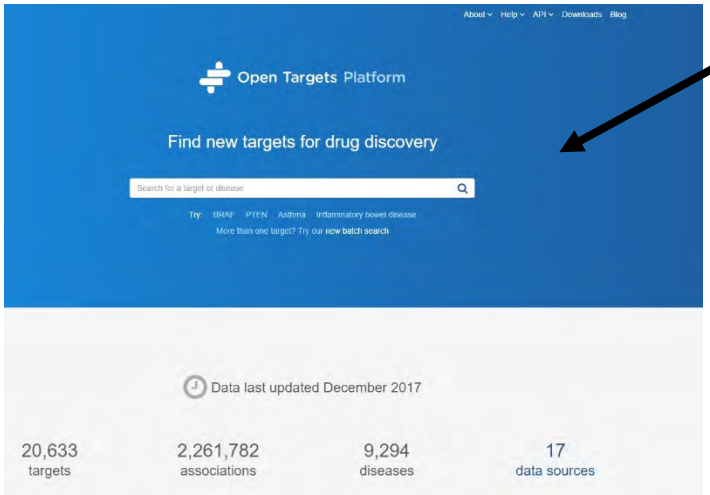
Using OpenTarget to Generate Countermeasures







Key Genes for individual tissues

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Output of OpenTarget

Open Targets Platform | About | Help | API | Downloads | Blog | Search for a target or disease

Summary page for 13 targets

Diseases associated

Therapeutic areas | Data types

Therapeutic areas: (sorted by relevance to your list)

Phenotype | Neoplasm | Kidney disease | Nervous system disease | Other disease | Cardiovascular disease | Genetic disorder | Endocrine system disease | More

Showing 1 to 10 of 1,823 entries
Search:

Disease	Relevance (pvalue)	Number of associated targets	Highest associated targets (max 10)
cognitive impairment	1e-9	13	GRIN2C IRS1 CCR3 PLCB1 CXCL12 RAPGEF5 PTPN11 FOS GRID2 GRM1 ...
ischemia	2e-8	13	GRIN2C CXCL12 FOS GRM1 RAPGEF5 IRS1 PTPN11 PIK3CD PLCB1 MYL2 ...
kidney neoplasm	2e-7	13	PTPN11 CXCL12 PIK3CD MYL2 GRM1 IRS1 RAPGEF5 CCR3 PLCB1 GRIN2C ...
drug dependence	2e-7	13	GRIN2C RAPGEF5 PTPN11 PLCB1 CXCL12 MYL2 PIK3CD FOS IRS1 GRM1 ...
sign or symptom	2e-7	13	GRIN2C CXCL12 GRM1 PTPN11 PLCB1 FOS RAPGEF5 CCR3 IRS1 PIK3CD ...
sensory system disease	3e-7	13	PTPN11 GRIN2C GRID2 GRM1 FOS GNAZ CCR3 CXCL12 RAPGEF5 IRS1 ...
hypertension	3e-7	13	RAPGEF5 CXCL12 IRS1 FOS CCR3 PIK3CD GRM1 MYL2 PLCB1 PTPN11 ...
Rare genetic endocrine disease	4e-7	13	PTPN11 GRIN2C GRM1 GRID2 FOS CXCL12 GNAZ CCR3 RAPGEF5 PLCB1 ...
bronchial disease	6e-7	12	PIK3CD CXCL12 GRIN2C CCR3 PTPN11 RAPGEF5 FOS PLCB1 GNAZ GRM1
whooping cough	8e-7	11	CXCL12 PLCB1 GNAZ CCR3 PTPN11 GRM1 FOS

Show 10 entries

Previous | 1 | 2 | 3 | 4 | 5 | ... | 183 | Next

Pathways

Showing 1 to 10 of 193 entries
Search:

Pathway	Relevance (pvalue)	Number of targets	Targets in pathway
Signaling by Leptin	0.000077	2	PTPN11, IRS1
Constitutive Signaling by Aber...	0.000099	3	PIK3CD, PTPN11, IRS1
PI3K/AKT Signaling in Cancer	0.00024	3	PIK3CD, PTPN11, IRS1
PI5P, PP2A and IER3 Regulate P...	0.00025	3	PIK3CD, PTPN11, IRS1
Negative regulation of the PI3...	0.00030	3	PIK3CD, PTPN11, IRS1
Signal Transduction	0.00078	6	PIK3CD, PTPN11, IRS1, CXCL12, CCR3, GNAZ, PLCB1, GRM1, GRIN2C
G alpha (i) signalling events	0.00092	4	CCR3, CXCL12, GNAZ, PLCB1
RET signaling	0.0010	2	PIK3CD, PTPN11
PLC beta mediated events	0.0012	2	GNAZ, PLCB1
GPCR downstream signalling	0.0012	4	PIK3CD, CCR3, CXCL12, GNAZ, PLCB1, GRM1

Show 10 entries

Previous | 1 | 2 | 3 | 4 | 5 | ... | 20 | Next

Gene Ontology

Showing 1 to 10 of 20 entries
Search:

GO term description	Category	Relevance (pvalue)	Number of targets	Targets
glutamate receptor signaling pathway	Biological Process	3.37e-04	4	GRID2, GRM1, GRIN2C, PLCB1
glutamate receptor activity	Molecular Function	1.23e-03	3	GRID2, GRM1, GRIN2C
cell surface receptor signaling pathway	Biological Process	1.54e-03	10	CXCL12, GRID2, GRM1, GRIN2C, IRS1, FOS, PIK3CD, PTPN11, PLCB1, CCR3
response to cytokine	Biological Process	3.16e-03	7	CXCL12, IRS1, FOS, PIK3CD, PTPN11, PLCB1, CCR3
1-phosphatidylinositol-3-kinase activity	Molecular Function	5.15e-03	3	IRS1, PIK3CD, PTPN11
cytokine-mediated signaling pathway	Biological Process	5.71e-03	6	CXCL12, IRS1, PIK3CD, PTPN11, PLCB1, CCR3
cellular extravasation	Biological Process	6.76e-03	3	CXCL12, PIK3CD, PLCB1
plasma membrane receptor complex	Cellular component	8.13e-03	4	GRID2, GRM1, GRIN2C, IRS1
phosphatidylinositol-3-phosphate biosynthetic process	Biological Process	8.16e-03	3	IRS1, PIK3CD, PTPN11
phosphatidylinositol kinase activity	Molecular Function	8.16e-03	3	IRS1, PIK3CD, PTPN11

Show 10 entries

Previous | 1 | 2 | Next

Drugs

Showing 1 to 10 of 51 entries
Search:

Drug	Target	Max phase	Molecule type
MEMANTINE	GRIN2C	Phase IV	Small molecule
AMANTADINE	GRIN2C	Phase IV	Small molecule
IDELALISIB	PIK3CD	Phase IV	Small molecule
FELBAMATE	GRIN2C	Phase IV	Small molecule
ORPHENADRINE	GRIN2C	Phase IV	Small molecule
ACAMPROSATE	GRIN2C	Phase IV	Small molecule
KETAMINE	GRIN2C	Phase IV	Small molecule
ESKETAMINE	GRIN2C	Phase IV	Small molecule
TGR-1202	PIK3CD	Phase III	Small molecule
OMECAMTIV MECARBIL	MYL2	Phase III	Small molecule

Show 10 entries

Previous | 1 | 2 | 3 | 4 | 5 | 6 | Next

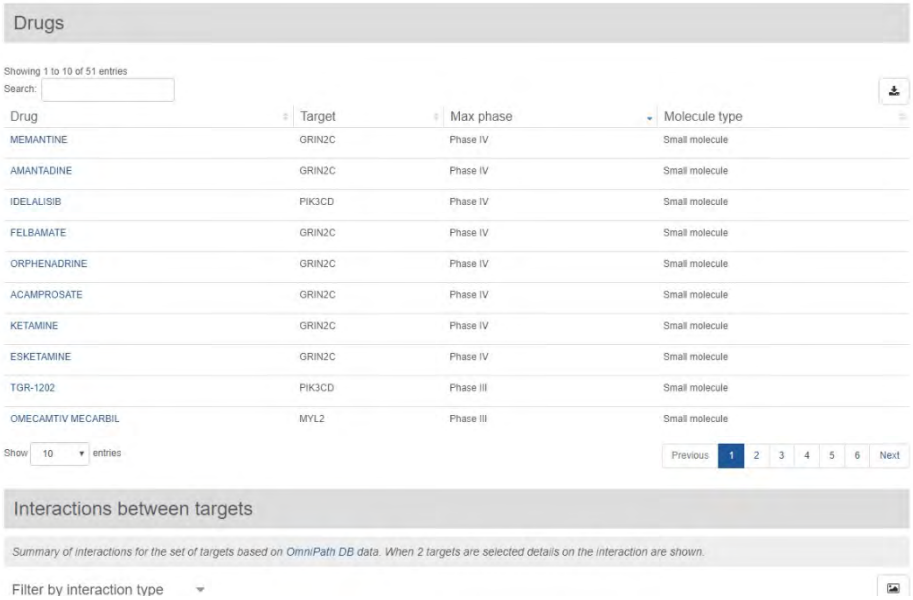
Interactions between targets

Summary of interactions for the set of targets based on OmniPath DB data. When 2 targets are selected details on the interaction are shown.

Filter by interaction type

Steps to Determine Potential Drugs for Countermeasures

1. Determine drugs targets for each tissue from “key genes”



Tissues/datasets that provided a list of drug hits from the key genes: RR1: Soleus muscle, RR1: Quadricep, RR1: gastrocnemius, RR1: extensor digitorum longus, RR1: Tibialis Anterior, GLDS-21: skeletal muscle , GLDS-62: Skin, RR1: adrenal gland, RR1: Kidney, GLDS-4: Thymus, RR1: Liver, GLDS-25: Liver

2. Find common drugs targets that exist between all the tissues

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Information of Common Drugs

Drugs	Target	Common	Prediction	Status	Terminated
UCN-01	**PRKCQ**	**6**	**Y**	**Completed**	**N**
MIDOSTAURIN	**PRKCQ**	**5**	**Y**	**Active. Recruiting**	**N**
DACTOLISIB	PIK3CD	5	Y	Withdrawn, Terminated, Completed	Y
PICTILISIB	PIK3CD	5	Y	Completed, terminated, recruiting	Y
GSK-690693	PRKCZ	4	Y	Withdrawn, Terminated	Y
APITOLISIB	PIK3CD	5	N	Completed, active	N
BGT-226	PIK3CD	5	N	Completed	N
DS-7423	PIK3CD	5	N	Completed	N
RG-7666	PIK3CD	5	N	Completed	N
SF-1126	PIK3CD	5	N	Recruiting, completed	N
TASELISIB	PIK3CD	5	N	Completed, Active, recruiting	N
VOXTALISIB	PIK3CD	5	N	Completed	N
ZSTK-474	PIK3CD	5	N	Completed	N
BUPARLISIB	PIK3CD	5	N	Completed, active, withdrawn, recruiting, terminated, recruiting	Y
COPANLISIB	PIK3CD	5	N	Suspended, terminated, recruiting, active, completed	Y
GEDATOLISIB	PIK3CD	5	N	Terminated, recruiting, active, completed	Y
GSK-1059615	PIK3CD	5	N	Terminated	Y
PF-04691502	PIK3CD	5	N	Withdrawn, Terminated, Completed	Y
VS-5584	PIK3CD	5	N	Terminated	Y
WX-037	PIK3CD	5	N	Terminated	Y
LY-3023414	PIK3CD	5	?	Recruiting	N
OMIPALISIB	PIK3CD	5	?	Completed	N
PA-799	PIK3CD	5	?	Completed	N
PILARALISIB	PIK3CD	5	?	Completed	N
Sonolisib	PIK3CD	5	?	Completed	N
ENMD-981693	HCK	4	?	Completed	N
Panulisib	PIK3CD	5	?	Suspended	Y
SOTRASTAURIN	PRKCQ	4	N	Terminated, completed, recruiting	Y

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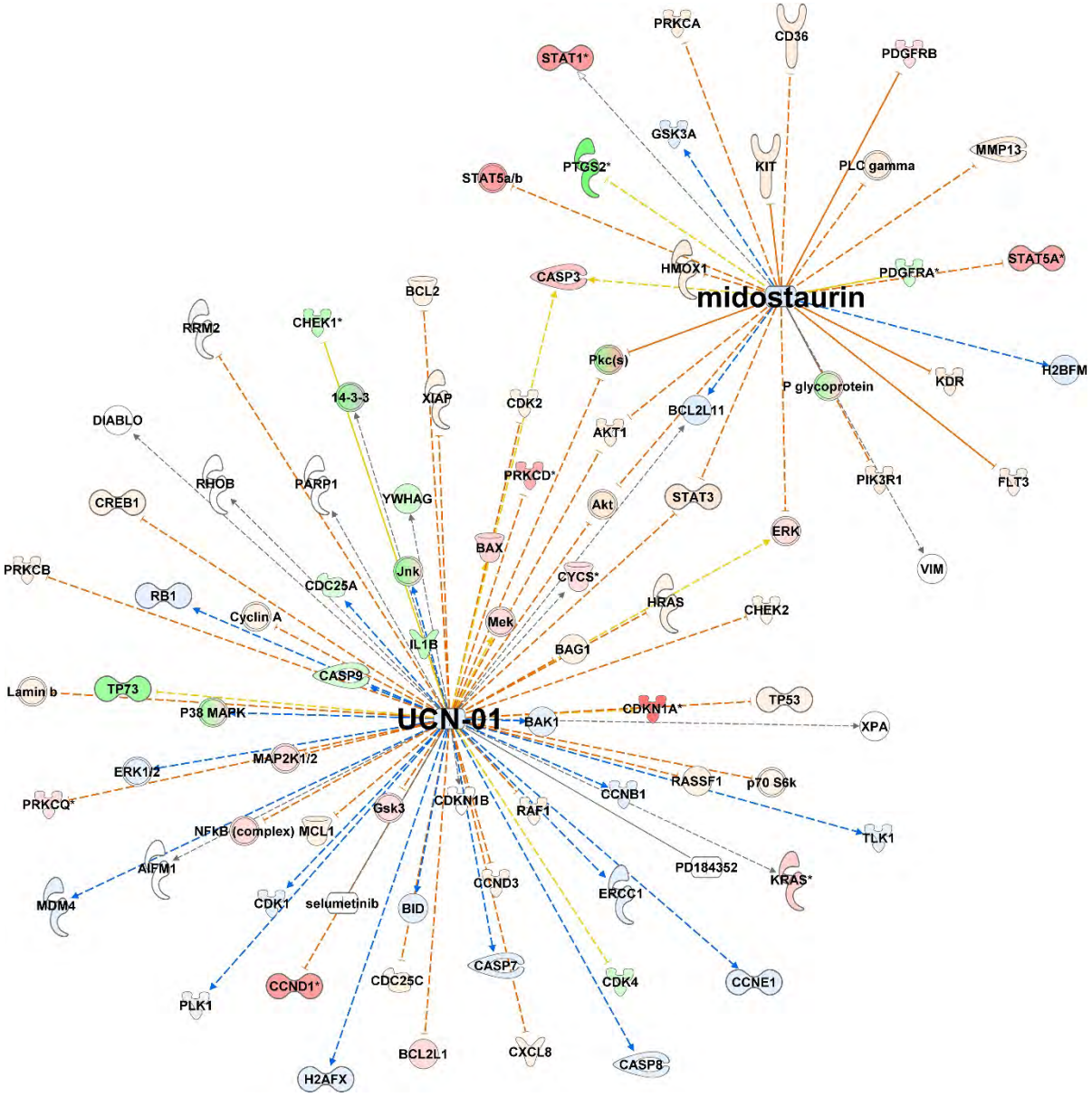
Two possible drug candidate for countermeasures against Spaceflight



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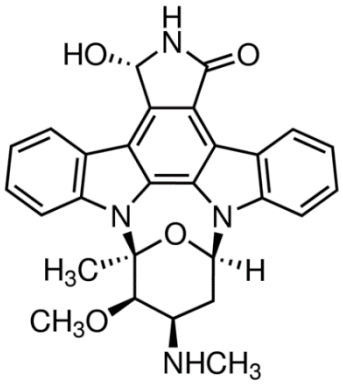
Two Drug Candidates: UCN-01

- Also known as: 7-hydroxystaurosporine
- Inhibits many phosphokinases, including the serine/threonine kinase AKT, calcium-dependent protein kinase C, and cyclin-dependent kinases
  - arrests tumor cells in the G1/S of the cell cycle and prevents nucleotide excision repair by inhibiting the G2 checkpoint kinase chk1, resulting in apoptosis
  - Phase 1 and 2 clinical trails with drug for various cancers (information available on ClinicalTrials.gov)
    - Pancreatic Cancer: Completed, No results listed
    - Small Cell Lung Cancer: Completed, Response rate: 2/19 patients with CR or PR and 9/19 with Stable Disease
    - Melanoma: Terminated, early termination for discouraging results
    - Lymphoma, Terminated, due to low accrual and cost
    - Kidney Cancer: Completed, No results listed
    - Advanced Solid Tumors: Completed, No results listed



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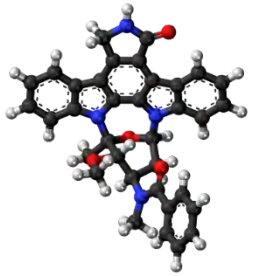
Two Drug Candidates: Midostaurin

- (sold under the name Rydapt) is a multi-targeted protein kinase inhibitor that has been investigated for the treatment of acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) and advanced systemic mastocytosis.
- It is a semi-synthetic derivative of staurosporine, an alkaloid from the bacterium Streptomyces staurosporeus.
- a multikinase inhibitor for oral use
- a small molecule that inhibits multiple receptor tyrosine kinases
  - inhibit the activity of wild type FLT3, FLT3 mutant kinases (ITD and TKD), KIT (wild type and D816V mutant), PDGFRα/β, VEGFR2, as well as members of the serine/threonine kinase PKC (protein kinase C) family.
  - Midostaurin demonstrated the ability to inhibit FLT3 receptor signaling and cell proliferation, and it induced apoptosis in leukemic cells expressing ITD and TKD mutant FLT3 receptors or overexpressing wild type FLT3 and PDGF receptors
- **Approved FDA drug (2017)**



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UCN-01 and Midostaurin and potential countermeasure use

- Both UCN-01 and midostaurin inhibit cytosolic PKC
  - Jirousek & Goekjian, Expert Opin Investig Drugs. 2001 Dec;10(12):2117-40
- Can these anti-cancer drugs be applied to the negative health effects associated with long term space missions?
  - Midostaurin has been shown to improve Bone Loss effects
    - Brounais et al, Clin Cancer Res. 2008 Sep 1;14(17):5400-9. doi: 10.1158/1078-0432.CCR-07-4781.
  - Inhibiting FLT3 (inhibited by Midostaurin) can prevent immune related effects due to spaceflight
    - Whartenby et al, Expert Opin Investig Drugs. 2008 Nov; 17(11): 1685–1692.
- Inhibiting PKC (by Midostaurin and UCN-01) has beneficial effects with space related health risks
  - Can impact diabetic complications, heart failure, myocardial infarction, pain and bipolar disease
    - Mochly-Rosen et al, Nat Rev Drug Discov. 2012 Dec; 11(12): 937–957.
- **There are possible examples of how these two drugs can be adapted as a potential countermeasure**

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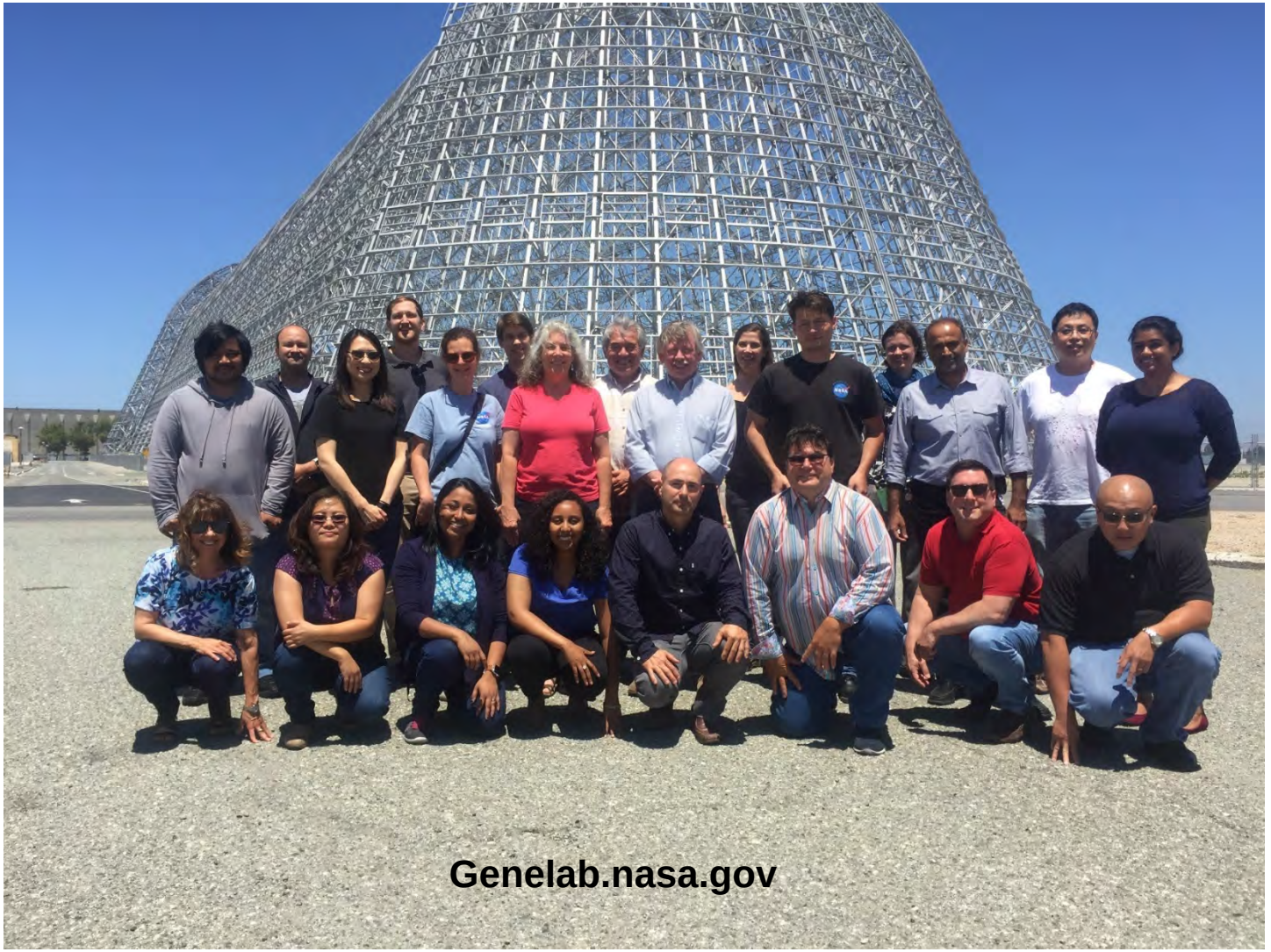

Questions and Discussion???