



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

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- 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.

The image displays three overlapping screenshots of the GeneLab platform:

- Top Left:** The GeneLab homepage. It features a search bar, navigation links (Home, Repository, Data, Data Mining Tools, Submit Data, Contact Us, Workspace), and a list of featured studies. Two studies are visible:
 

Organization	Factors	Assay Type	Release Date	Description
GLDS-136	Arabidopsis thaliana	Microarray	20 May 2017	Global gene expression analysis highlights microgravity sensitive key genes in Arabidopsis thaliana
GLD...	Longissimus dorsi	Microarray	23 May 2017	Global gene expression analysis highlights microgravity sensitive key genes in longissimus dorsi and tongue of 30 days space-flown mice
- Top Right:** The NASA GeneLab-GenomeSpace OpenID Login page. It includes fields for USERNAME and PASSWORD, and buttons for Sign In and Cancel. Below the login fields is a registration link and a password recovery link.
- Bottom:** A file browser interface showing a directory structure. The path is "Up to: Home > Public > genelab > genelab-data". The main area displays a table of files:
 

Filename	Tags	Owner	Size	Last Modified
GLDS-1		genelab		
GLDS-10		genelab		
GLDS-100		genelab		
GLDS-101		genelab		
GLDS-102		genelab		
GLDS-103		genelab		
GLDS-104		genelab		
GLDS-105		genelab		
GLDS-106		genelab		
GLDS-107		genelab		
GLDS-108		genelab		
GLDS-109		genelab		
GLDS-11		genelab		
GLDS-110		genelab		
GLDS-111		genelab		
GLDS-112		genelab		
GLDS-113		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.

The top left screenshot shows the GeneLab homepage with navigation links (Home, Repository, Data, Data Mining Tools, Submit Data, Contact Us, Workspace) and a search bar. Below are featured articles, such as 'Dissecting Low Atmospheric Pressure Stress: Transcriptional Responses to the Components of Hypobaric in Arabidopsis [Experiment 2]' and 'Global gene expression analysis highlights microgravity sensitive key genes in longissimus dorsi and tongue of 30 days space-flown mice'.

The top right screenshot shows the 'NASA GeneLab-GenomeSpace OpenID Login' page with fields for USERNAME and PASSWORD, and buttons for 'Sign In' and 'Cancel'. Below the login fields is a disclaimer: 'This is a US Government system and is for authorized users only. By accessing this system you are consenting to complete monitoring with no expectation of privacy. Unauthorized access or use may subject you to disciplinary action and criminal prosecution. Unauthorized use of the computer accounts and computer resources to which I am granted access is a violation of Federal law, constitutes theft, and is punishable by law. I understand that I am the only individual to access these accounts and will not knowingly permit access by others without written approval. I understand that my misuse of assigned accounts and my accessing others' accounts without authorization is not allowed. I understand that this/these system(s) and resources are subject to monitoring and recording and I will have no expectation of...'.

The bottom screenshot shows a file browser interface for 'genelab-data'. It displays a list of files with columns for Filename, Tags, Owner, Size, and Last Modified. The files listed include GLDs-1 through GLDs-113.



A screenshot of the 'studydefinition' interface in GeneLab. The interface is divided into several sections: 'study view utilities options help' at the top, a 'study' section on the left with a tree view of files and folders, and a 'studydefinition' section on the right with a form for entering study details. The form includes fields for 'Study Title', 'Project Type', 'Flight Program', 'Experiment Platform', 'Managing NASA Center', 'Mission Name', and 'Mission Year Link'. There is also an 'Acknowledgments' section and a 'Study Public Release Date' field.



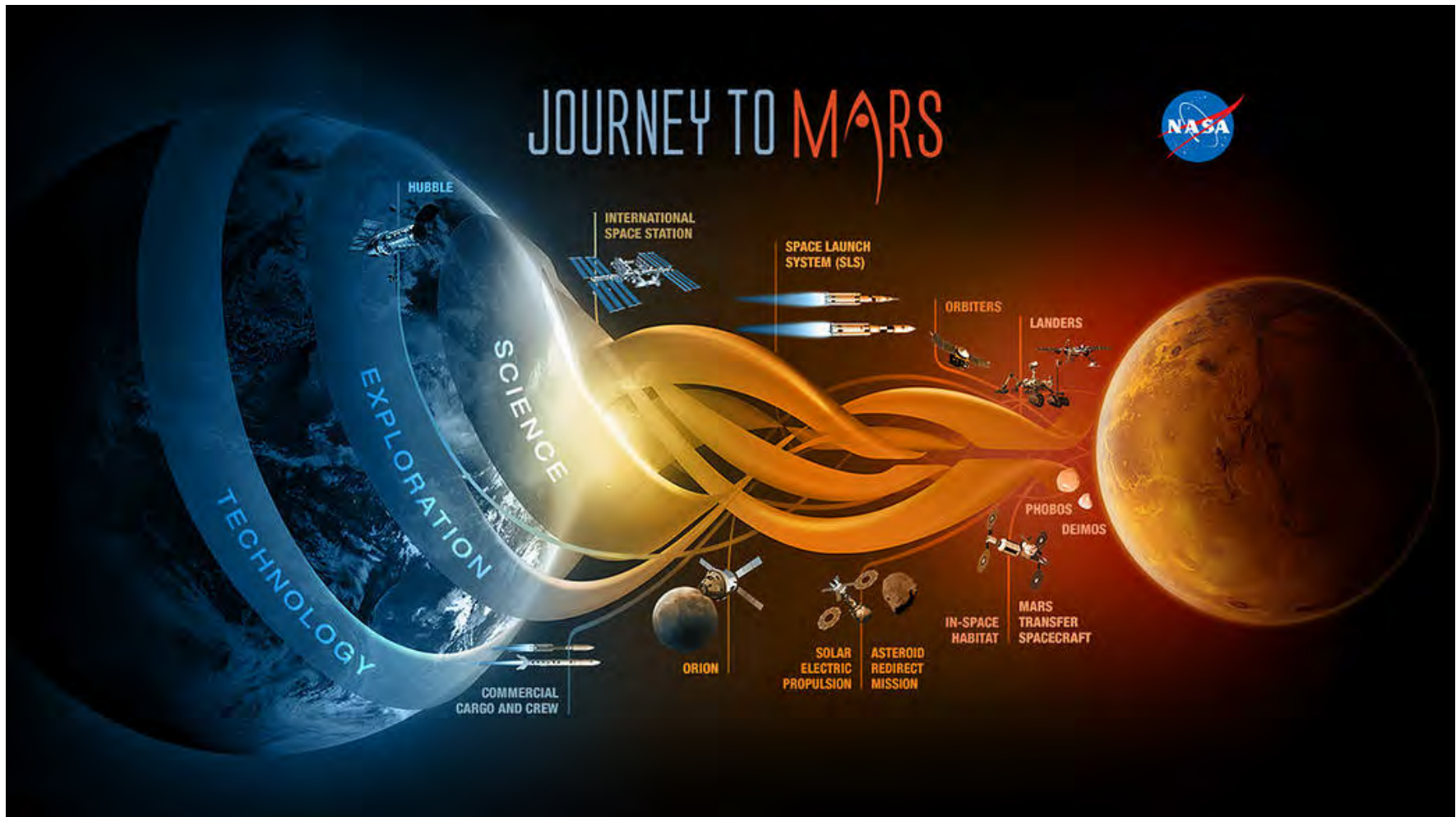


The collage features several screenshots from the GeneLab platform:

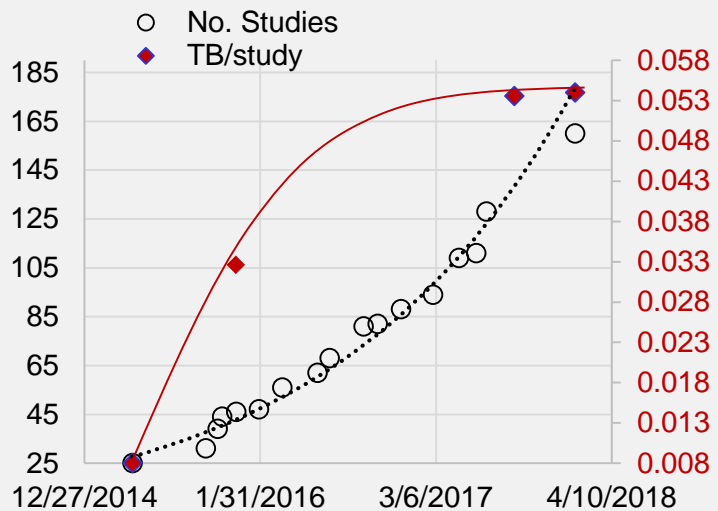
- Home Page:** Shows the GeneLab logo, navigation menu (Home, Repository, Data, Data Mining Tools, Submit Data, Contact Us, Workspace), and search filters (All, GeneLab, NIH GEO, EBI PRIDE, ANL/MG-RAST).
- Study Cards:** Displays two study cards: "Dissecting Low Atmospheric Pressure in Arabidopsis [Experiment 2]" (GLDS-156) and "Global gene expression analysis of tongue of 30 days space-flown mice" (GLDS-157).
- Login Page:** A "NASA GeneLab-GenomeSpace OpenID Login" form with fields for USERNAME and PASSWORD, and buttons for "Sign In" and "Cancel".
- Repository Table:** A table listing study files with columns for filename, user, size, and last modified. The table shows a list of GLDS files (GLDS-1 to GLDS-113) all associated with the user "genelab".
- Study Definition Page:** A detailed view of a study titled "Chaperonin Validation of Methods to Assess the Immunoglobulin Gene Rep...". It includes a description of the study, funding information (NASA grants NNX13AN34G and NNX13AB45G), and various metadata fields like "Study Submission Date", "Project Identifier", and "Mission Name".

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

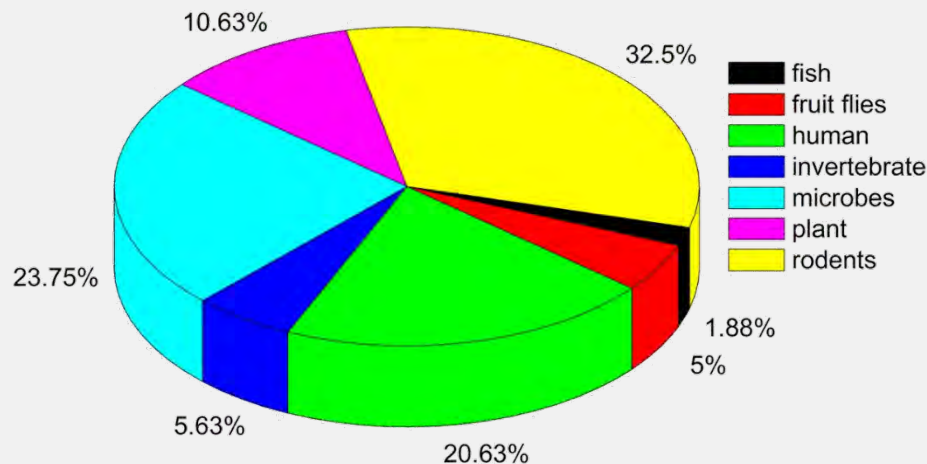
Overall, the goal of GeneLab is to allow for better understanding of the impact of spaceflight on biology!



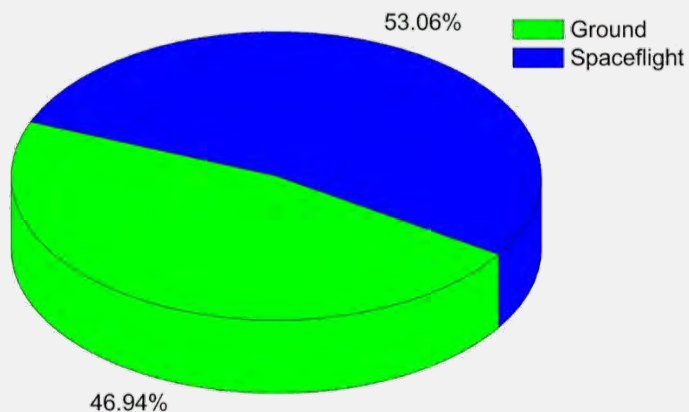
# What Already Exists on GeneLab Database: 154 data sets



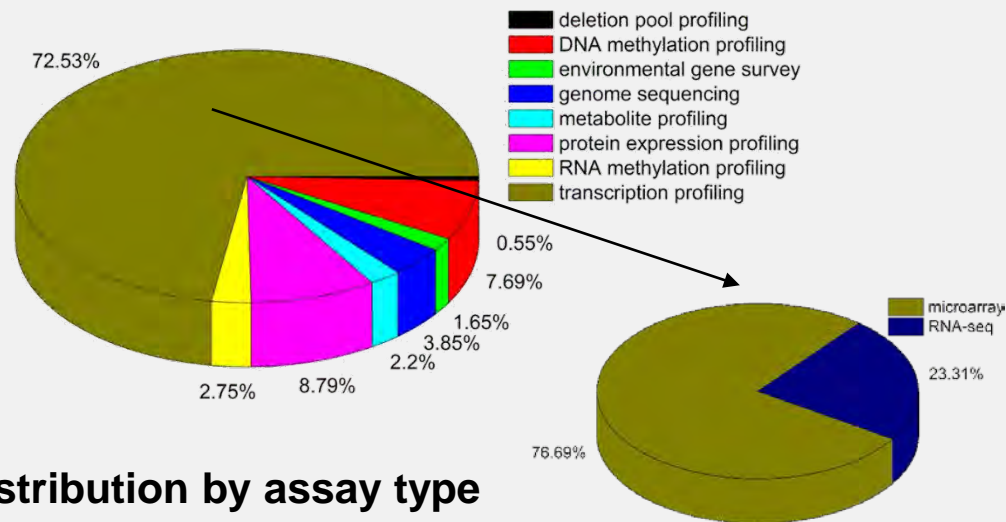
**Data Growth Since 2014**



**Distribution by organism type**



**Majority is spaceflight samples**



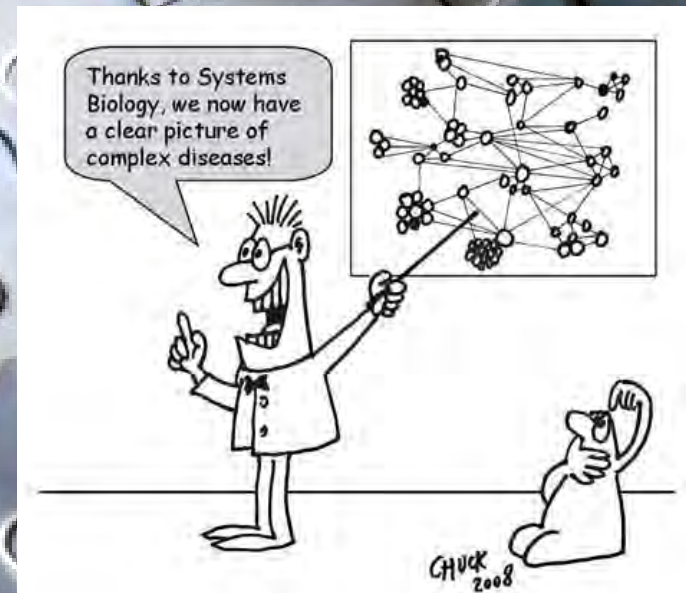
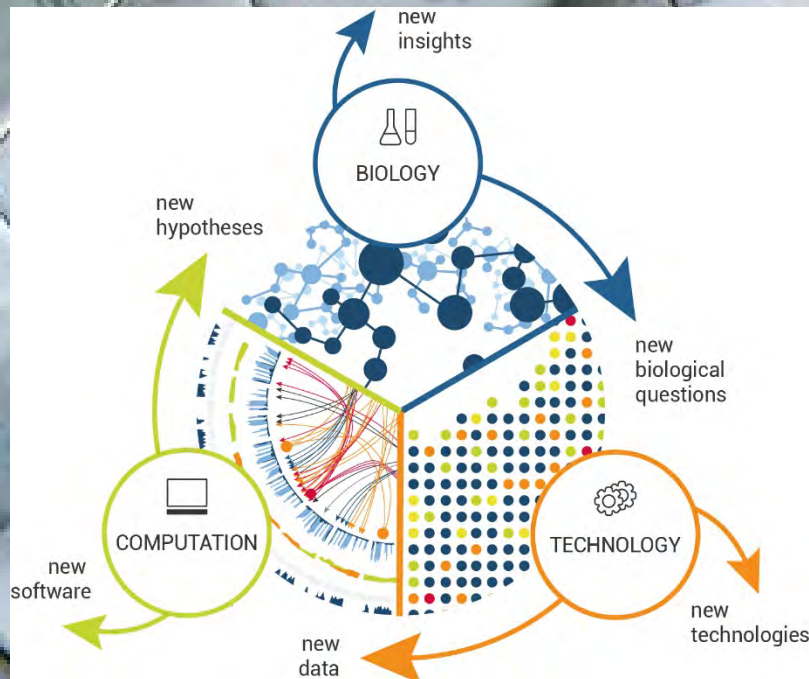
**Distribution by assay type**



- 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.

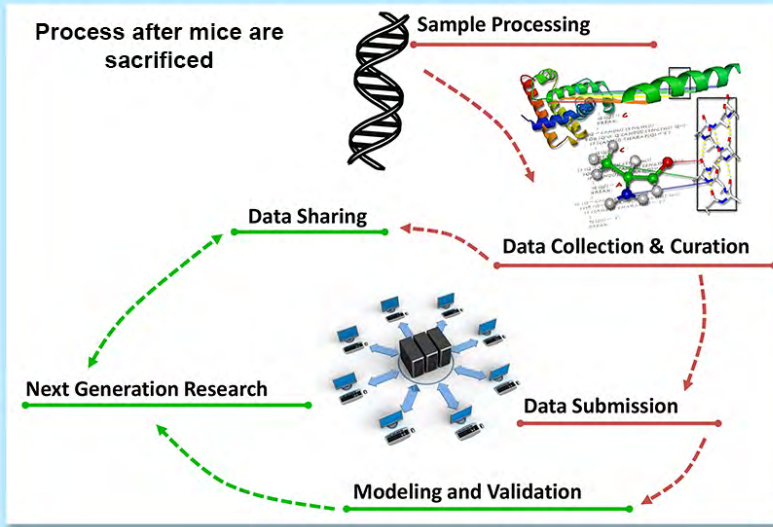


- Systems biology attempts to understand biological organisms or systems as a whole rather than researching their individual components in isolation from one another.
- NIH defines Systems Biology as: “Systems biology is an approach in biomedical research to understanding the larger picture—be it at 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.”

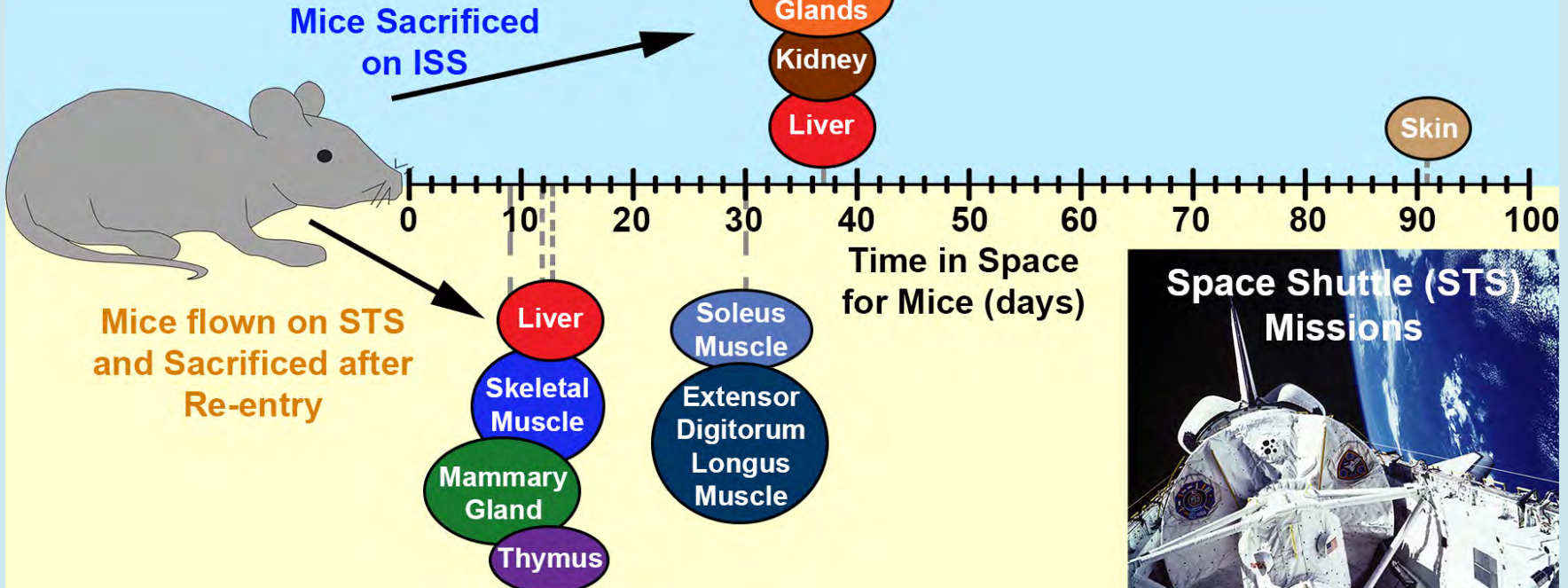




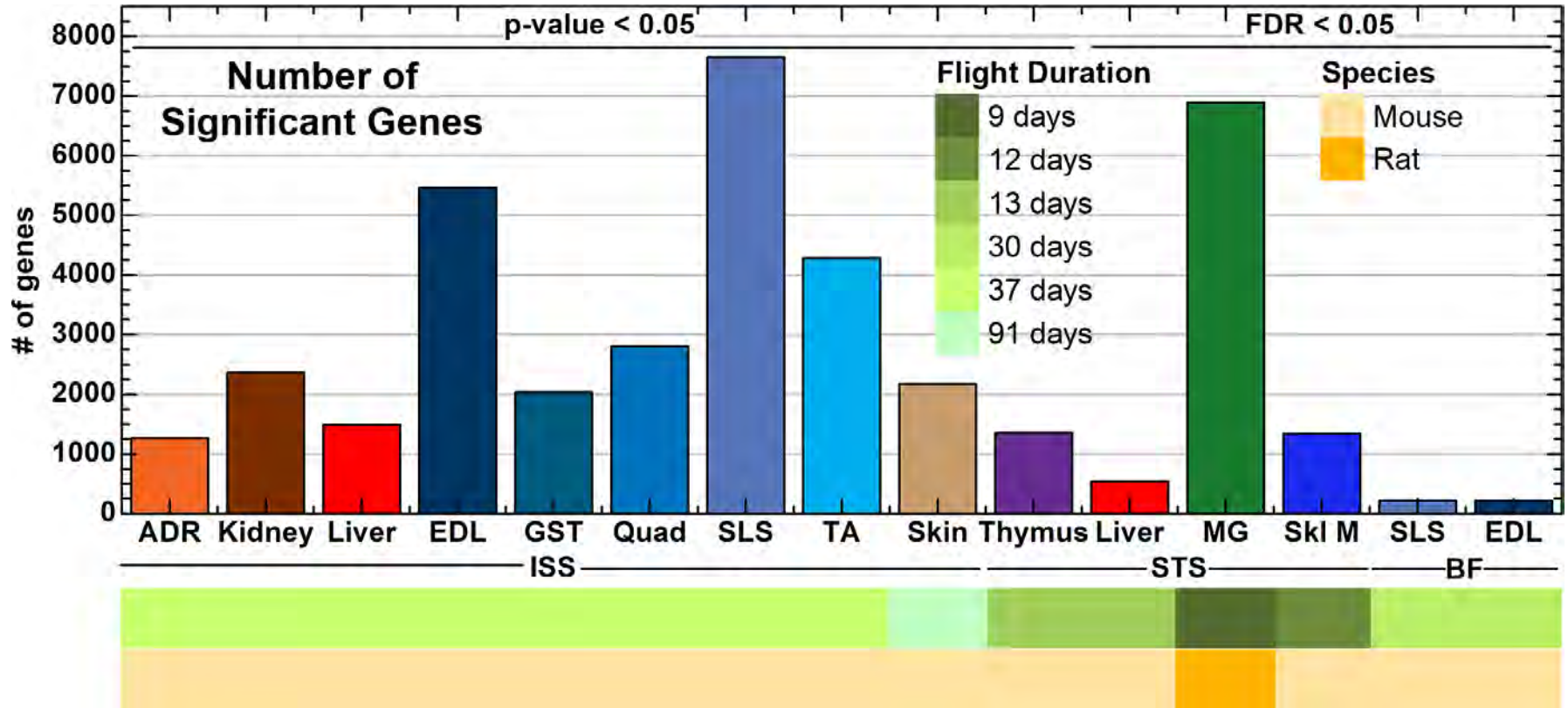
# Hypothesis generation from GeneLab Data



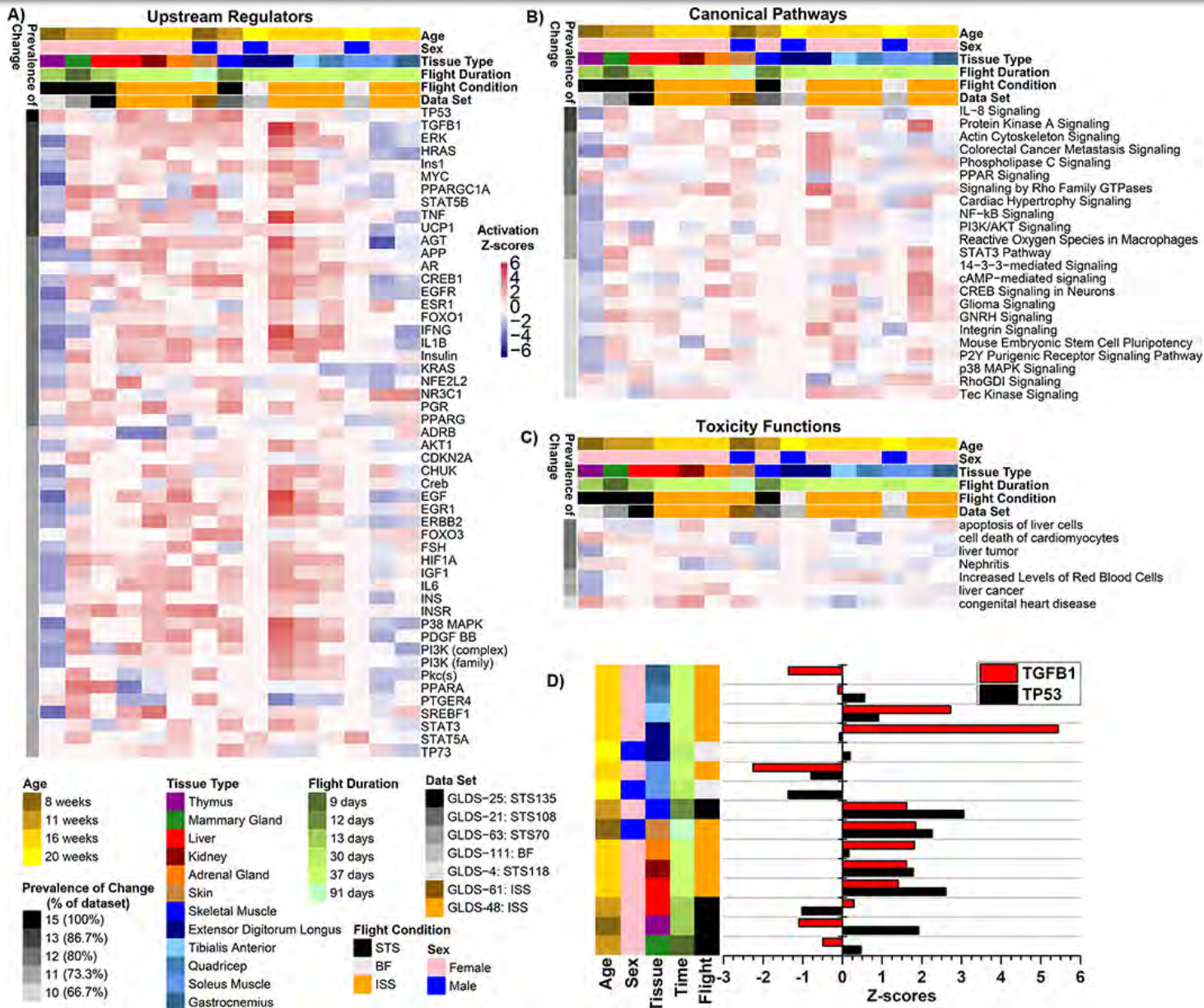
- Extensor Digitorum Longus Muscle
- Soleus Muscle
- Gastrocnemius Muscle
- Quadriceps
- Tibialis Anterior Muscle
- Adrenal Glands
- Kidney
- Liver



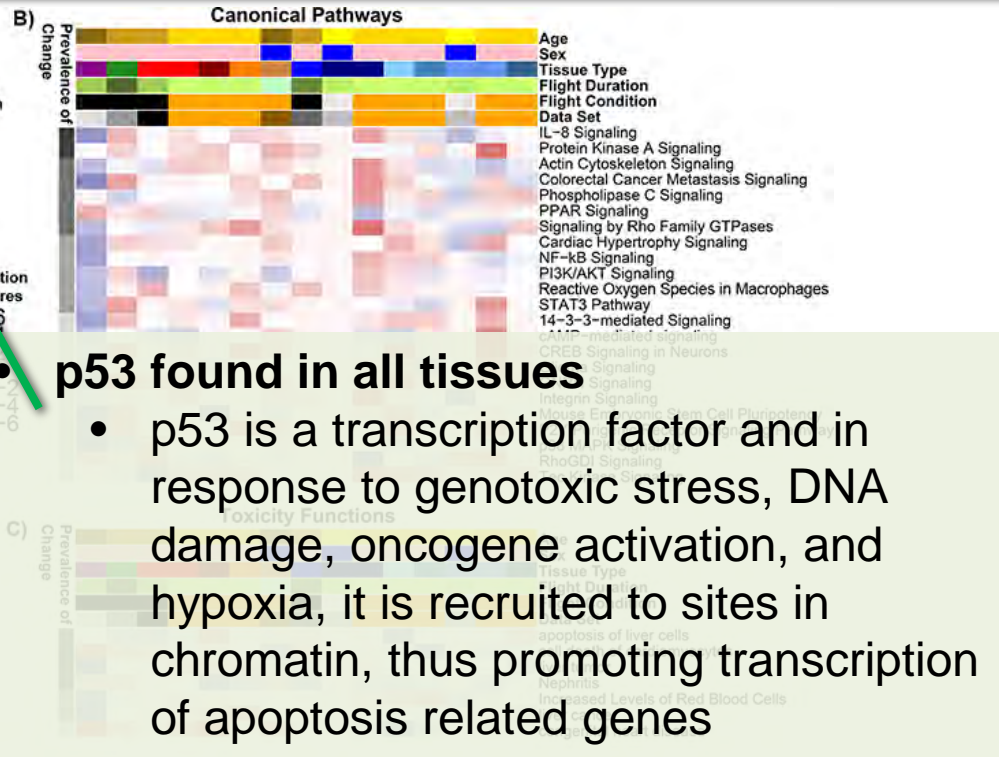
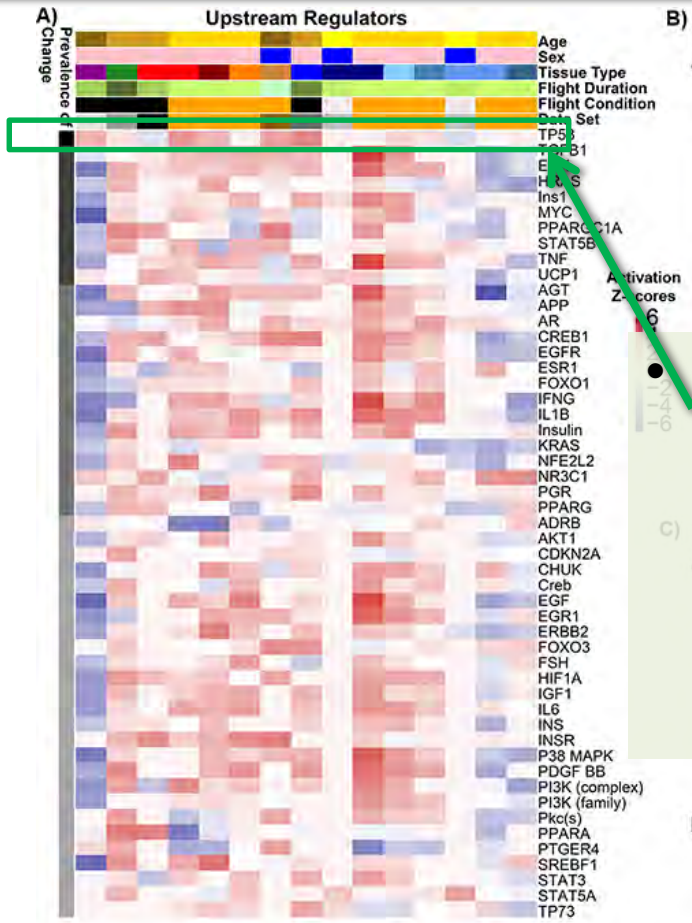
# Number of Significant Genes from Multiple Datasets





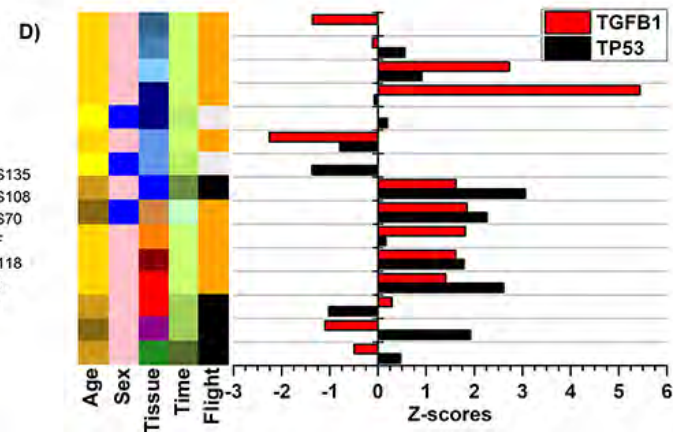
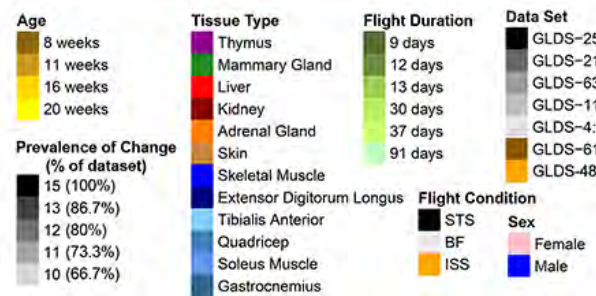




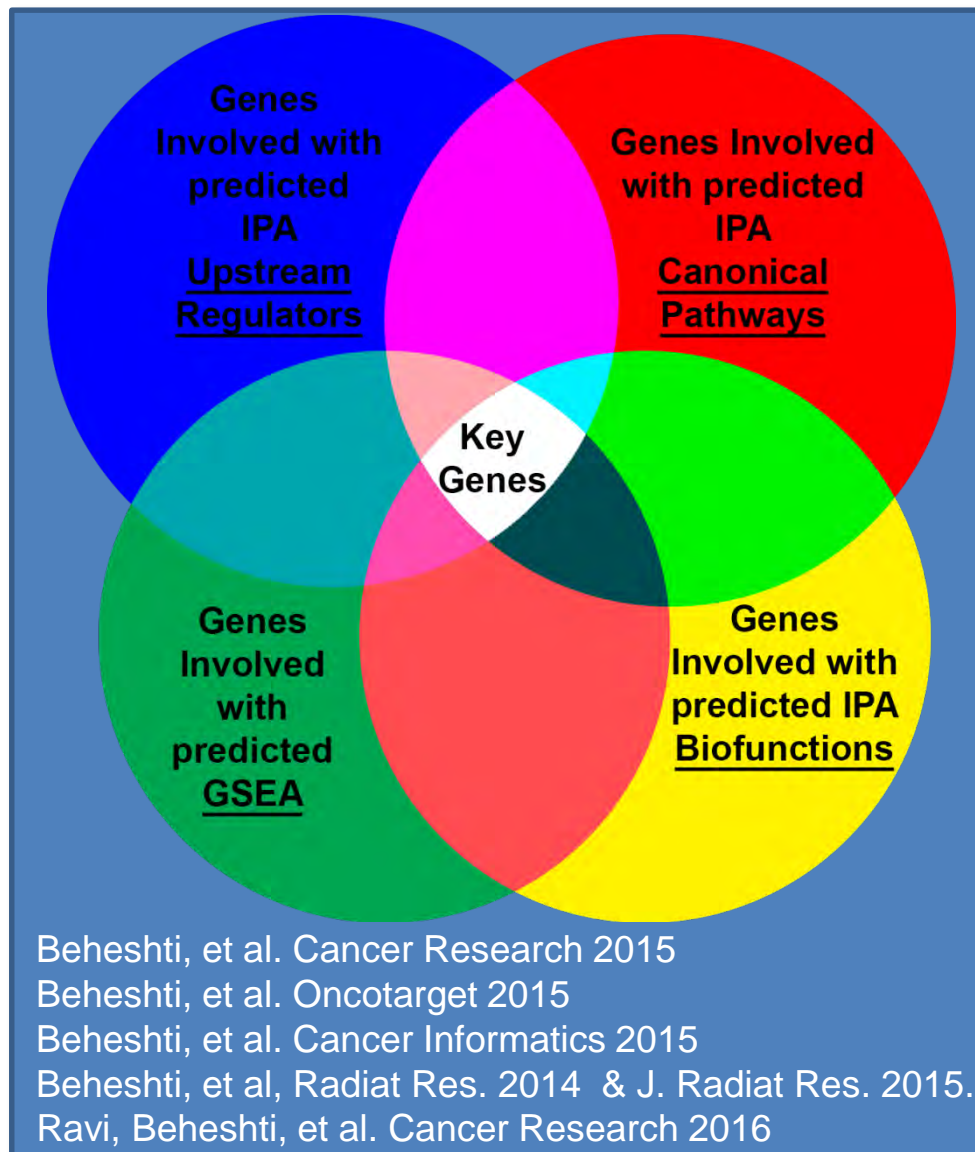


**p53 found in all tissues**

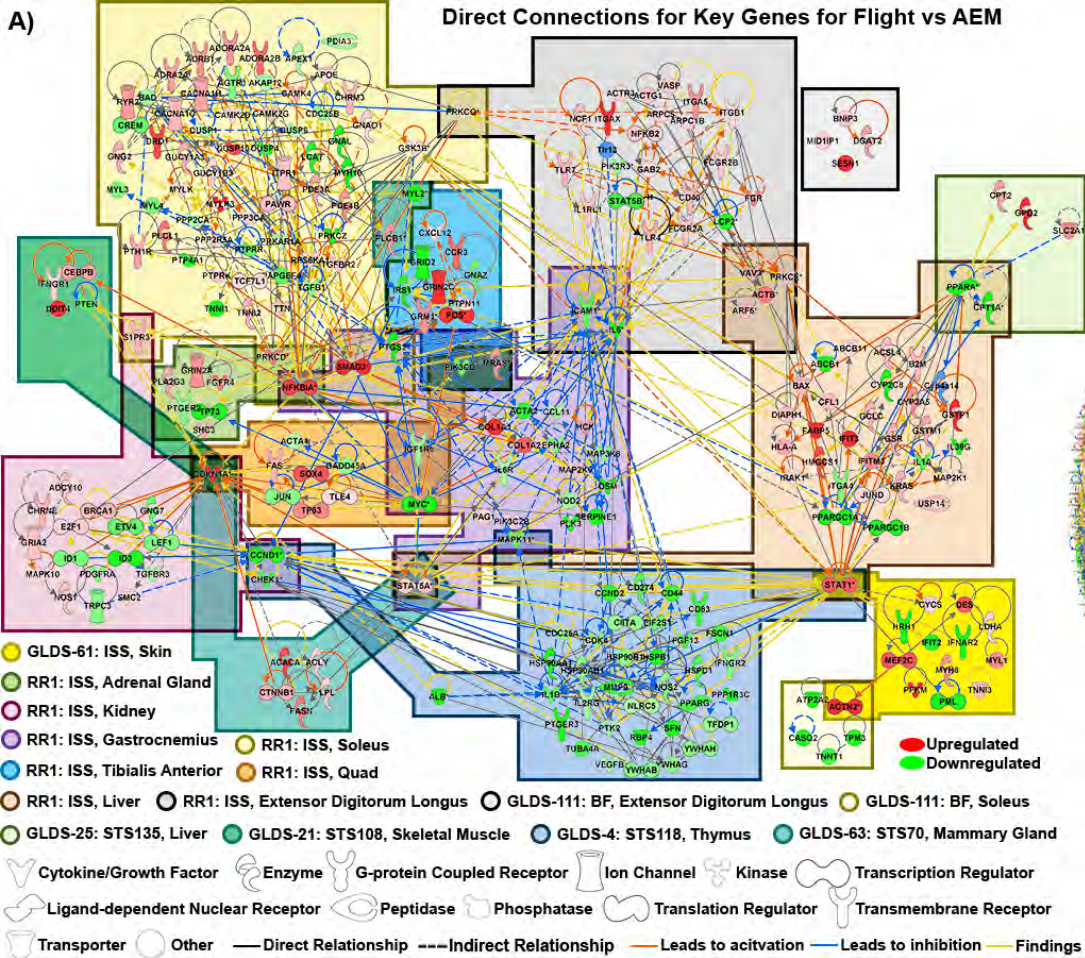
- p53 is a transcription factor and in response to genotoxic stress, DNA damage, oncogene activation, and hypoxia, it is recruited to sites in chromatin, thus promoting transcription of apoptosis related genes



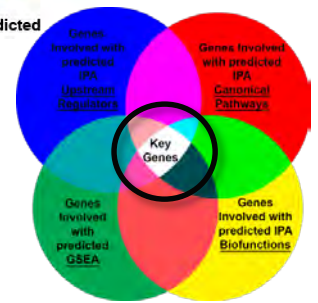
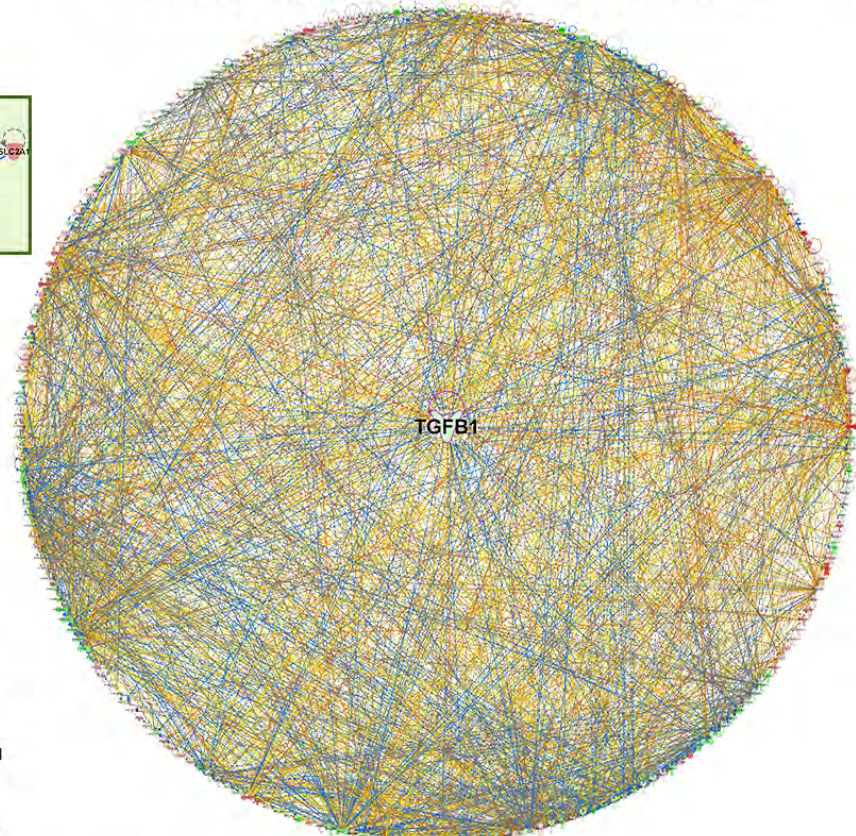
# Determination of Key Genes/Drivers







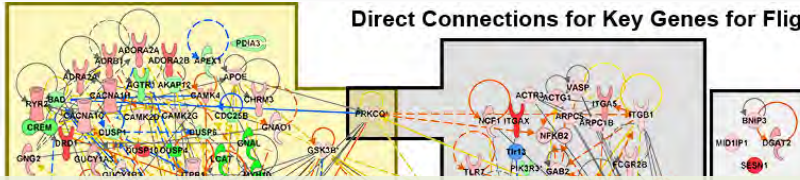
**B) Connections Between all Key Genes for all Datasets (Flight vs AEM): Radial Plot with the most Connected Gene in the Middle**



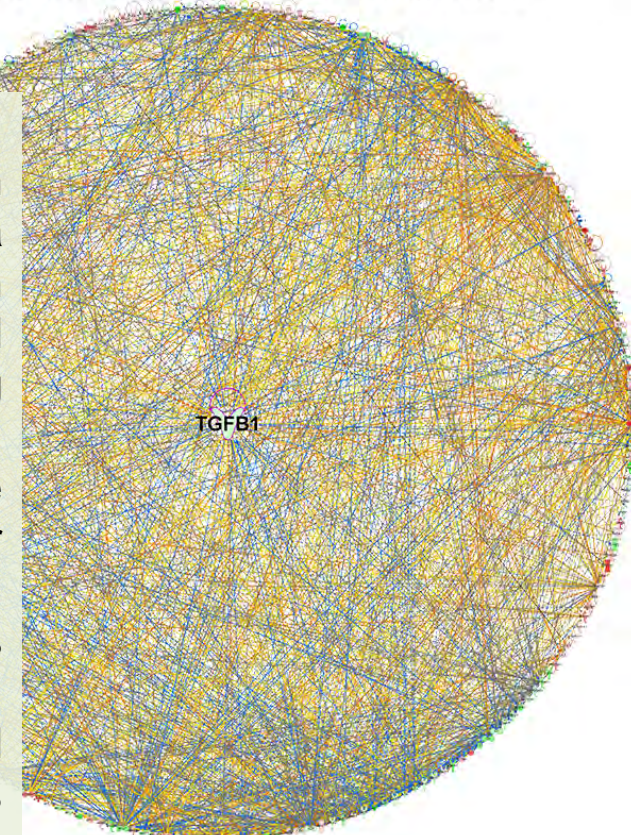


A)

Direct Connections for Key Genes for Flight vs AEM



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

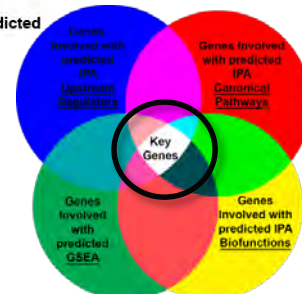


- **TGFβ1 found to be central regulator of key genes**

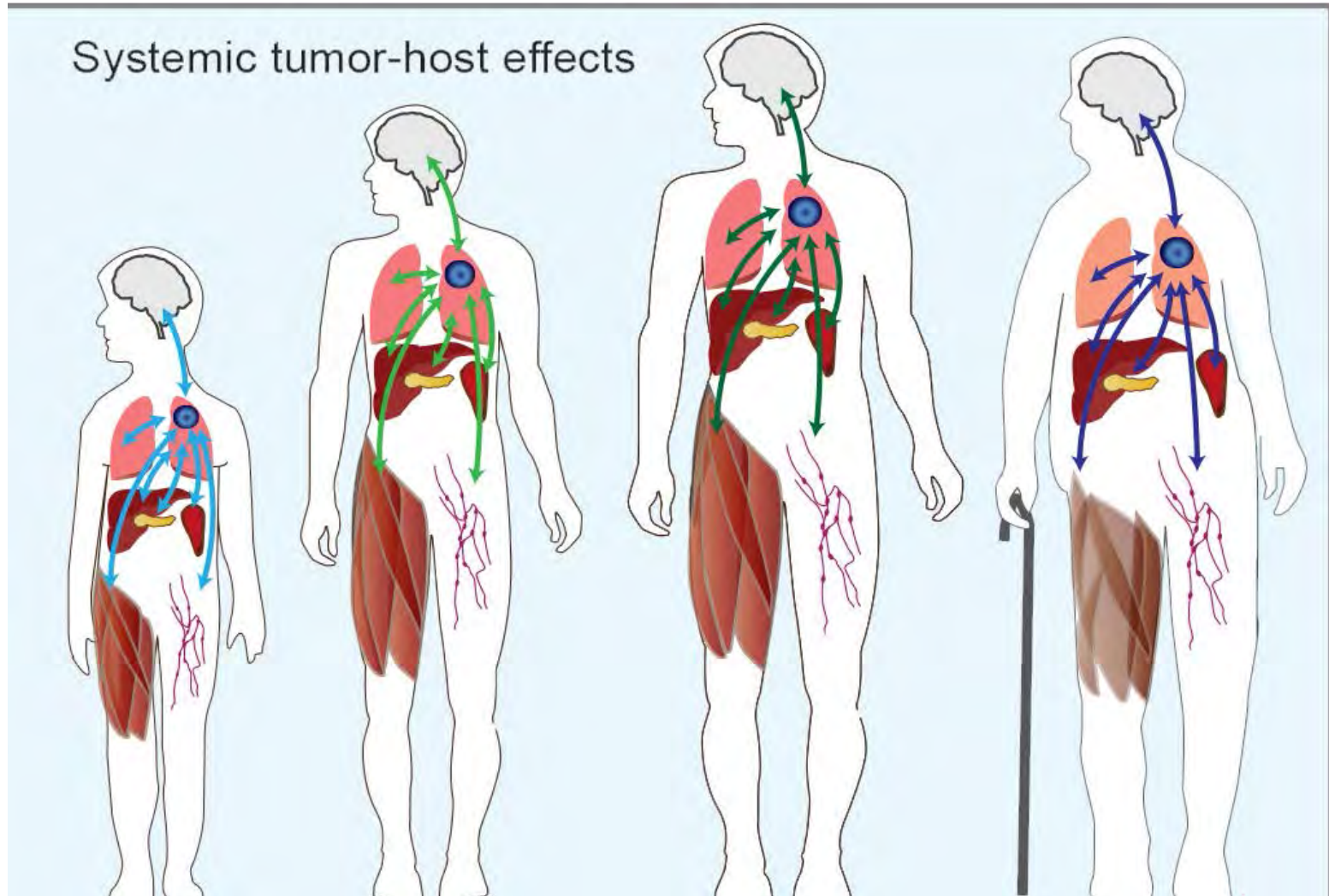
- TGFβ is known to play a context specific role in sustaining tissue homeostasis predominantly via transcriptional regulation of genes involved in differentiation, cell motility, proliferation, cell survival along with regulating immune responses during homeostasis and infection.

- 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

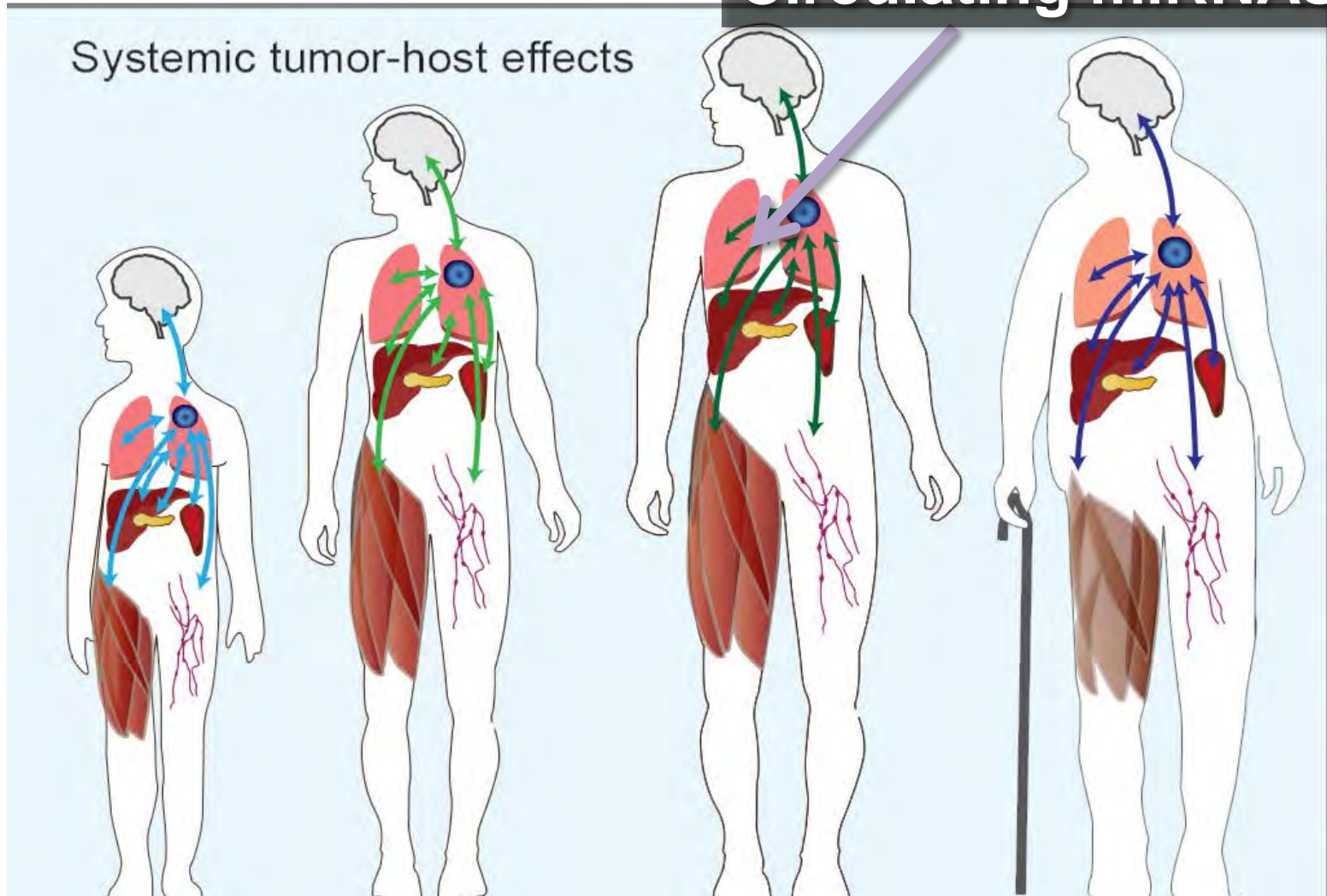




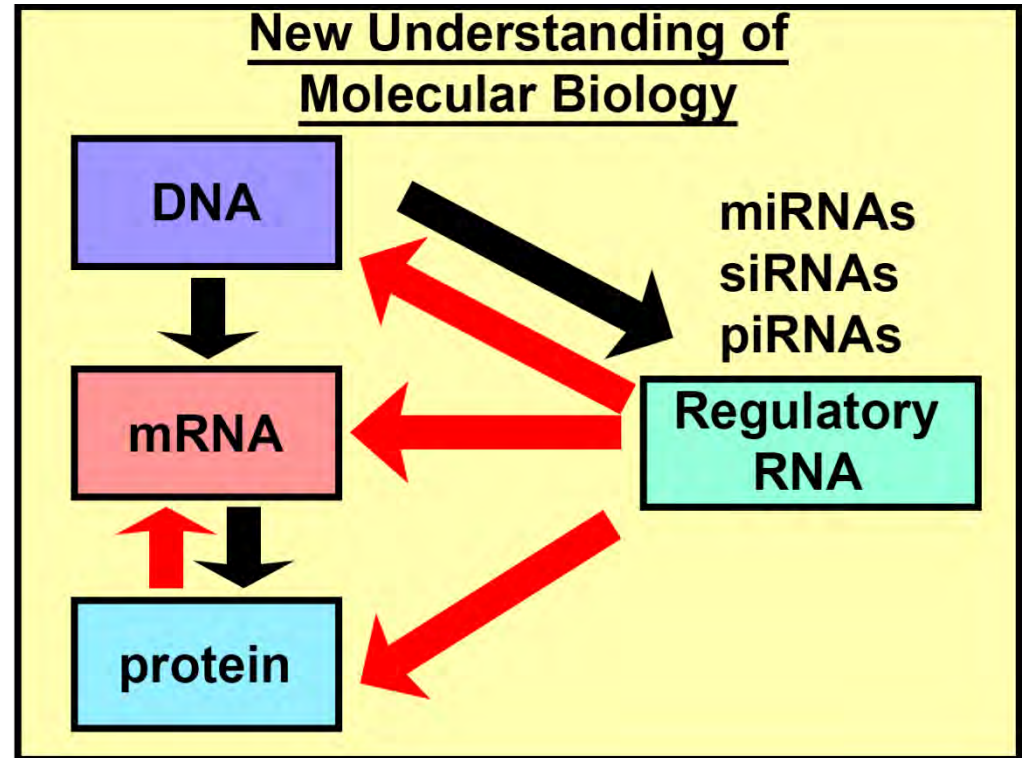
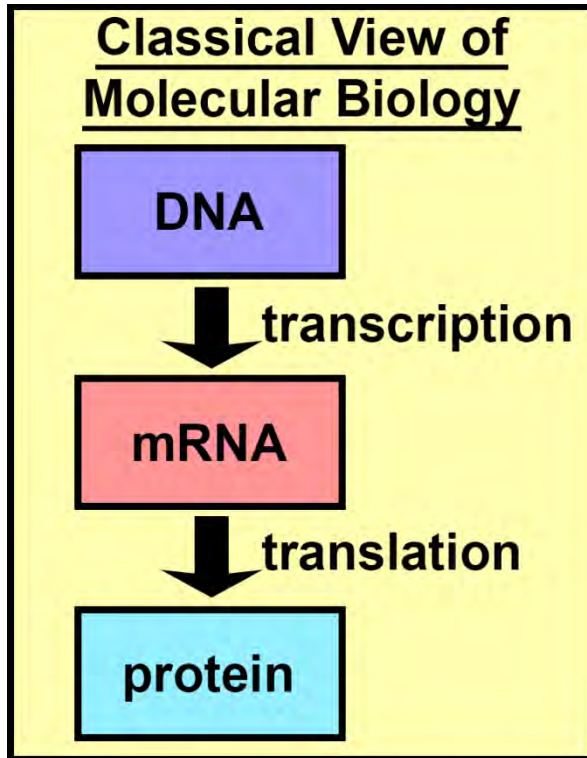


## Circulating miRNAs

Systemic tumor-host effects





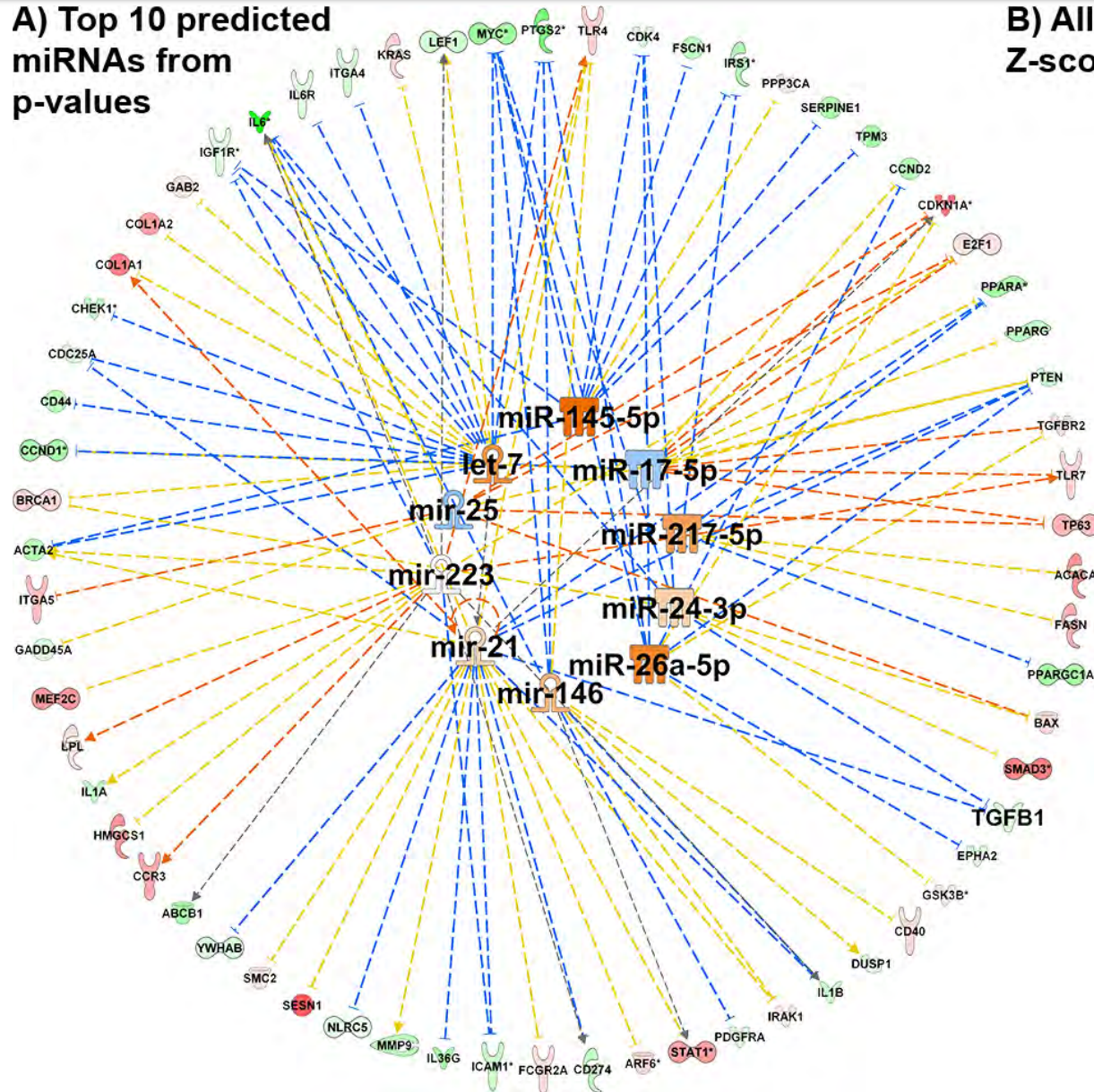


- A single miRNA has been estimated to regulate up to 500 mRNAs
- miRNAs are single-stranded RNA sequences, of about 22 nucleotides in length, processed from longer transcripts.
- miRNAs are important regulators that repress the translation of mRNA transcripts

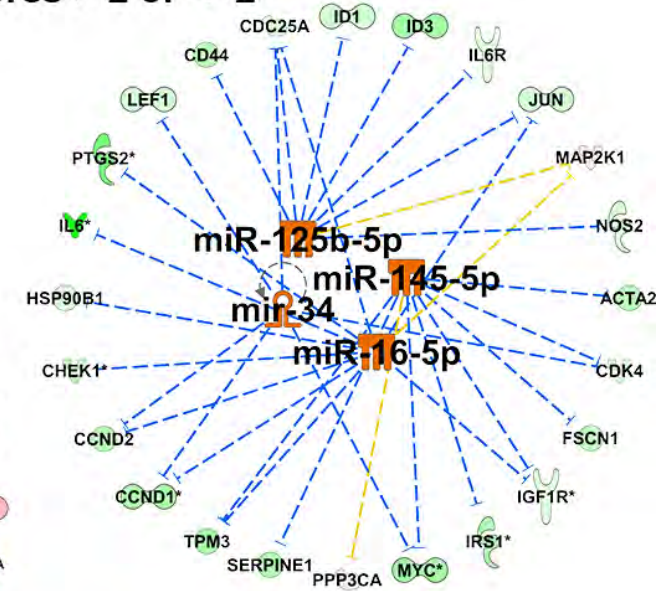
# Predicted miRNAs Involved with Microgravity Effects



**A) Top 10 predicted miRNAs from p-values**



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



- Upregulated
- Downregulated
- Predicted Activation
- Predicted Inhibition
- Leads to activation
- Leads to inhibition
- Findings inconsistent with state of downstream molecule
- Effect not predicted







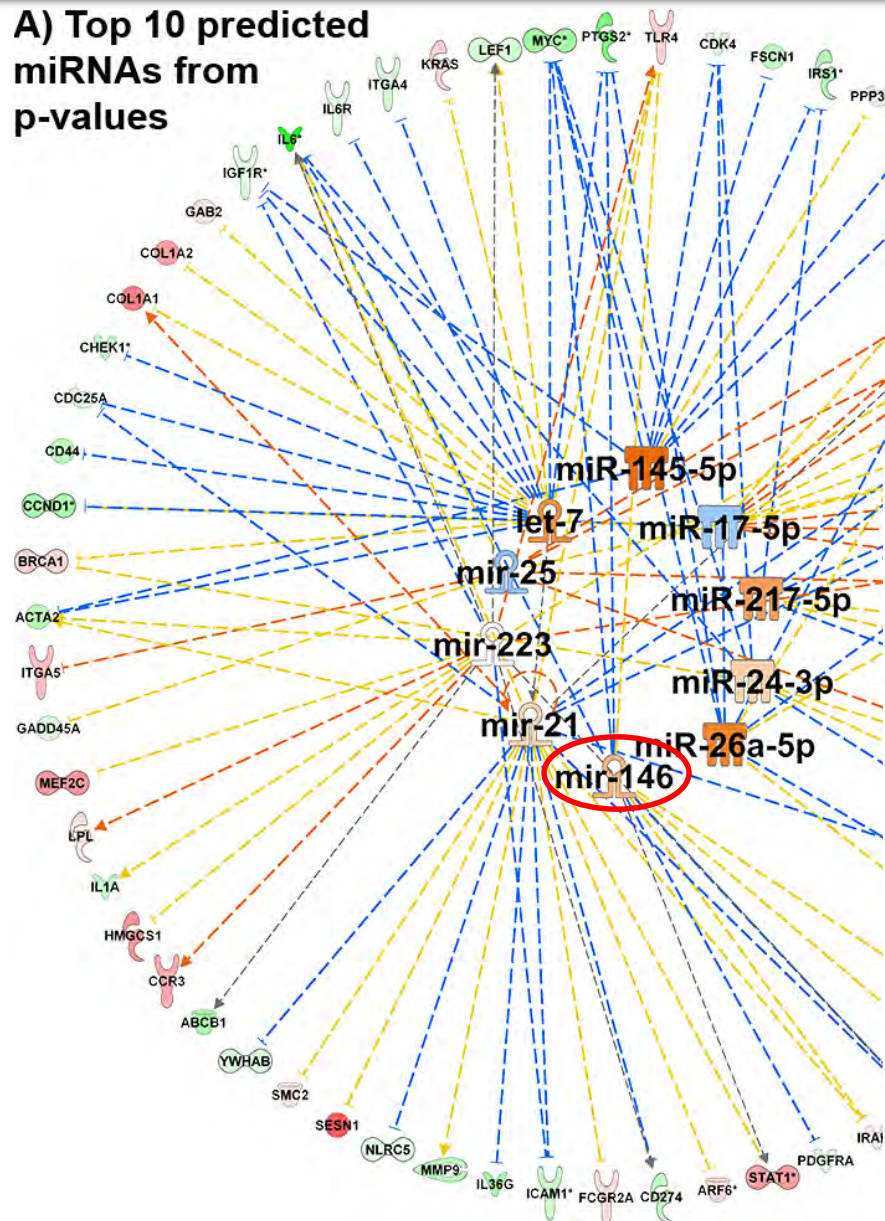




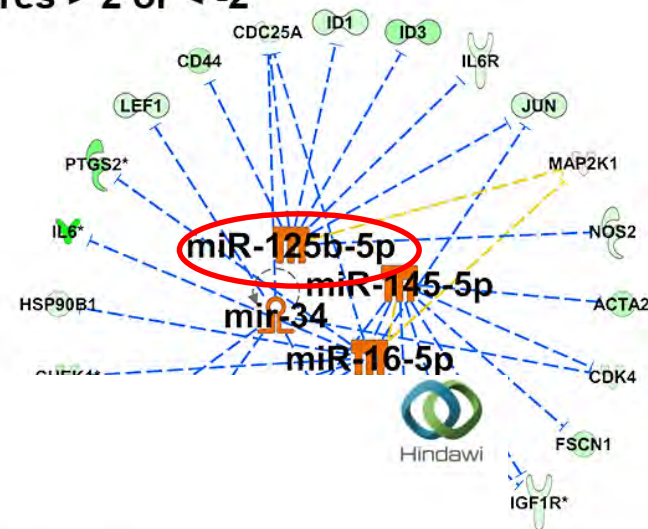
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BioMed Research International  
Volume 2014, Article ID 296747, 16 pages  
<http://dx.doi.org/10.1155/2014/296747>

Research Article

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

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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 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 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.

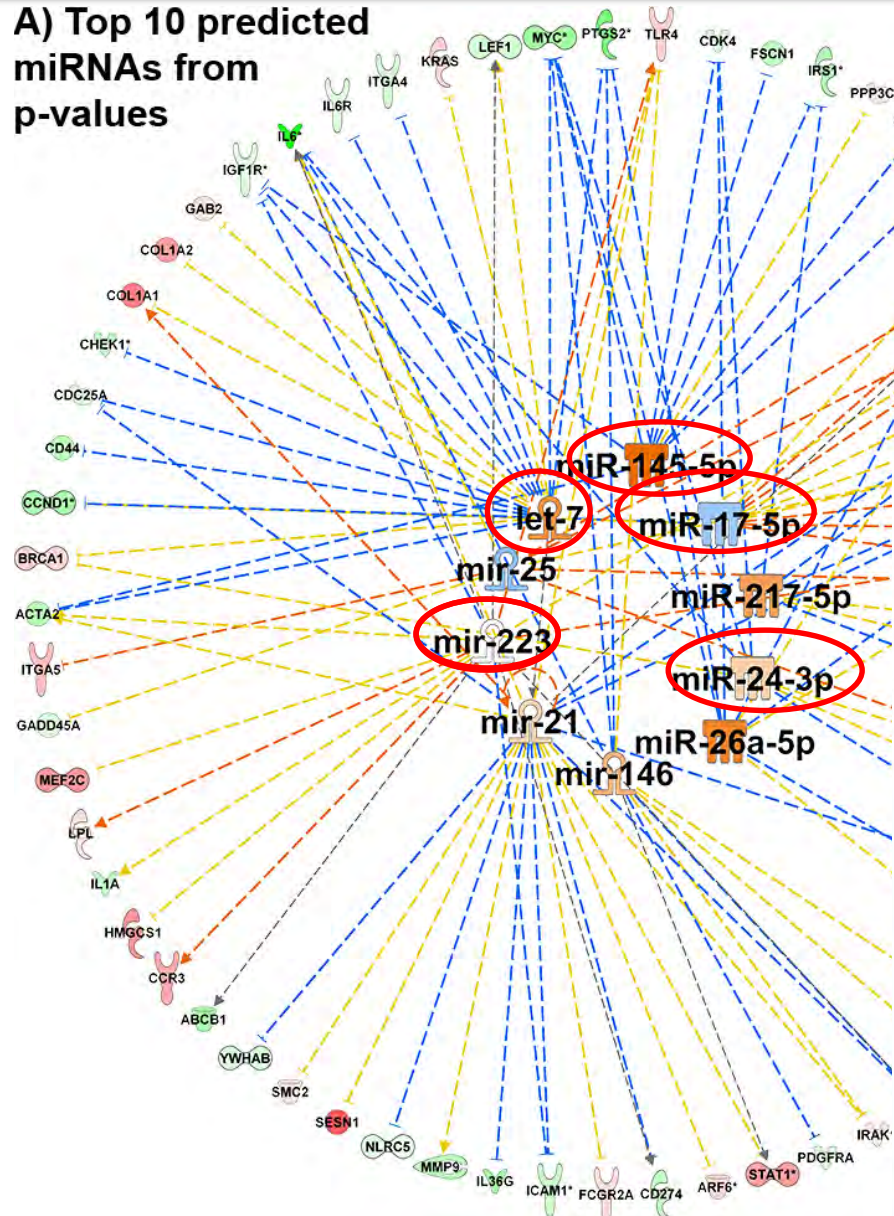
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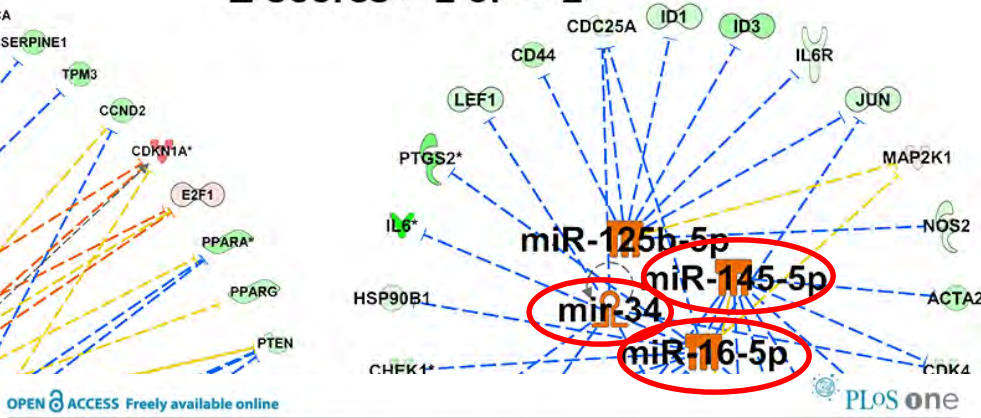
# Predicted miRNAs Involved with Microgravity Effects



A) Top 10 predicted miRNAs from p-values



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



OPEN ACCESS Freely available online

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

Cristina Girardi<sup>1\*</sup>, Cristiano De Pittà<sup>1\*</sup>, Silvia Casara<sup>1</sup>, Gabriele Sales<sup>1</sup>, Gerolamo Lanfranchi<sup>1</sup>, Lucia Celotti<sup>1,2</sup>, Maddalena Mognato<sup>1\*</sup>

<sup>1</sup>Dipartimento di Biologia, Università degli Studi di Padova, Padova, Italy, <sup>2</sup>Laboratori Nazionali di Legnaro, INFN, Padova, Italy

### 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  $\gamma$ -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 affect the DNA-damage response to IR in human PBL.

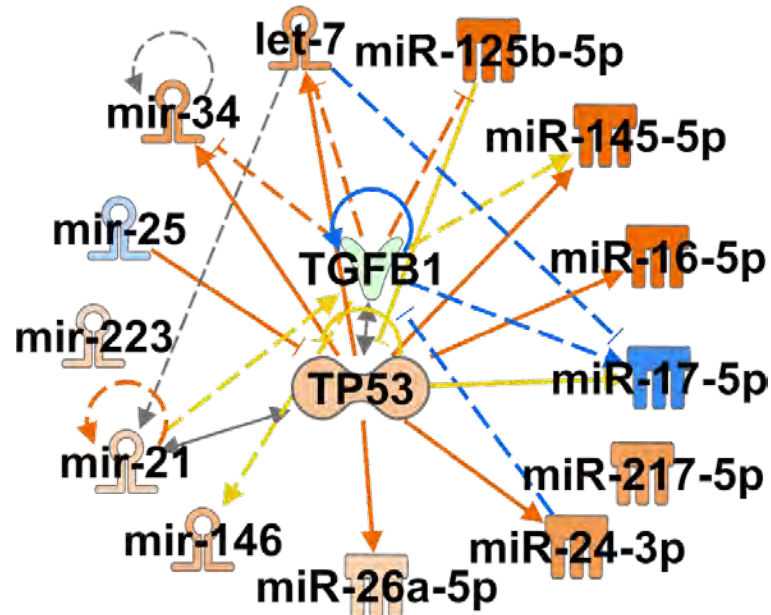
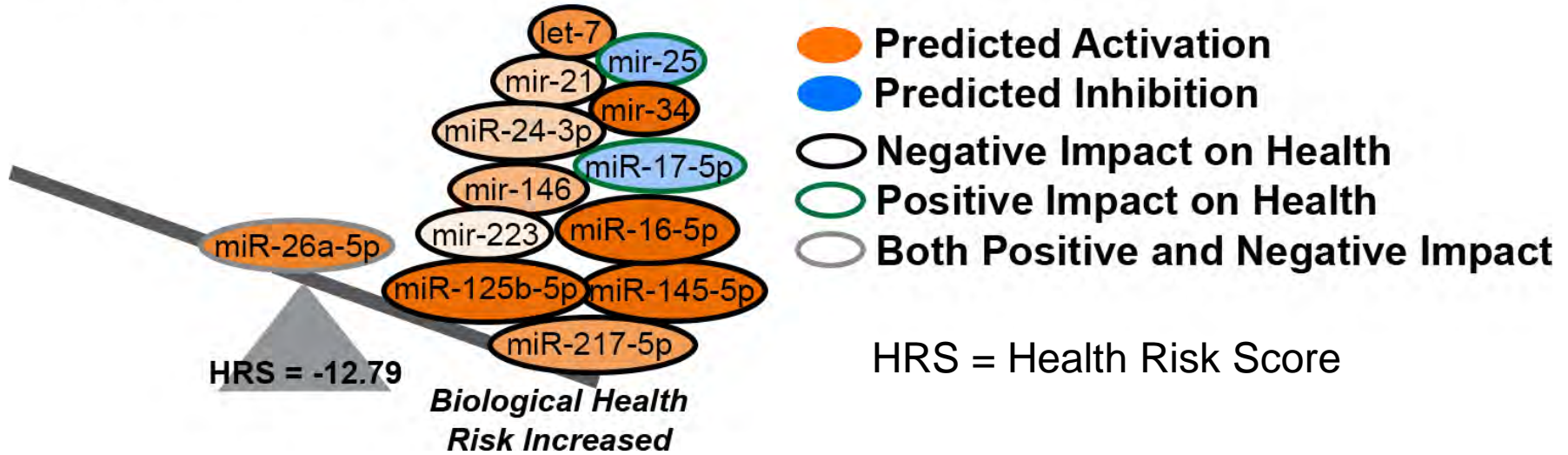




# Predicted miRNAs Involved with Microgravity Effects

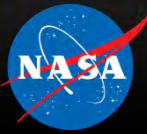


## Health Risk Due to miRNAs





# Predicted miRNAs Involved with Microgravity Effects

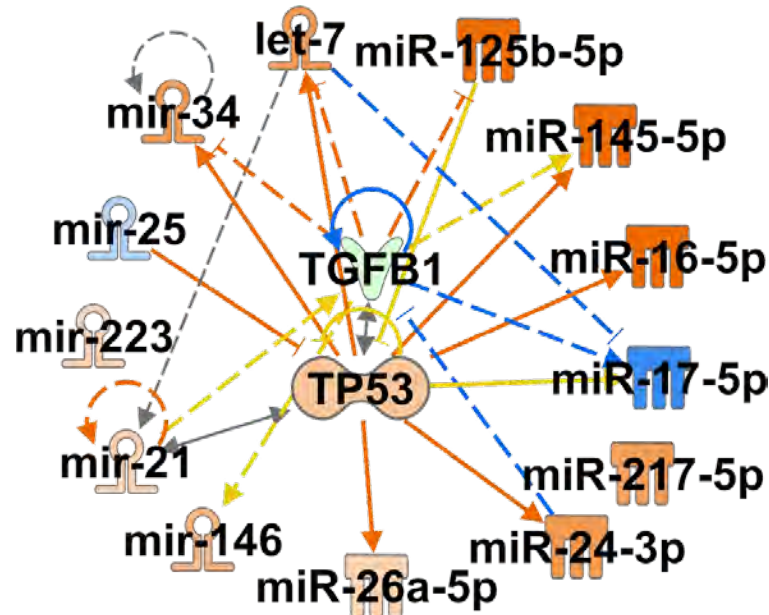


## Health Risk Due to miRNAs

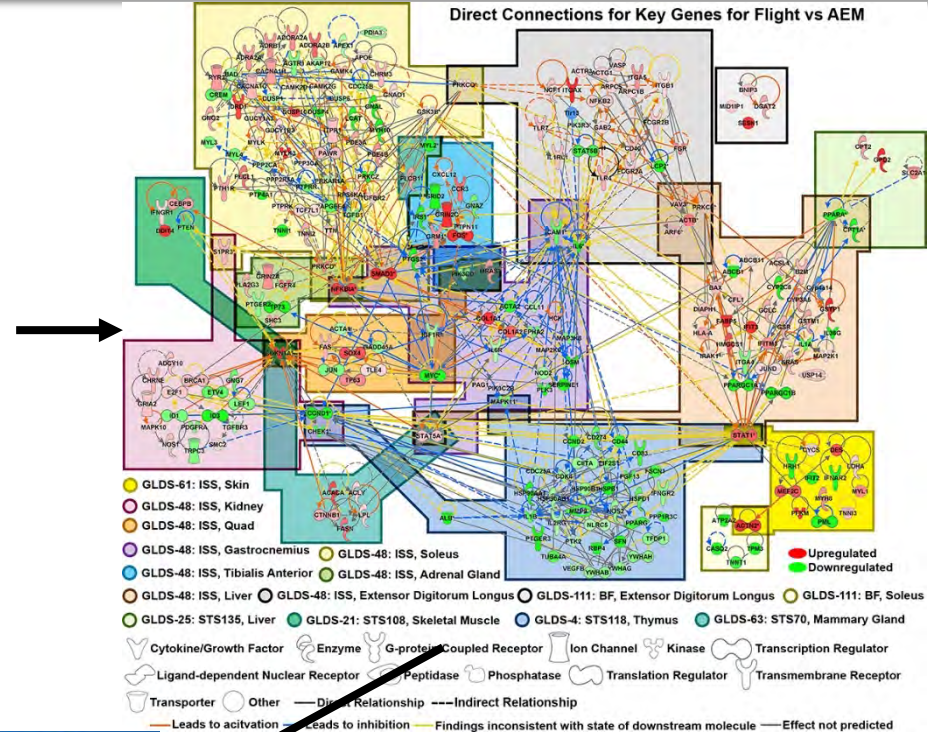
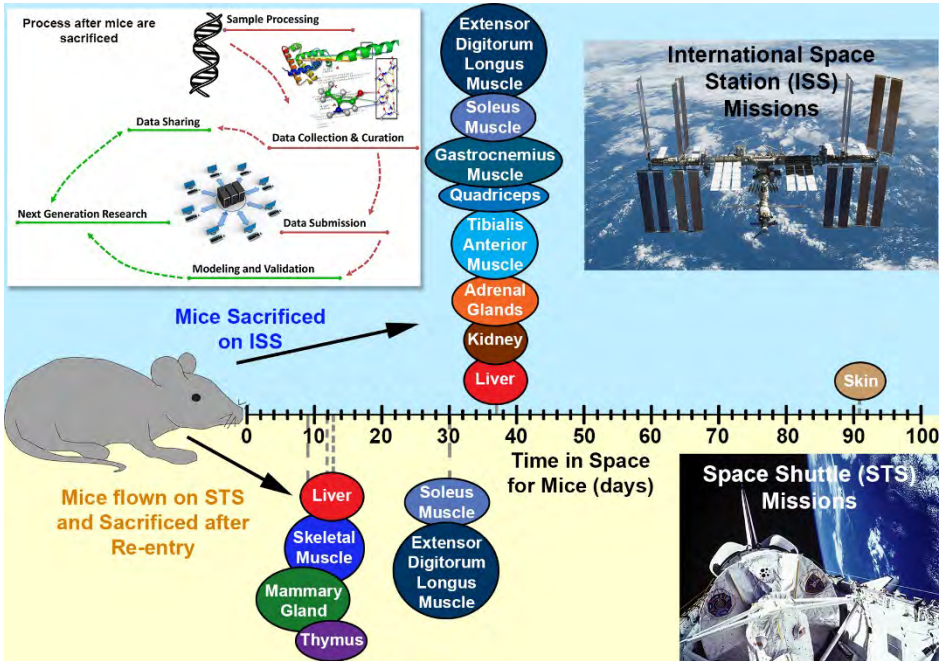


- A recent report showed that inactivation of p53 altered TGF- $\beta$  signaling, which ironically displayed both tumor-suppressive and pro-oncogenic functions. p53 functions to integrate crosstalk between Ras/MAPK and TGF- $\beta$  signaling via binding to Smad3, dislocating the Smad3/Smad4 complex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

*Biological Health  
Risk Increased*



# Using OpenTarget to Generate Countermeasures



**Open Targets Platform**

Find new targets for drug discovery

Search for a target or disease

Try: BRCA1, PI3K, Asthma, Inflammatory bowel disease

More than one target? Try our new batch search.

Data last updated December 2017

20,633 targets    2,261,782 associations    9,294 diseases    17 data sources

**Key Genes for individual tissues**





## Summary page for 13 targets

### Diseases associated

Therapeutic areas:

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	10	GRIN2C IRS1 CCR3 PLCB1 CXCL12 RAPGEF5 PTPN11 FOS GRID2 GRM1 ...
ischemia	2e-8	10	GRIN2C CXCL12 FOS GRM1 RAPGEF5 IRS1 PTPN11 PIK3CD PLCB1 MYL2 ...
kidney neoplasm	2e-7	10	PTPN11 CXCL12 PIK3CD MYL2 GRM1 IRS1 RAPGEF5 CCR3 PLCB1 GRIN2C ...
drug dependence	2e-7	10	GRIN2C RAPGEF5 PTPN11 PLCB1 CXCL12 MYL2 PIK3CD FOS IRS1 GRM1 ...
sign or symptom	2e-7	10	GRIN2C CXCL12 GRM1 PTPN11 PLCB1 FOS RAPGEF5 CCR3 IRS1 PIK3CD ...
sensory system disease	3e-7	10	PTPN11 GRIN2C GRID2 GRM1 FOS GNAZ CCR3 CXCL12 RAPGEF5 IRS1 ...
hypertension	3e-7	10	RAPGEF5 CXCL12 IRS1 FOS CCR3 PIK3CD GRM1 MYL2 PLCB1 PTPN11 ...
Rare genetic endocrine disease	4e-7	10	PTPN11 GRIN2C GRM1 GRID2 FOS CXCL12 GNAZ CCR3 RAPGEF5 PLCB1 ...
bronchial disease	6e-7	10	PIK3CD CXCL12 GRIN2C CCR3 PTPN11 RAPGEF5 FOS PLCB1 GNAZ GRM1 ...
whooping cough	8e-7	10	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	10	PTPN11, IRS1
Constitutive Signaling by Aber...	0.000099	10	PIK3CD, PTPN11, IRS1
PI3K/AKT Signaling in Cancer	0.00024	10	PIK3CD, PTPN11, IRS1
PI3P, PP2A and IER3 Regulate P...	0.00025	10	PIK3CD, PTPN11, IRS1
Negative regulation of the PI3...	0.00030	10	PIK3CD, PTPN11, IRS1
Signal Transduction	0.00078	10	PIK3CD, PTPN11, IRS1, CXCL12, CCR3, GNAZ, PLCB1, GRM1, GRIN2C
G alpha (i) signalling events	0.00092	10	CCR3, CXCL12, GNAZ, PLCB1
RET signaling	0.0010	10	PIK3CD, PTPN11
PLC beta mediated events	0.0012	10	GNAZ, PLCB1
GPCR downstream signalling	0.0012	10	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	6.78e-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

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

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

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

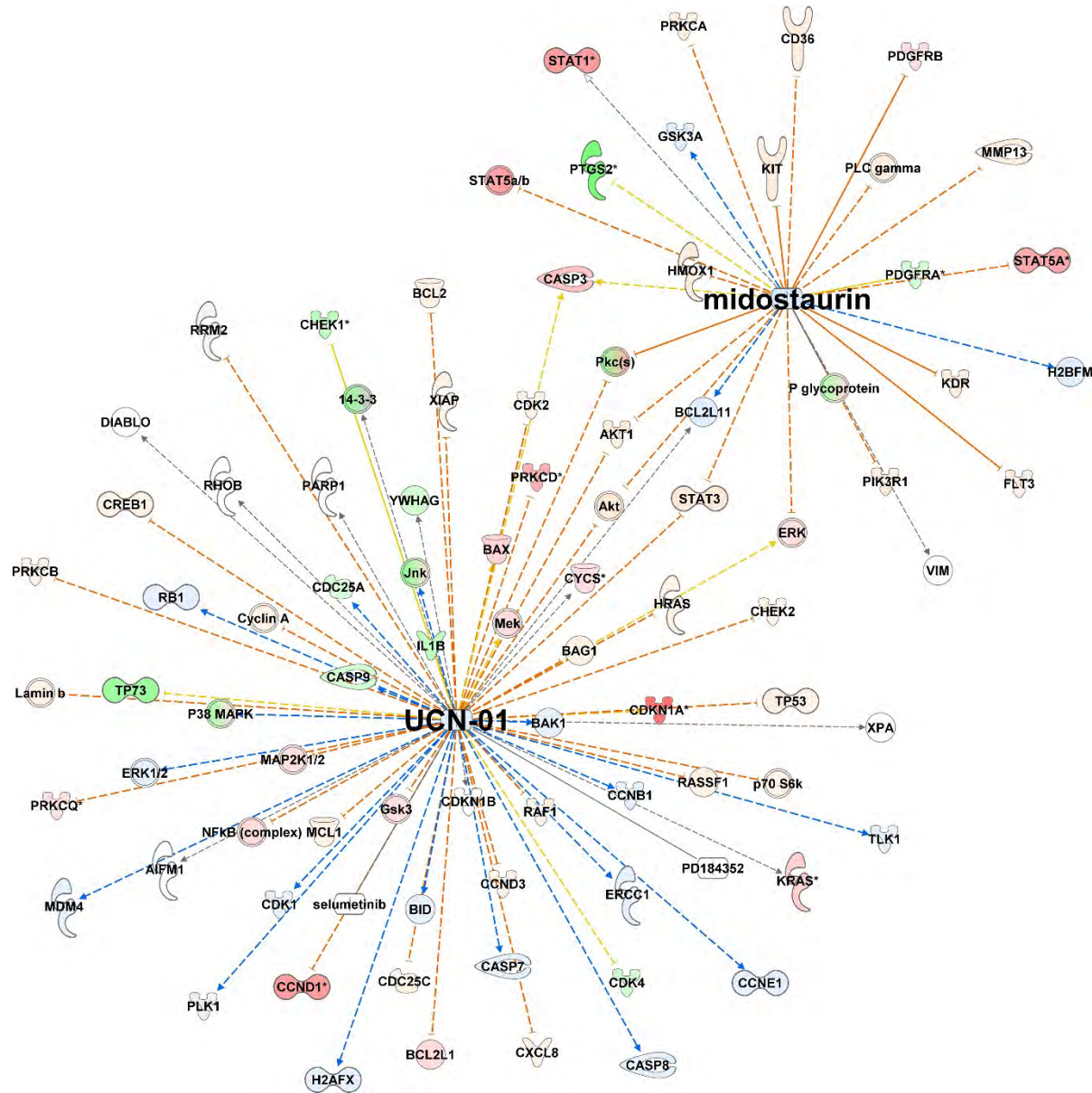
## 2. Find common drugs targets that exist between all the tissues





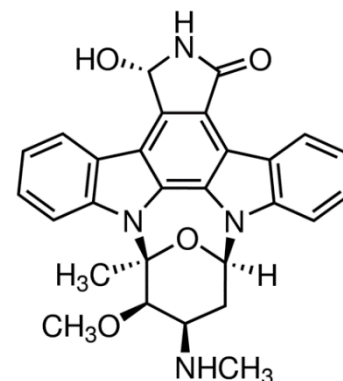
Drugs	Target	Common	Prediction	Status	Terminated
<b>UCN-01</b>	<b>PRKCQ</b>	<b>6</b>	<b>Y</b>	<b>Completed</b>	<b>N</b>
<b>MIDOSTAURIN</b>	<b>PRKCQ</b>	<b>5</b>	<b>Y</b>	<b>Active. Recruiting</b>	<b>N</b>
DACTOLISIB	PIK3CD	5	Y	Withdrawn, Terminated, Completed	Y
PICTILISIB	PIK3CD	5	Y	Completed, terminated, 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
SOTRASTAUIN	PRKCQ	4	N	Terminated, completed, recruiting	Y

# Two possible drug candidate for countermeasures against Spaceflight



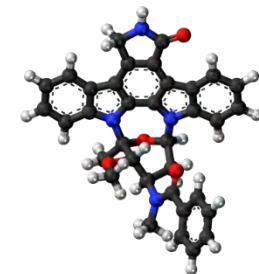


- Also known as: 7-hydroxystaurosporine
- Inhibits many phosphokinases, including the serine/threonine kinase AKT, calcium-dependent protein kinase C, and cyclin-dependent kinases
  - arrests tumor cells in the G1/S of the cell cycle and prevents nucleotide excision repair by inhibiting the G2 checkpoint kinase chk1, resulting in apoptosis
  - Phase 1 and 2 clinical trials with drug for various cancers (information available on [ClinicalTrials.gov](http://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





- (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), PDGFR $\alpha/\beta$ , 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)**

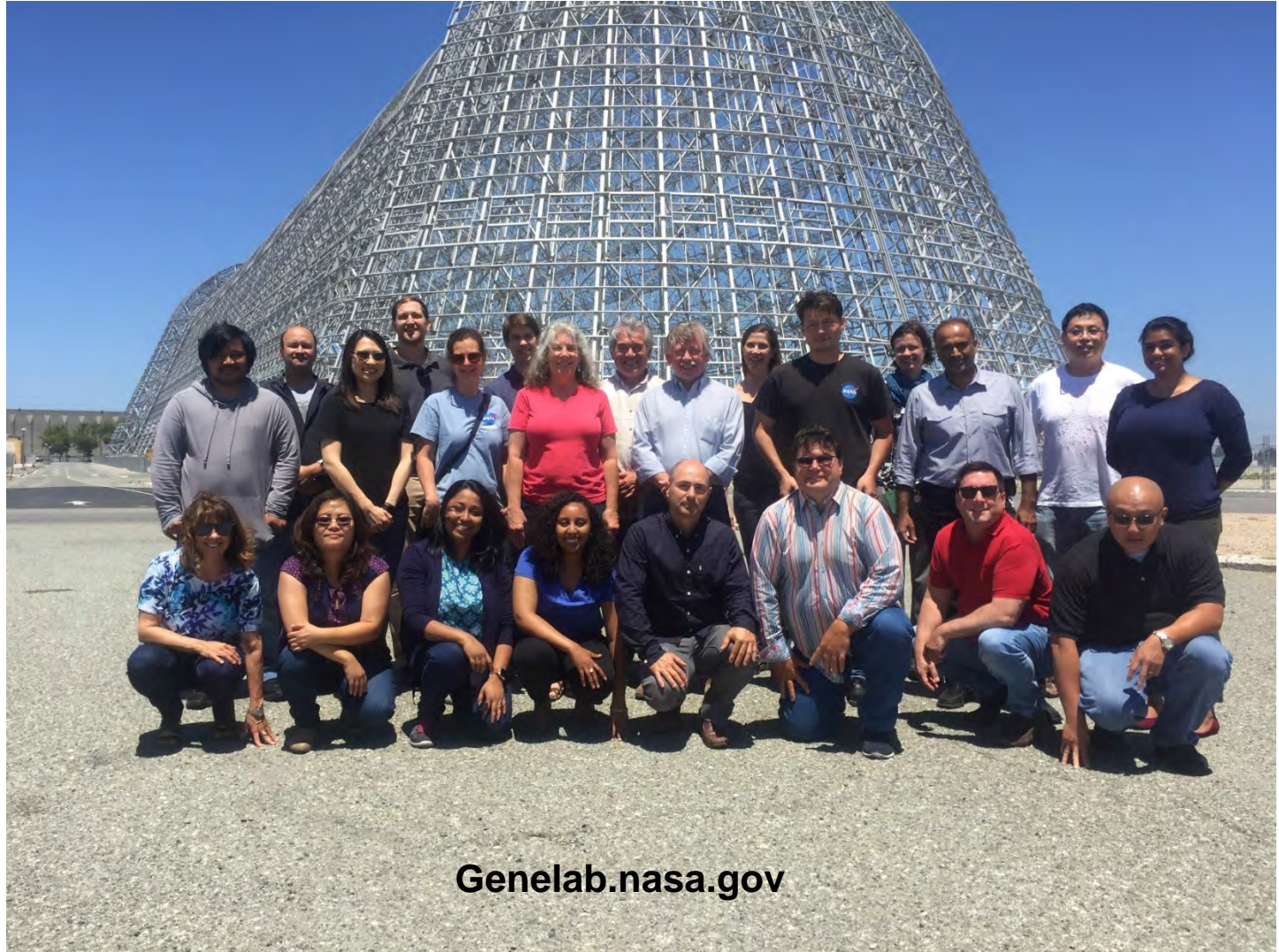






- Both UCN-01 and midostaurin inhibit cytosolic PKC
  - Jirousek & Goekjian, Expert Opin Investig Drugs. 2001 Dec;10(12):2117-40
- Can these anti-cancer drugs be applied to the negative health effects associated with long term space missions?
  - Midostaurin has been shown to improve Bone Loss effects
    - 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???