NASA GeneLab Project: Bridging Space Radiation Omics with Ground Studies

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ABSTRACT

Accurate assessment of risk factors for long-term space missions is critical for human space exploration: therefore it is essential to have a detailed understanding of the biological effects on humans living and working in deep space. Ionizing radiation from Galactic Cosmic Rays (GCR) is one of the major risk factors factor that will impact health of astronauts on extended missions outside the protective effects of the Earth's magnetic field. Currently there are gaps in our knowledge of the health risks associated with chronic low dose, low dose rate ionizing radiation, specifically ions associated with high (H) atomic number (Z) and energy (E). The GeneLab project (genelab.nasa.gov) aims to provide a detailed library of Omics datasets associated with biological samples exposed to HZE. The GeneLab Data System (GLDS) currently includes datasets from both spaceflight and ground-based studies, a majority of which involve exposure to ionizing radiation. In addition to detailed information for ground-based studies, we are in the process of adding detailed, curated dosimetry information for spaceflight missions. GeneLab is the first comprehensive Omics database for space related research from which an investigator can generate hypotheses to direct future experiments utilizing both ground and space biological radiation data. In addition to previously acquired data, the GLDS is continually expanding as Omics related data are generated by the space life sciences community. Here we provide a brief summary of space radiation related data available at GeneLab.

INTRODUCTION

The radiation biology community has a need for data to assess the impact of exposure to chronic low dose, low dose-rate highly-ionizing radiation. Acquisition of such data for animals or cell cultures is possible only at a small number of facilities world-wide (*1-7*).

NASA's GeneLab Data Systems (GLDS) (genelab.nasa.gov) have included a steadily growing library of Omics datasets with associated detailed curated dosimetry information since 2015 (**Fig 1**). This repository is helping bridge the gap between irradiation studies performed on earth and biological experiments conducted in space since the early 1990's. In this commentary, we provide a quick summary of the content of the repository in terms of species, radiation quality and dosimetry method, as well as the types of omics data being collected. We also include a comparison of dose and dose rates for samples used in ground studies versus spaceflight specimens.

Most of these studies were funded by the NASA Human Research Program, which has supported

numerous ground-based studies with high-LET radiation generated at the NASA Space Radiation Laboratory (NSRL) (*3*); the DOE low dose program providing primarily low-LET data; and the NASA Space Biology Program providing primarily data from specimens flown in space.

There is a diverse set of space related Omics data available on GeneLab. A total of 154 datasets from space related Omics research are currently available. These entries include data from a wide variety of different organisms including: rodents, human cells, plants, microbes, invertebrates, drosophila, and fish (**Fig 2A**). 53% of the datasets were gathered from spaceflight experiments and 47% from ground related space studies (which includes radiation studies done at NSRL) (**Fig 2B**).

GeneLab currently hosts datasets employing with a variety of Omics assay objectives (**Fig 2C**). with the majority being transcription profiling, and a majority of these (77%) using oligonucleotide microarray techniques, but a growing fraction (currently 23%) employing RNA sequencing techniques. We strongly encourage readers with published or unpublished Omics data related to space research to join our effort by contributing their datasets (instructions for which are on the web site).

RADIATION GROUND STUDIES CURRENTLY IN GENELAB

There are a total of 69 GeneLab datasets which are ground (earth-based) space research with 28 datasets specifically related to radiation work and the majority of these were radiation experiments done at NSRL (**Fig 3A**) (*3*). Investigations of simulated microgravity comprise the rest of the ground experiments (*8-16*), together with a small number studying atmospheric pressure (*17*), clinical treatment and exercise/nutrition (*18*), freezing (*19*), genotype (*20-27*), hypergravity (*8, 28-30*), sample collection protocols (*31*), temperature (*8, 32, 33*), or timepoints (*34*). The majority of the ground-based radiation experiments were done using mice (**Fig 3B**). *In vitro* experiments involving human tissues make up most of the rest the experiments with one study each of microbes, plants, and rats. Gamma exposure experiments comprise the majority of the radiation datasets available in the repository (**Fig 3C**). These datasets were mainly done by investigators for comparisons to HZE radiation. Proton and ^{56}Fe radiation experiments (*27, 35-41*) comprise the majority of simulated space radiation-related datasets available on GeneLab with a few experiments related to ^{16}O (*42*), ^{12}C (*43*), ^{28}Si (*44*), and neutrons (*45*) (**Fig 3C**).

The GLDS also contains extensive information on parameters related to the ionizing radiation experiments/datasets. Most datasets include the following information: ion, total dose, dose rate, LET, and energies associated with the radiation. The distribution of dose rates vs total dose (**Fig 4A**) illustrates the wide range of radiation-related datasets available to the public ranging from low doses (0.1Gy) to high doses (30Gy) with dose rates ranging from 0.001Gy/min to 5.66Gy/min. Typically, microbes and plants were exposed to higher total doses, while the majority of the rodent research used doses between 0.1 Gy and 3 Gy (with some gamma experiments done at higher doses). The linear energy transfer (LET) for these experiments ranged from 0.24 keV/µm to 150 keV/µm (**Fig 4B**). Since GeneLab relies on the investigators to provide these metadata, and not all datasets are complete: there are 13 datasets with missing dose rate information. It is critical for all investigators submitting data to GeneLab to provide as much information as possible about irradiation conditions.

SPACE RADIATION DOSIMETRY

GeneLab has recently begun documenting the absorbed radiation dose received by samples flown in space for experiments primarily testing the effects of microgravity, and, only incidentally examining space-radiation effects. To date OMICS data is available on GeneLab which includes experiments conducted on three types of vehicles that have carried samples in space: the "Space Shuttle" (or Space Transportation System, STS), free flying satellites (BION, FOTON) (*46*, *47*), and the International Space Station (ISS). The dosimetry measuring techniques varied from vehicle to vehicle and, for ISS, from module to module. Because the primary purpose of on-board dosimetry on crewed vehicles is monitoring astronaut health and, on free flyers, whole-environmental monitoring, biology experiments typically have not flown with "dedicated" dosimeters (i.e., dosimeters integrated into experiment platform housing). Therefore, doses to which study samples are exposed frequently must be interpolated and/or extrapolated from the closest dosimeters. Both passive and active dosimetry have been used on these vehicles. For STS, 3 passive dosimeter packages were fixed in locations on the shuttle middeck, where biological samples were located (**Fig 5A**). In the case of BION (*46, 47*) (**Fig 5B**) and ISS, both passive (thermoluminescent dosimeters, TLD, plastic nuclear track detectors, PNTD) and active (solid state, tissue equivalent proportional counters (TEPC)) were used. Two qualities of radiation are considered: low-LET (photons and electrons) and high-LET (charged nuclei). For passive dosimeters, TLD are sensitive to low-LET charged particles (< 10 keV/µm) and PNTD to high-LET (> 10 keV/µm). Active dosimeters are sensitive to a wider range in LET and, depending on the detector, can provide time resolution, LET spectra and some particle identification. By integrating the dose from the time-resolved data over the duration of the experiment, the total absorbed dose can be calculated. Depending on the configuration of dosimeters in the vicinity of the samples, absorbed dose may be reported as averaged with other detectors, or individually.

Taking into account the wide variety of dosimetry scenarios, we have chosen to report the "lowest common denominator" data: the data that are common to most if not all dosimeters, whether passive or active. Therefore, each omics dataset in the GeneLab repository with samples flown in space has a corresponding metadata set which includes the exposure duration, and the average, minimum and maximum absorbed dose received, broken out into low LET and high LET charged particles (when LET resolution is available). The duration of the exposure is defined as the time a sample was in space and biologically active, *i.e.* when the sample has returned to Earth or when it is chemically fixed or frozen in space.

It is important to note that the absorbed doses we provide in these metadata are an approximation, due to several limiting factors. First, there is known contribution of sensitivity in charge and LET for each detector being used. For example, even though TLDs detect low-LET radiation, the detected dose also includes some contribution from charged nuclei depending on the charge and speed of the nuclei traversing the detector. Similarly, active detectors even if tuned to specific energies and charges can still have traces dose from low-LET particles and neutrons. Second, reported dosimetry does not take into account the additional shielding provided by the sample enclosure. For low energy particles or low-LET this hardware could have significant attenuating effect and would be unique for each mission and experiment. Therefore, in addition to the radiation metadata for individual dataset, GeneLab also reports dosimetry measurements for all detectors available for each mission, in a "reference information" section of the GeneLab database. A glance at these data show that a wide range of total absorbed dose over the various spaceflight experimental environments (**Fig 5C**). For example, rodents flown on the BION-M1 missions (*48-50*) obtained the largest dose of ionizing radiation (30.2 mGy), while the rodents on-board STS missions only received in the range of 1 mGy to 4.7 mGy. GeneLab is currently assembling all the

dosimetry information for the ISS related datasets and will have it available in the near future. Our aim is that by providing these data, we will facilitate more detailed analyses of these kinds of environments by other investigators.

SUMMARY

The goal of GeneLab is to provide users with a data repository and analytical and visualization tools for molecular signals relating to a host of factors known to influence biological response, including radiation dose, dose rate, and quality. Standardizing the dosimetry information in the entire repository is an essential first step towards accomplishing this task and we hope the radiation biology community will be excited about this new source of information and will visit the database often.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the NASA GeneLab team.

CONFLICTS OF INTEREST

All authors declare no competing financial interests and conflict of interest with the data and information in this manuscript.

CONTRIBUTIONS

A.B. Analyzed all data, made figures, and wrote manuscript. Y.K. did radiation data acquisition and annotation. D.B. provided exchange of ideas and edited the manuscript. S.G. provided exchange of ideas and edited the manuscript. J.M. acquired radiation dosimetry information, provided exchange of ideas, and edited the manuscript. S.V.C. wrote manuscript, provided exchange of ideas, and edited the manuscript.

FUNDING

Research funding was provided by the GeneLab Project at NASA Ames Research Center, through NASA's Space Biology Program in the Division of Space Life and Physical Sciences Research and Applications (SLPSRA). Any use of trade names is for descriptive purposes only and does not imply endorsement by the US Government.

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FIGURE LEGENDS

Figure 1. The number of datasets on GeneLab over time. A scatter plot representing the number of datasets on GeneLab (left y-axis) that increase over time starting from the creation of GeneLab in 2014. The right axis and red data points represent the number terrabytes (TB) per study for the datasets on GeneLab. The lines represent exponential fits to the data.

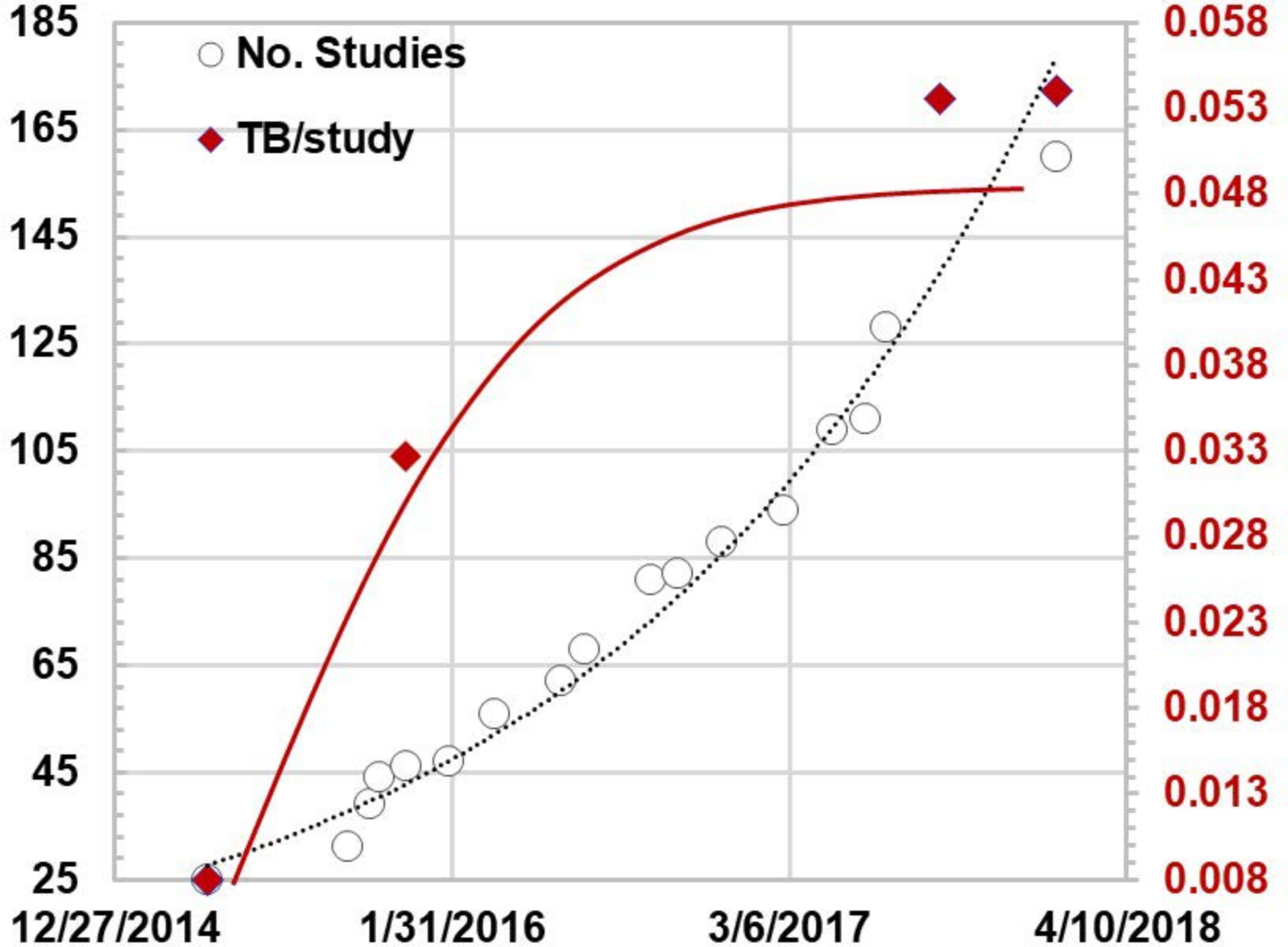
Figure 2. The type of data that is available on GeneLab. A) The distribution of organism datasets available on GeneLab. **B)** The representation of ground and spaceflight experiments on GeneLab. **C)** The types of Omics assays that are available on GeneLab.

Figure 3. The distribution of ground studies on GeneLab. A) The type of data on GeneLab associated with ground studies. **B)** The organism distribution of radiation ground study datasets available on GeneLab. **C)** The number of datasets associated with different ionizing radiation available on GeneLab.

Figure 4. Distribution dose rate, dose, and LET for ionizing radiation ground studies on GeneLab. A) Distribution of dose rate (Gy/min) vs total dose (Gy) for all radiation ground studies available on GeneLab. Some GeneLab radiation datasets have missing dose rate information due to the lack of information available from the investigator. **B)** LET (KeV/μm) vs Total Dose (Gy) for all radiation ground study datasets on GeneLab.

Figure 5. Summary of spaceflight datasets available on GeneLab. A) Image of the placement of the dosimeters on the space shuttle missions. **B)** Image of placement of dosimeters on BION-M1 mission. **C)** Distribution of total dose absorbed (mGy) per spaceflight mission for each

organism. This includes both space shuttle missions (STS) and BION-M1 missions. The mission number and time in space is provided next to each datapoint.


No. Studies
TB/study
185
165
145
125
105
85
65
45
25
0.058
0.053
0.048
0.043
0.038
0.033
0.028
0.023
0.018
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12/27/2014
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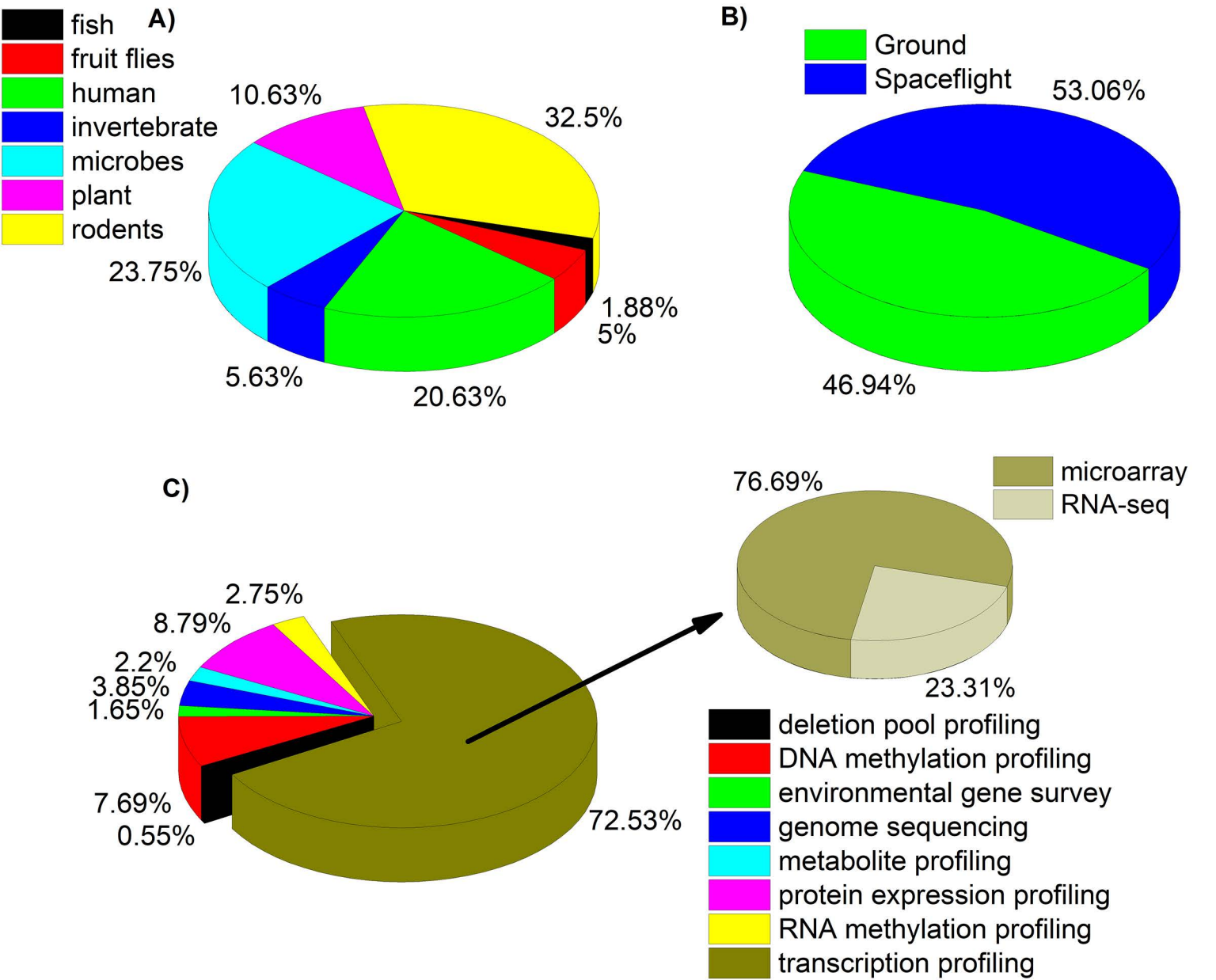
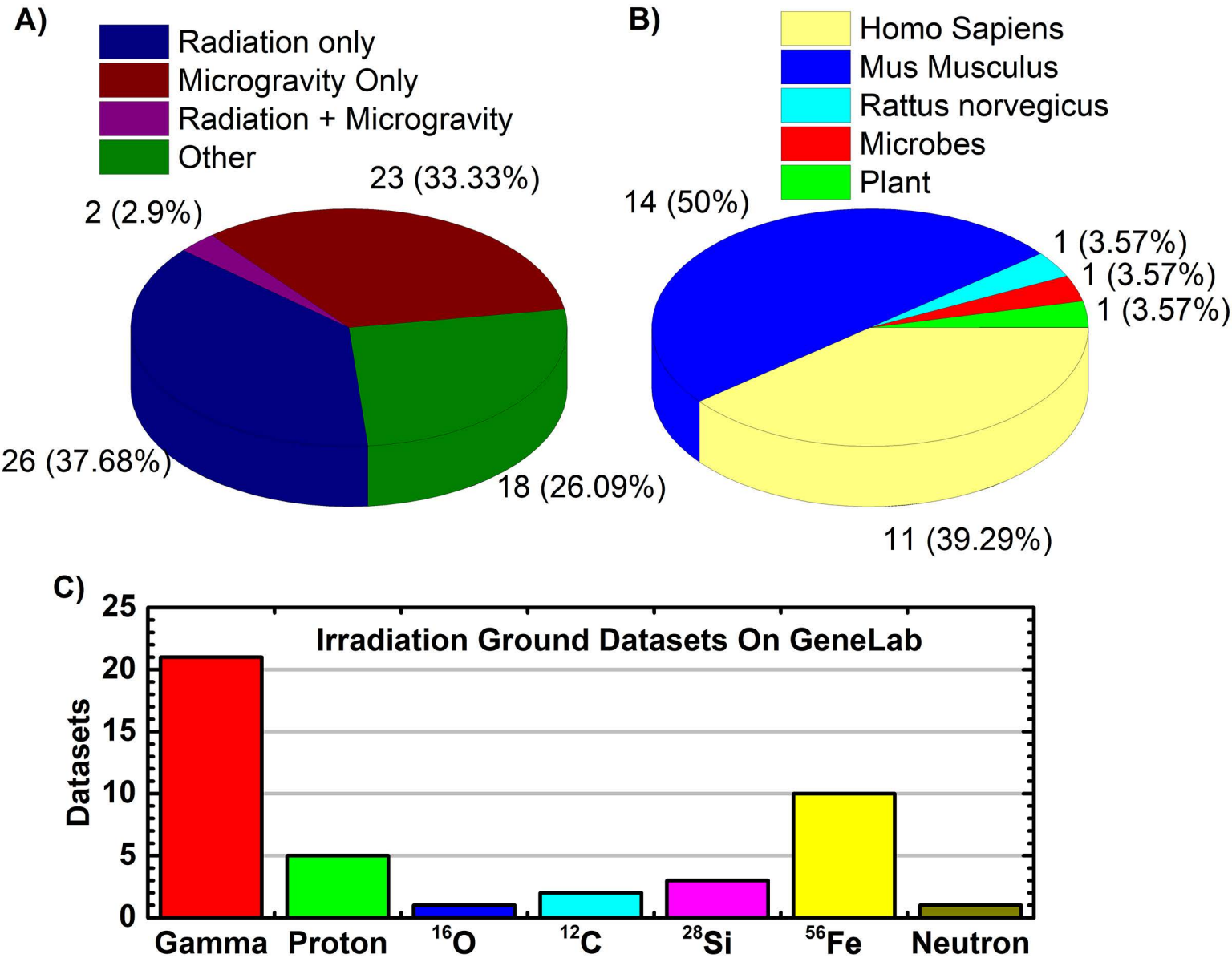
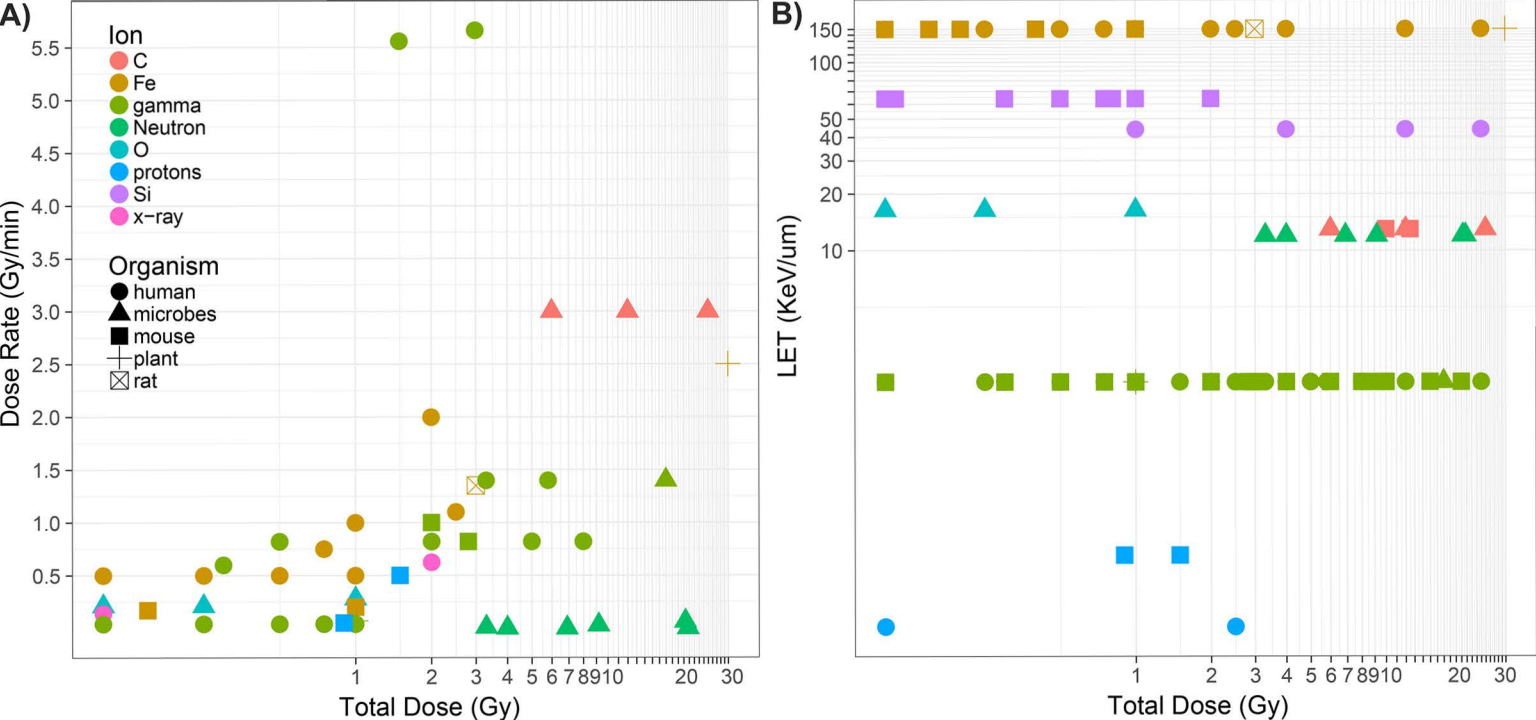
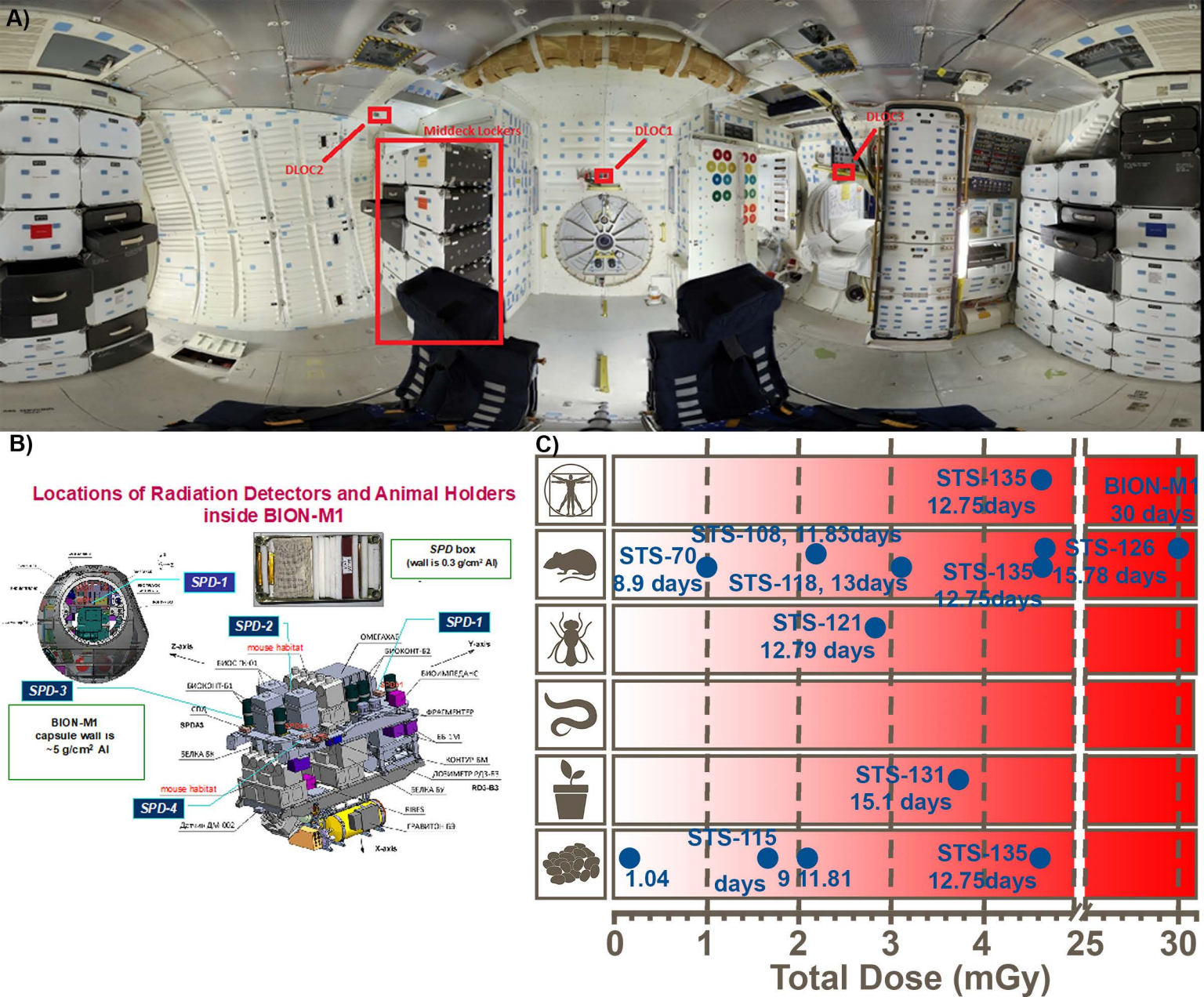
3/6/2017
4/10/2018


A)
fish
fruit flies
human
invertebrate
microbes
plant
rodents
10.63%
32.5%
23.75%
1.88%
5%
5.63%
20.63%
B)
Ground
Spaceflight
53.06%
46.94%
C)
2.75%
8.79%
2.2%
3.85%
1.65%
7.69%
0.55%
72.53%
76.69%
23.31%
microarray
RNA-seq
deletion pool profiling
DNA methylation profiling
environmental gene survey
genome sequencing
metabolite profiling
protein expression profiling
RNA methylation profiling
transcription profiling


A)
Radiation only
Microgravity Only
Radiation + Microgravity
Other
23 (33.33%)
2 (2.9%)
26 (37.68%)
18 (26.09%)
B)
Homo Sapiens
Mus Musculus
Rattus norvegicus
Microbes
Plant
14 (50%)
1 (3.57%)
1 (3.57%)
1 (3.57%)
11 (39.29%)
C)
Irradiation Ground Datasets On GeneLab
Datasets
25
20
15
10
5
0
Gamma
Proton
16O
12C
28Si
56Fe
Neutron


A)
Ion
C
Fe
gamma
Neutron
O
protons
Si
x−ray
Organism
human
microbes
mouse
plant
rat
Dose Rate (Gy/min)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
1
2
3
4
5
6
7
8
9
10
20
30
Total Dose (Gy)
B)
LET (KeV/um)
150
100
50
40
30
20
10
1
2
3
4
5
6
7
8
9
10
20
30
Total Dose (Gy)


A)
Middeck Lockers
DLOC1
DLOC2
DLOC3
B)
Locations of Radiation Detectors and Animal Holders inside BION-M1
SPD box (wall is 0.3 g/cm² Al)
SPD-1
SPD-2
SPD-3
SPD-4
BION-M1 capsule wall is ~5 g/cm² Al
mouse habitat
mouse habitat
Z-axis
Y-axis
X-axis
C)
STS-135 12.75days
BION-M1 30 days
STS-108, 11.83days
STS-70 8.9 days
STS-118, 13days
STS-126 15.78 days
STS-135 12.75days
STS-121 12.79 days
STS-131 15.1 days
STS-115 11.81 days
1.04
STS-135 12.75days
0
1
2
3
4
25
30
Total Dose (mGy)