The REPAIR project: Investigating the biological effects of sub-natural background radiation exposure

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REPAIR Collaboration members

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T.C. Tai	Research Faculty	NOSM
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Sergio Santa Maria	Research Scientist	NASA Ames
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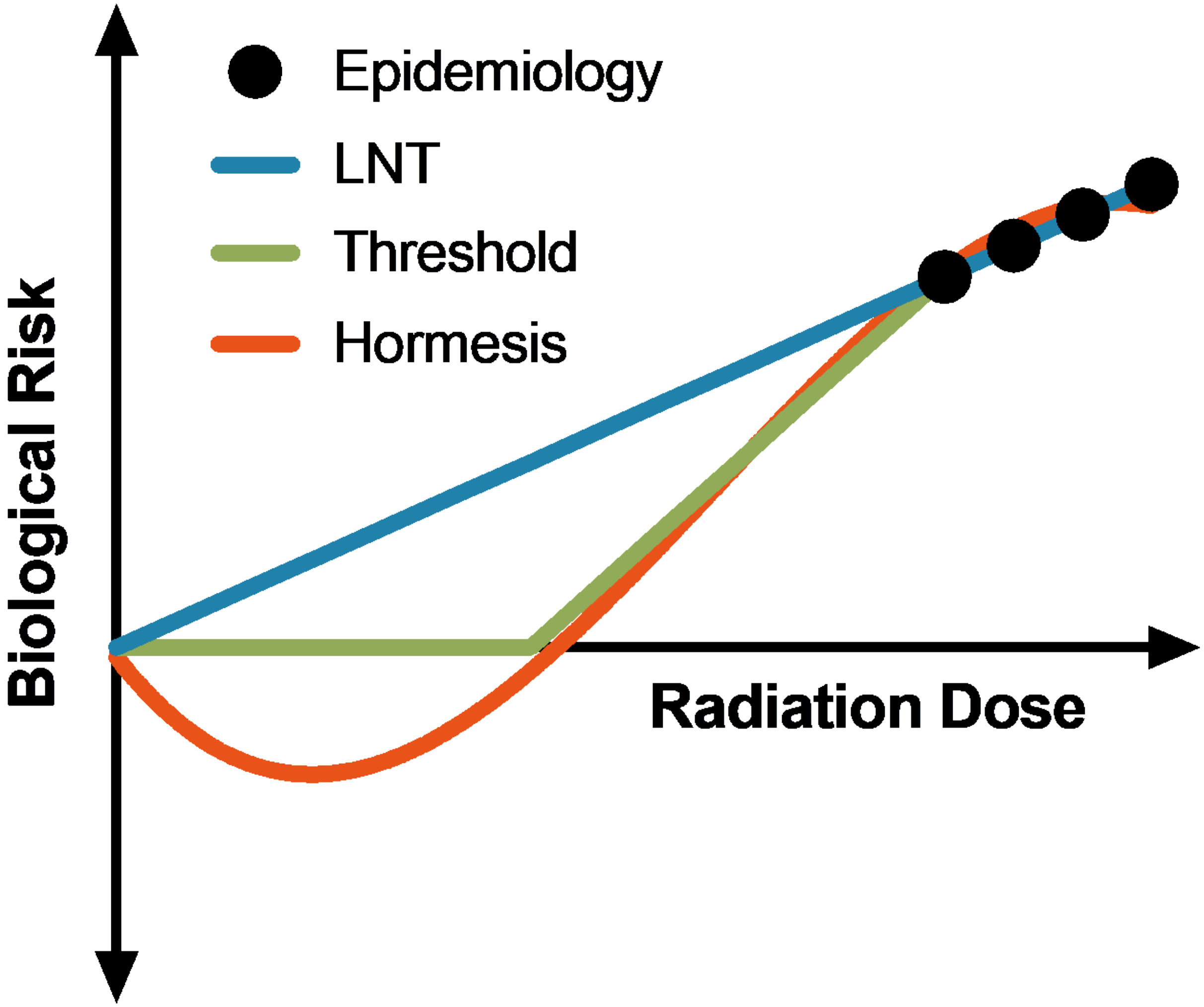
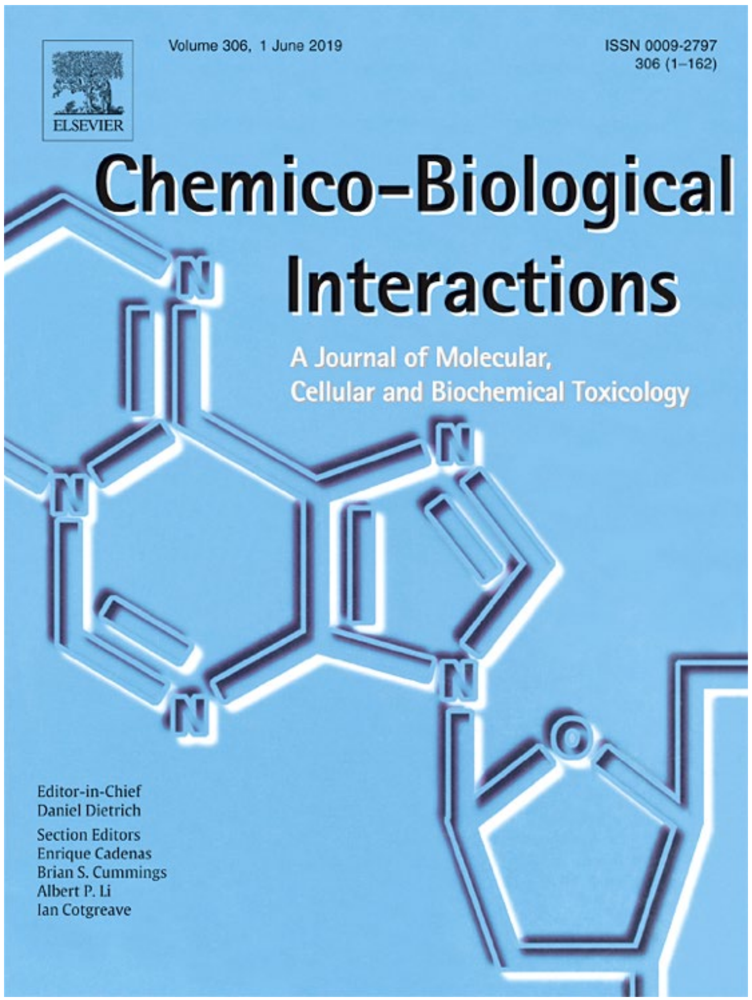
Krista Currie	PhD Candidate	Laurentian University
Konnor Kennedy	MSc Student	Laurentian University
Jayden Peterson	MSc Student	Laurentian University

Models of risk



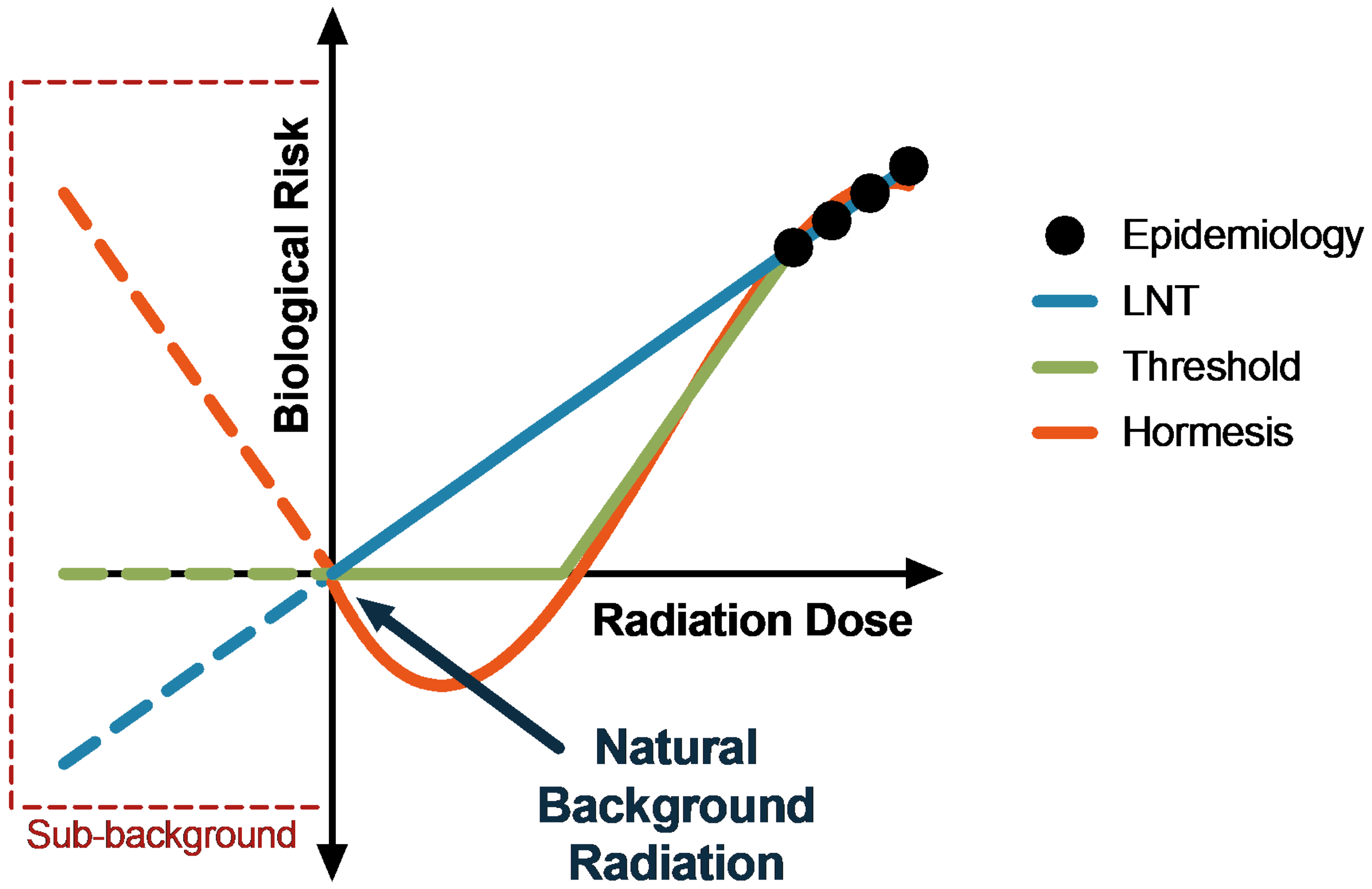
Chemico-Biological Interactions

Volume 301, March 2019



- Tharmalingam S, Sreetharan S, Brooks AL, Boreham DR. Re-evaluation of the Linear No-threshold (LNT) Model Using New Paradigms and Modern Molecular Studies. 54-67
- Zarnke AM, Tharmalingam S, Boreham, DR Brooks AL. BEIR VI Radon: The Rest of the Story. 81-87
- Ricci PF, Tharmalingam S. Ionizing Radiations Epidemiology Does Not Support the LNT Model.128-140
- Scott BR, Tharmalingam S. The LNT Model for Cancer Induction is Not Supported by Radiobiological Data. 34-53

Models of risk



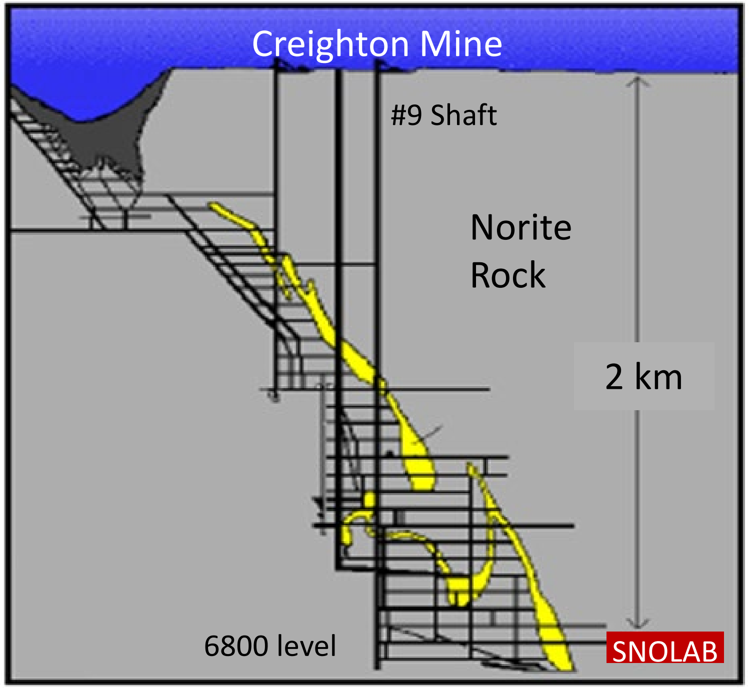
Hypothesis

Natural background radiation is essential for life and helps to maintain the stability of our genome

Prolonged exposure to a sub-background environment will be detrimental to living systems

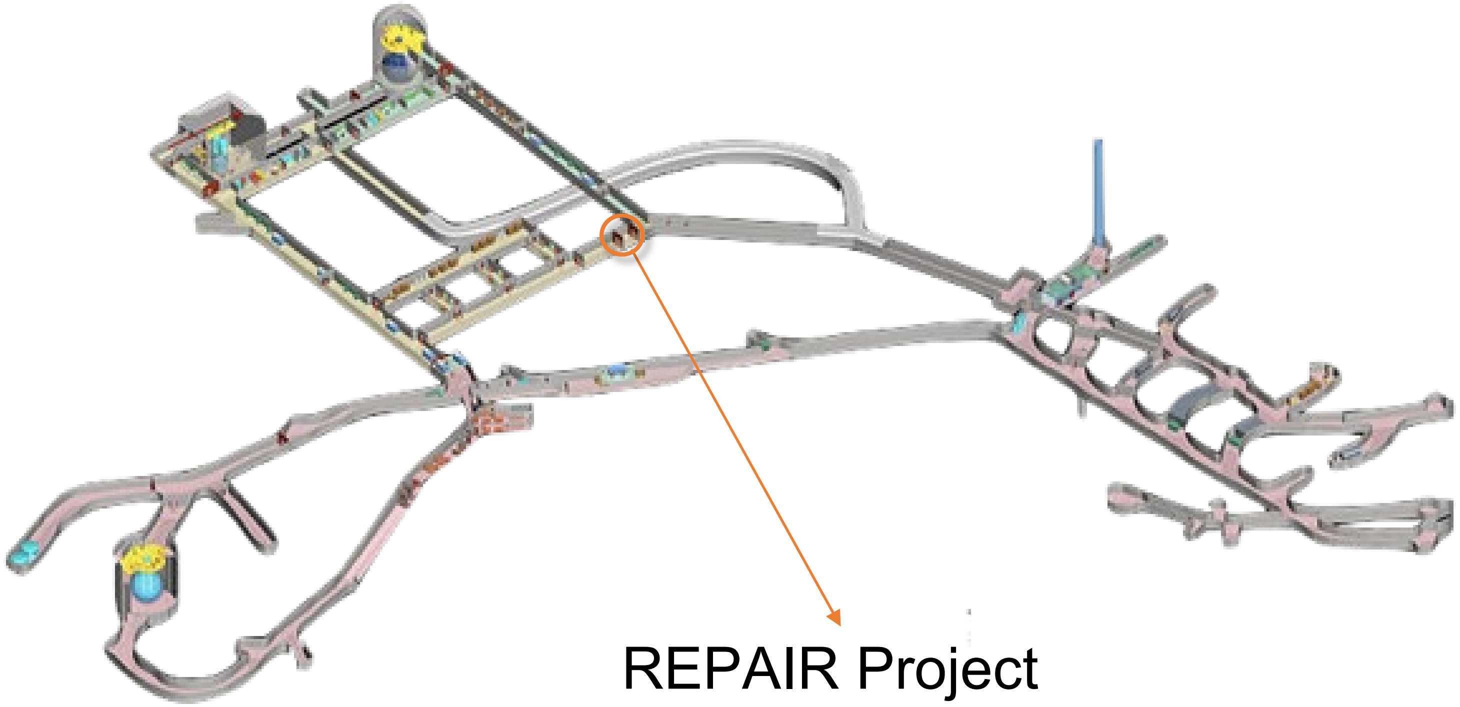
SNOLAB

- 2 km underground (6 km water equivalent)
- Class 2,000 clean room
- 50 million times less cosmic radiation
- Air filtration of 50 $m^3 s^{-1}$ for radon reduction

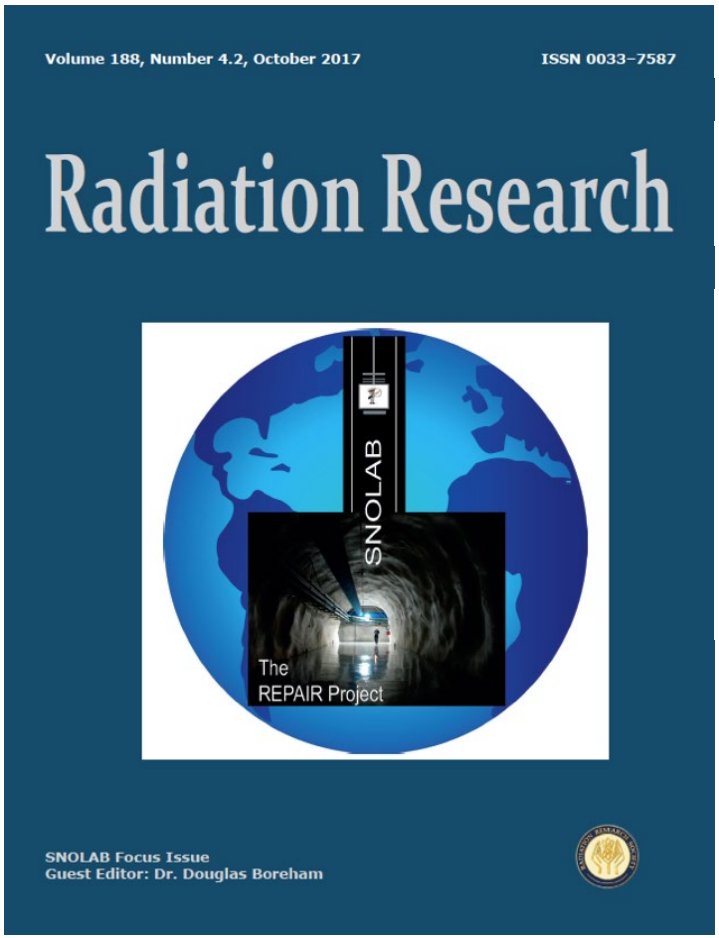


REPAIR Project

Researching the **E**ffects of the **P**resence and **A**bsence of **I**onizing **R**adiation



Radiation Research
SNOLAB Focus Issue
Volume 188, October 2017



FOREWORD

Foreword. Professor Emeritus Art McDonald

COMMENTARY

The REPAIR Project: Examining the Biological Impacts of Sub-Background Radiation Exposure within SNOLAB, a Deep Underground Laboratory. Christopher Thome, Sujeenthar Tharmalingam, Jake Pirkkanen, Andrew Zarnke, Taylor Laframboise and Douglas R. Boreham

REGULAR ARTICLES

Initial Characterization of the Growth Stimulation and Heat-Shock-Induced Adaptive Response in Developing Lake Whitefish Embryos after Ionizing Radiation Exposure. Christopher Thome, Charles Mitz, Emily N. Hulley, Christopher M. Somers, Richard G. Manzon, Joanna Y. Wilson and Douglas R. Boreham

Is There a Trade-Off between Radiation-Stimulated Growth and Metabolic Efficiency? Charles Mitz, Christopher Thome, Mary Ellen Cybulski, Christopher M. Somers, Richard G. Manzon, Joanna Y. Wilson and Douglas R. Boreham

Multiple CT Scans Extend Lifespan by Delaying Cancer Progression in Cancer-Prone Mice. Jennifer A. Lemon, Nghi Phan and Douglas R. Boreham

Single CT Scan Prolongs Survival by Extending Cancer Latency in *Trp53* Heterozygous Mice. Jennifer A. Lemon, Nghi Phan and Douglas R. Boreham

REVIEWS

The CGL1 (HeLa × Normal Skin Fibroblast) Human Hybrid Cell Line: A History of Ionizing Radiation Induced Effects on Neoplastic Transformation and Novel Future Directions in SNOLAB. Jake S. Pirkkanen, Douglas R. Boreham and Marc S. Mendonca

Low-Dose Ionizing Radiation Exposure, Oxidative Stress and Epigenetic Programing of Health and Disease. Sujeenthar Tharmalingam, Shayenthiran Sreetharan, Adomas V. Kulesza, Douglas R. Boreham and T. C. Tai

Impact of Ionizing Radiation on the Cardiovascular System: A Review. Stephanie Puukila, Jennifer A. Lemon, Simon J. Lees, T. C. Tai, Douglas R. Boreham and Neelam Khaper

REPAIR project

Phase I: Lake whitefish

Whole organism model for examining growth and development

Phase II: Cell culture

Single-celled model for examining survival, DNA damage and carcinogenesis

Phase III: Yeast

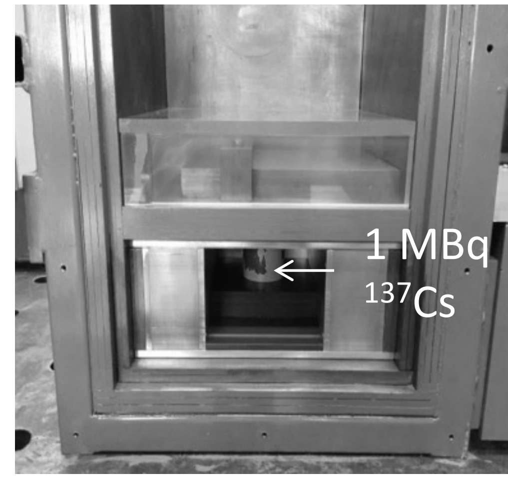
Single-celled model for examining survival and transcriptional regulation

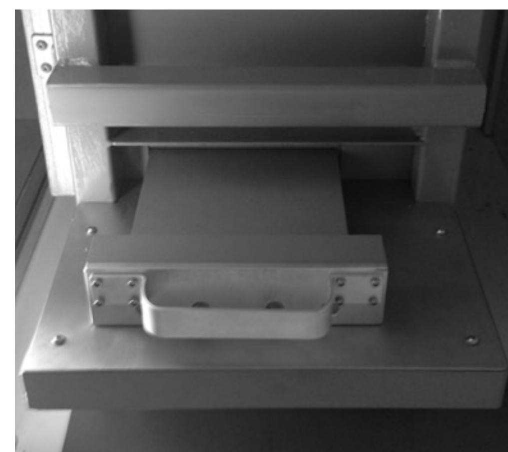
Lake whitefish

Thome et al. 2017

Lake whitefish

Distance (cm)	Dose rate (mGy/day)
81.44	0.06 ± 0.01
67.15	0.11 ± 0.02
52.86	0.19 ± 0.03
38.58	0.39 ± 0.04
24.29	1.05 ± 0.09
10.01	4.40 ± 0.78





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Thome et al. 2017

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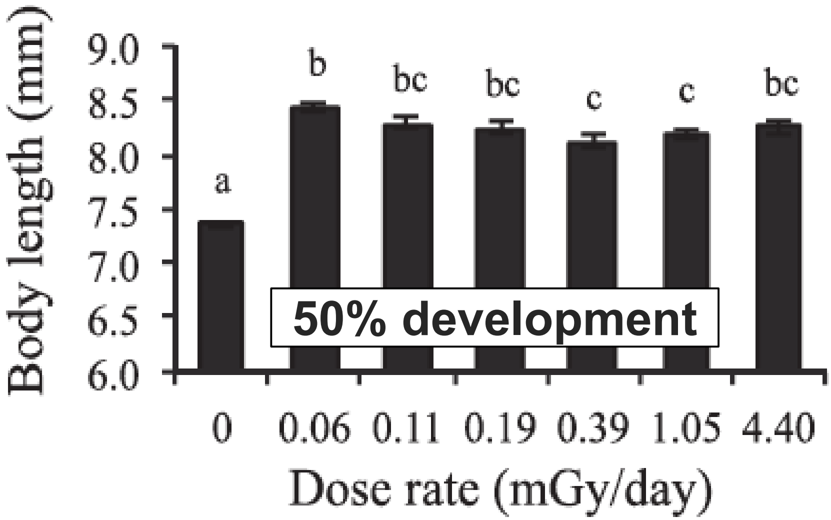
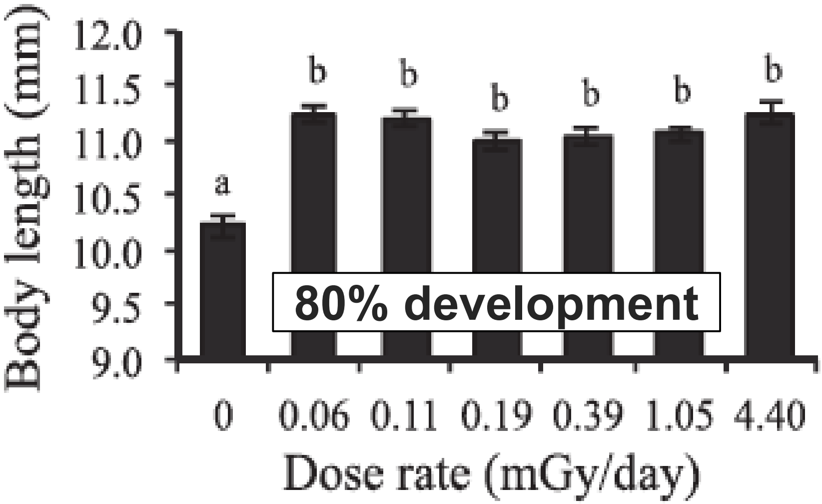




Lake whitefish

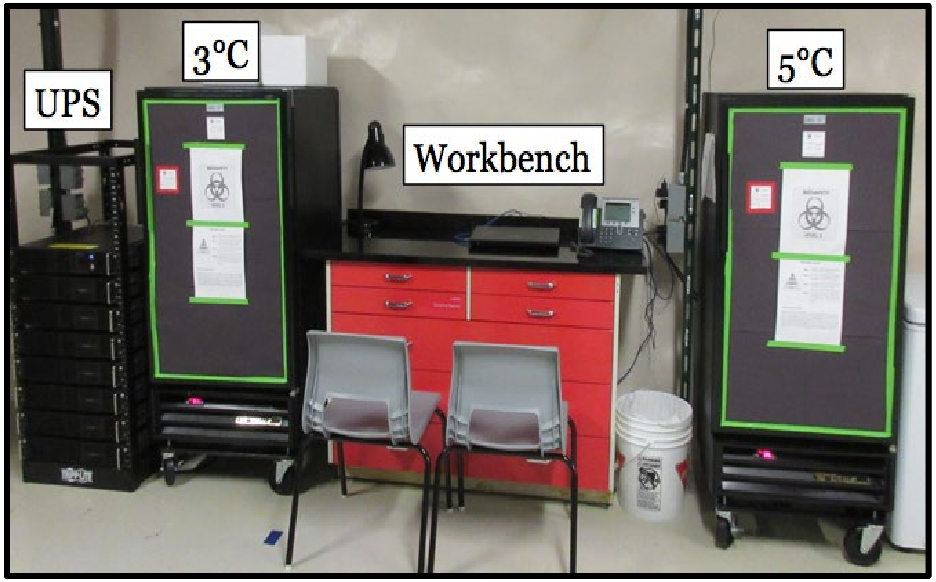
Embryos were reared at 2 temperatures:
- 5ºC, 3ºC

Embryos were analyzed at three timepoints:
- 40%, 60%, 80% development

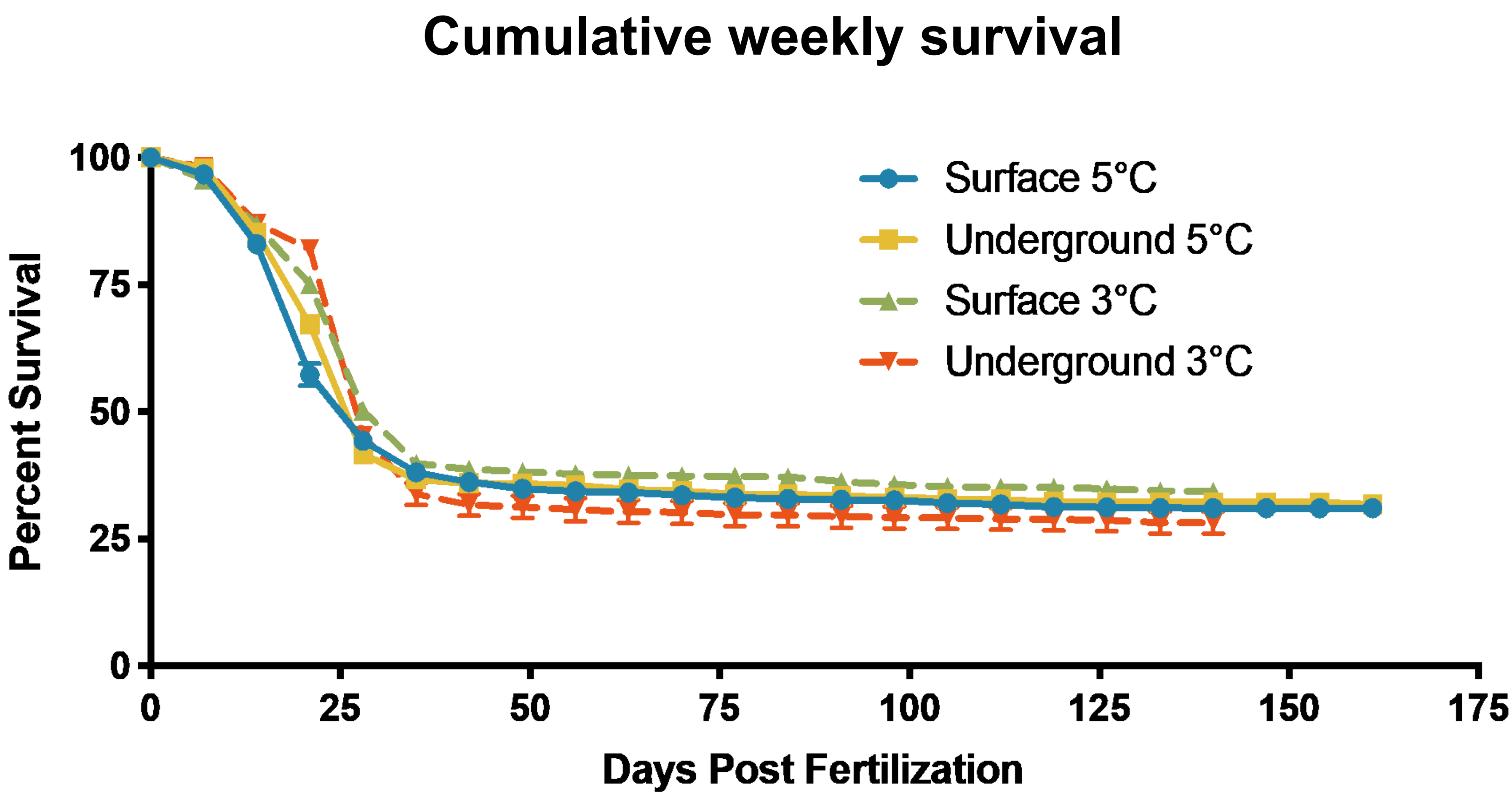
	Temperature			Sampling timepoint (dpf*)		
	(°C ± SD)	Dishes	Embryos	40%	60%	80%
Surface 5°C	4.7 ± 0.2	39	1,950	38	58	79
Underground 5°C	4.6 ± 0.3	43	2,150	38	58	79
Surface 3°C	3.3 ± 0.4	38	1,900	50	73	101
Underground 3°C	3.4 ± 0.2	42	2,100	50	73	101

Lake whitefish

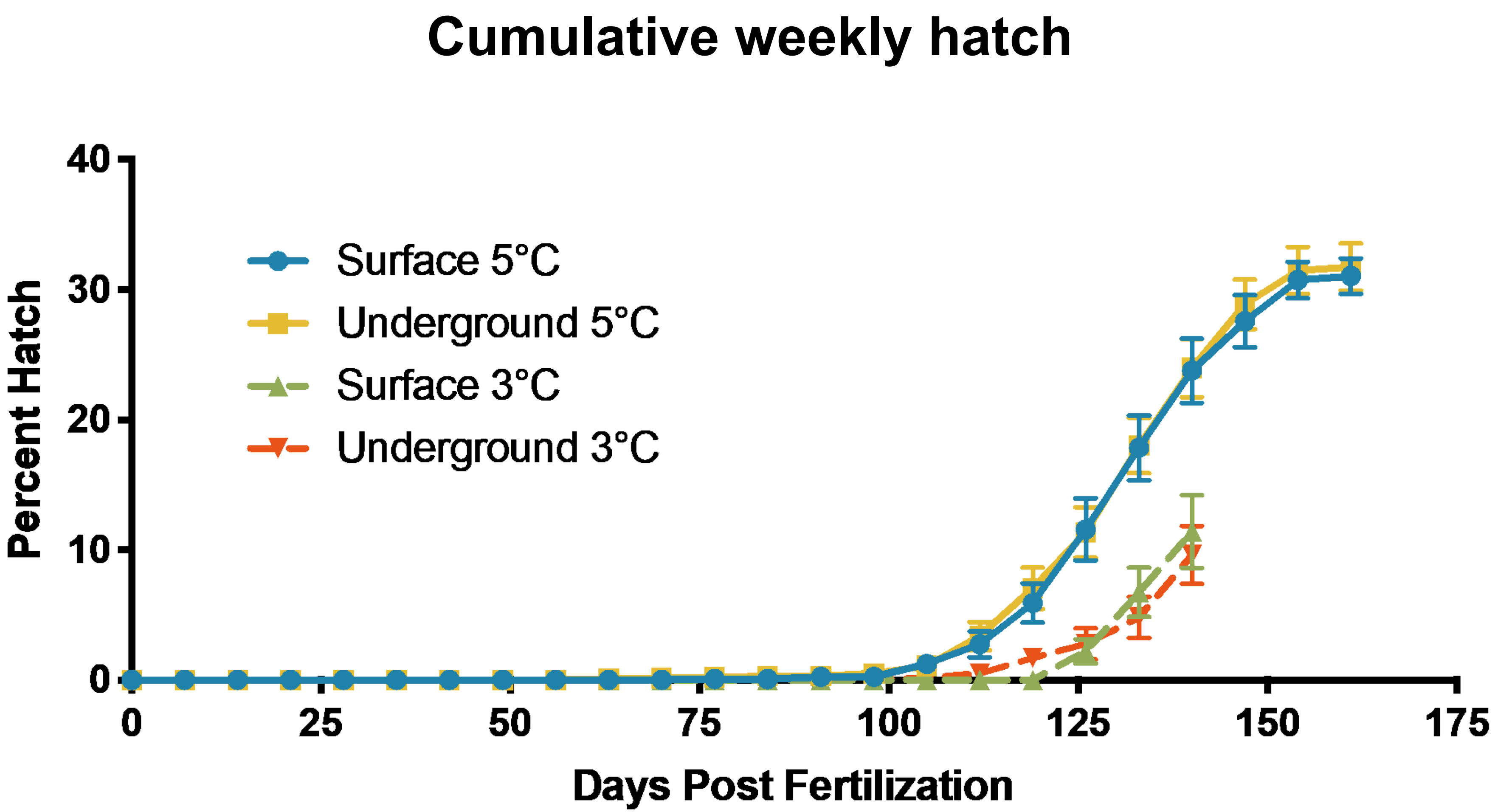
Life Sciences Laboratory
2015 - 2017



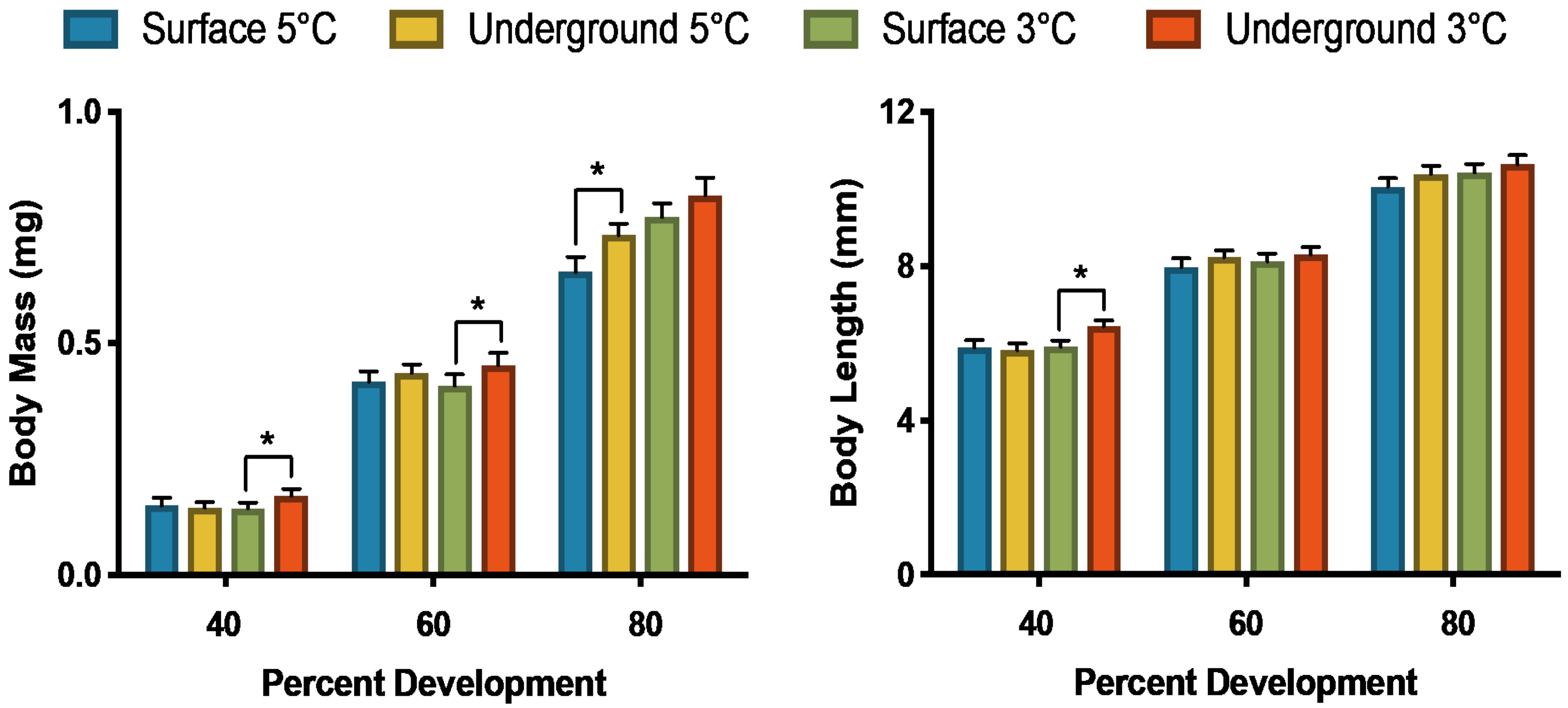
Lake whitefish



Lake whitefish

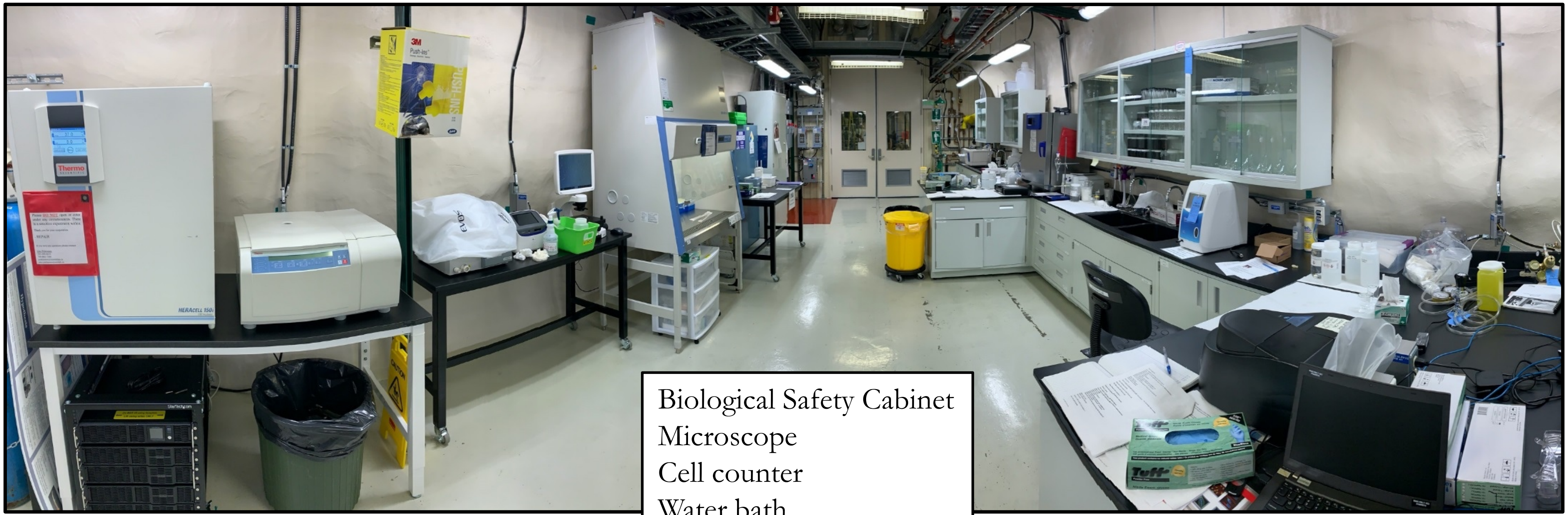


Lake whitefish



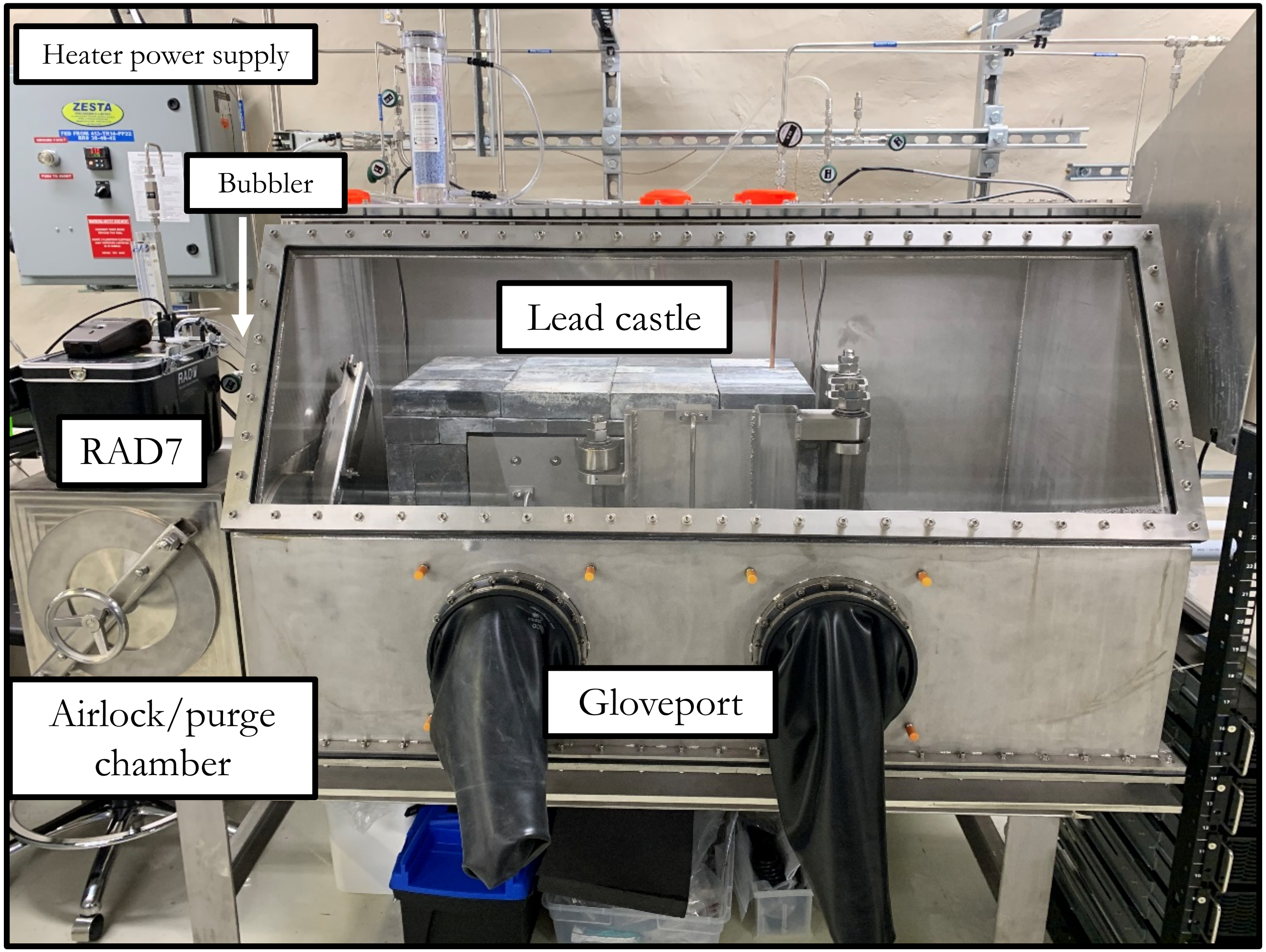
Cell culture

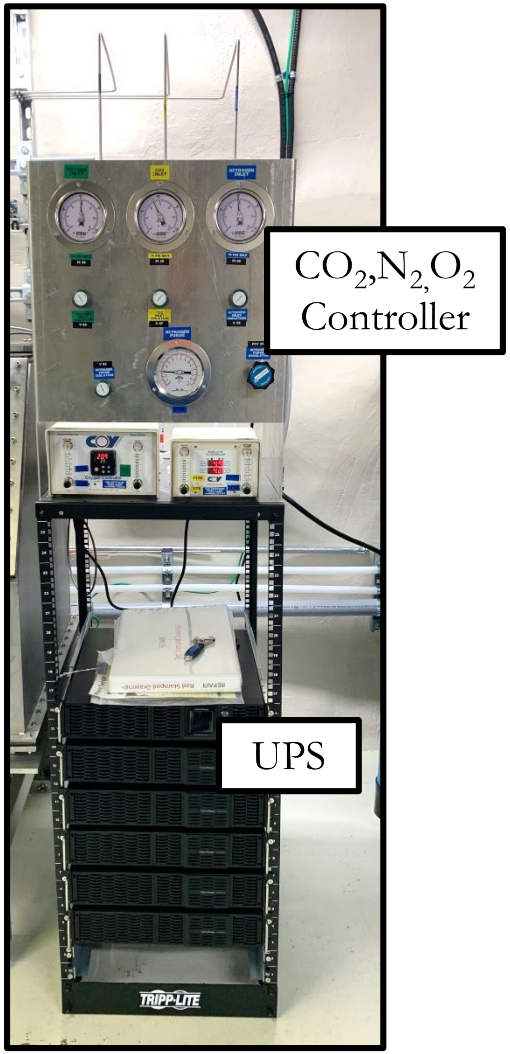
Life Sciences Laboratory
2019



Biological Safety Cabinet
Microscope
Cell counter
Water bath
Centrifuge
Tissue culture incubator
UPS

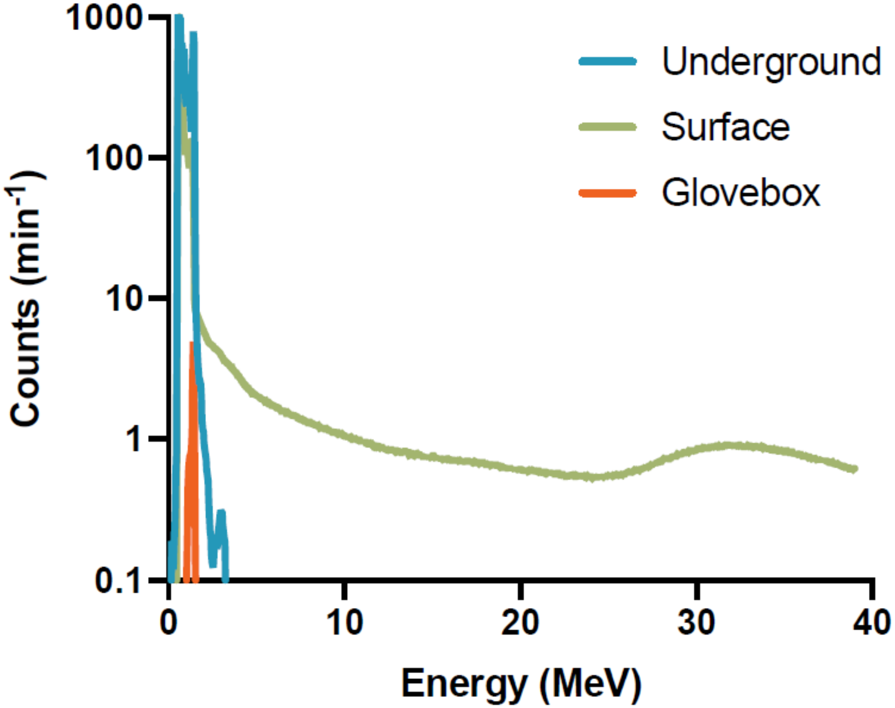
Tissue Culture Incubator Glovebox

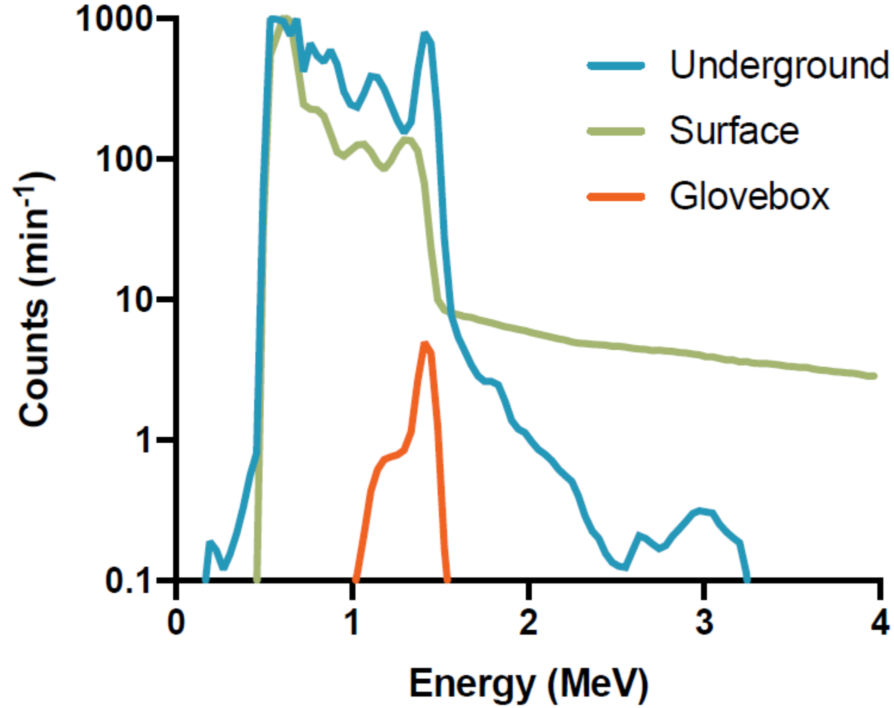




Background Radiation Characterization

Gamma





Background Radiation Characterization

Neutrons

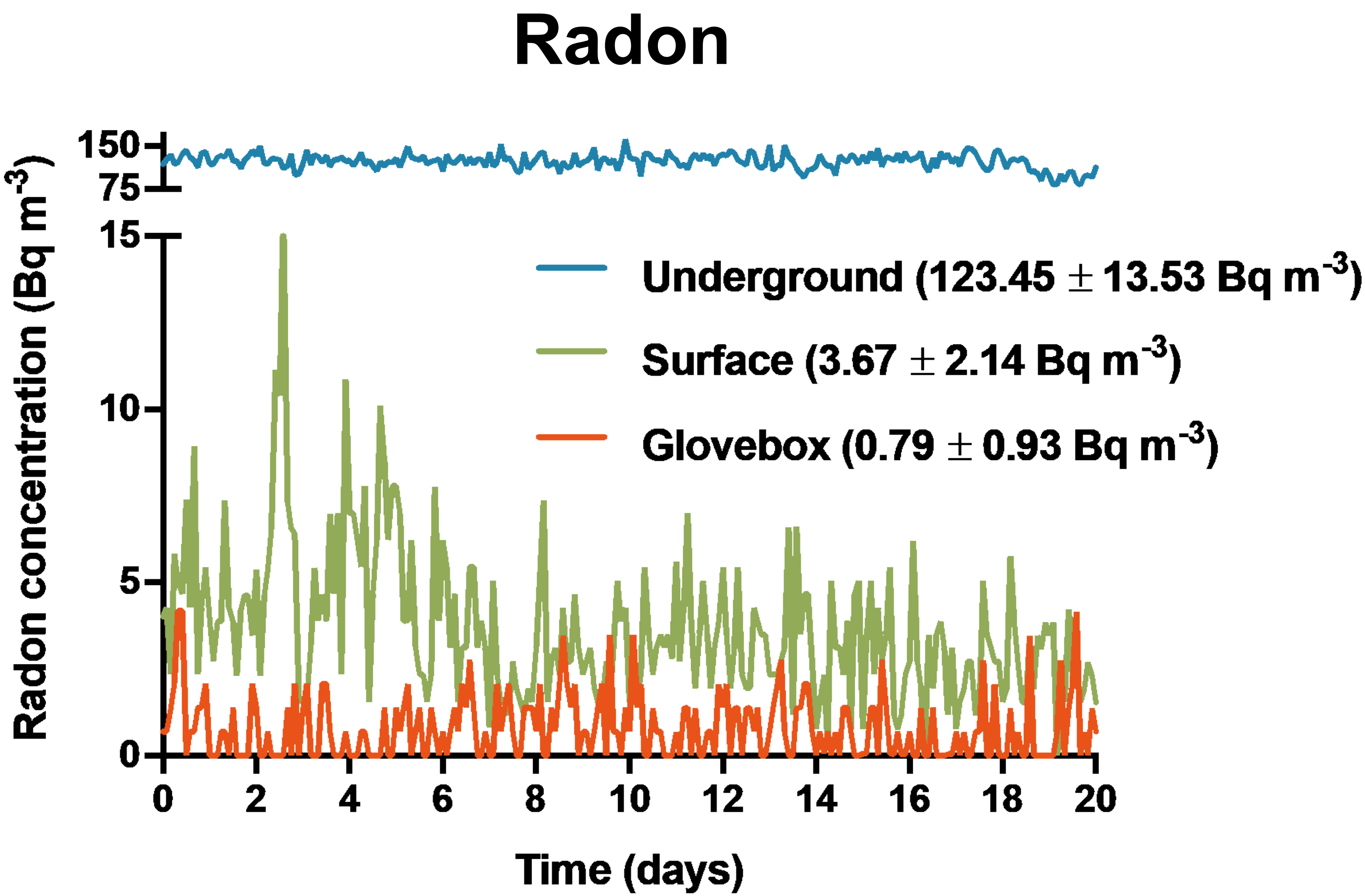
Laboratory	Neutron Flux (cm^{-2} s^{-1})
Underground	4.8×10^{-6} to 1×10^{-5}
Surface	1×10^{-2} to 3×10^{-2}

Neutrons ~1000 x less underground

Beta

Currently measuring radionuclide concentrations within cell culture media. [^{14}C, ^{40}K, etc.]

Background Radiation Characterization



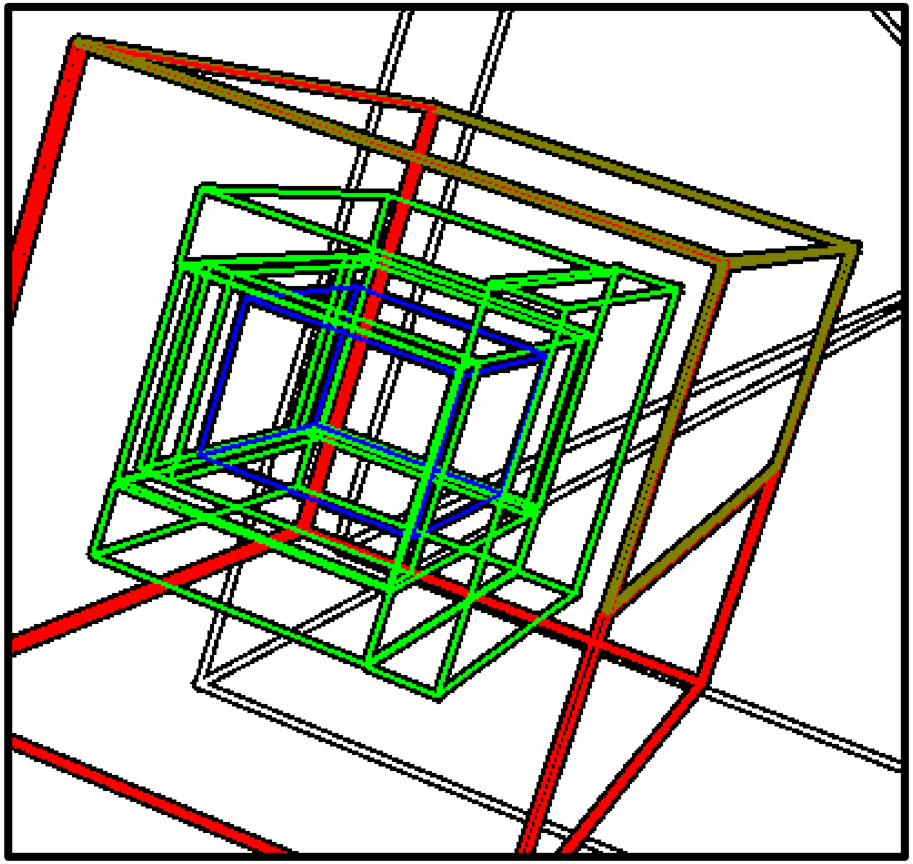
Background Radiation Characterization

Currently using GEANT4 to run Monte Carlo simulations to determine background dose rates within the 3 radiation environments

1. UG standard incubator

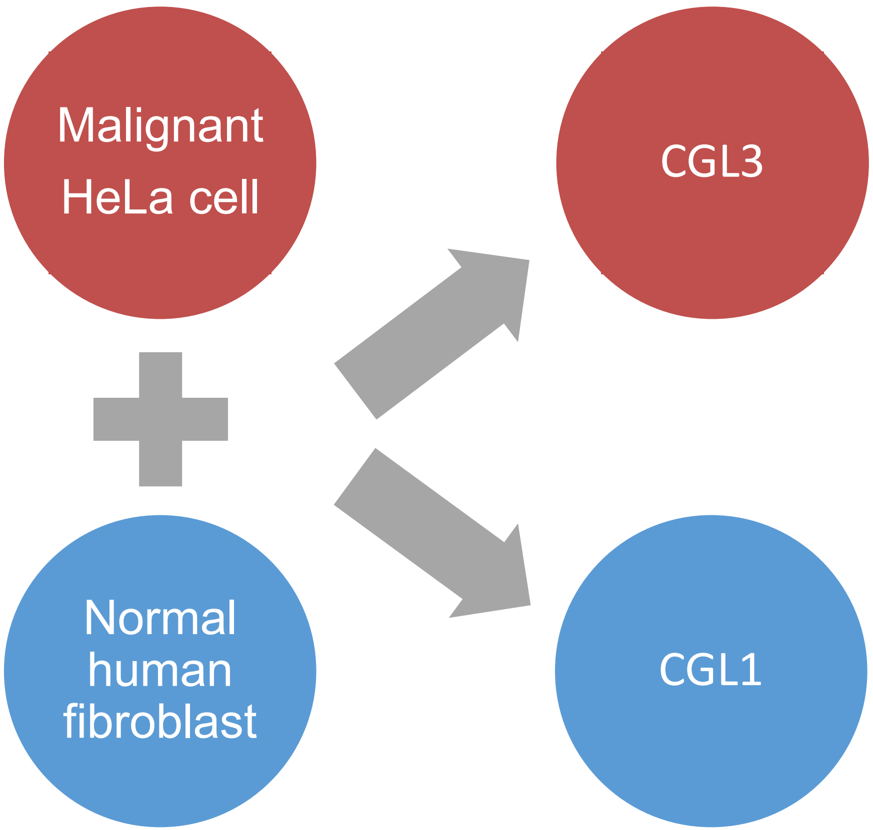
2. UG REPAIR glovebox

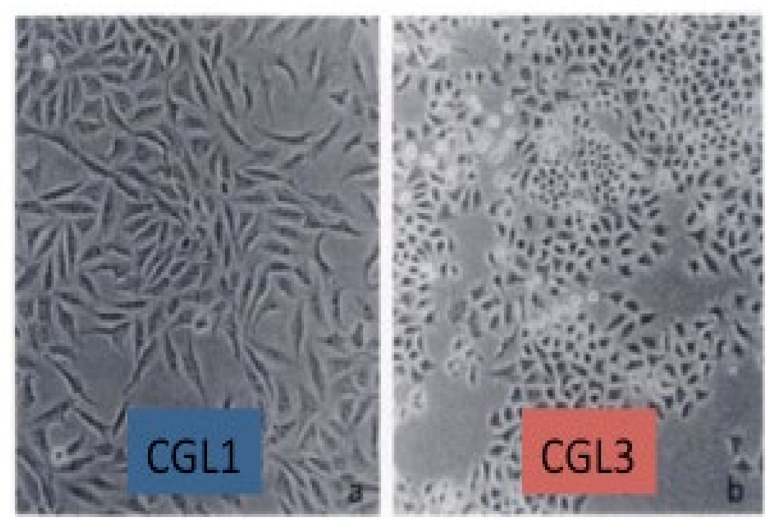
3. Surface standard incubator



E.x. model geometry of the glovebox and internal components within the UG REPAIR laboratory environment

CGL1 model system

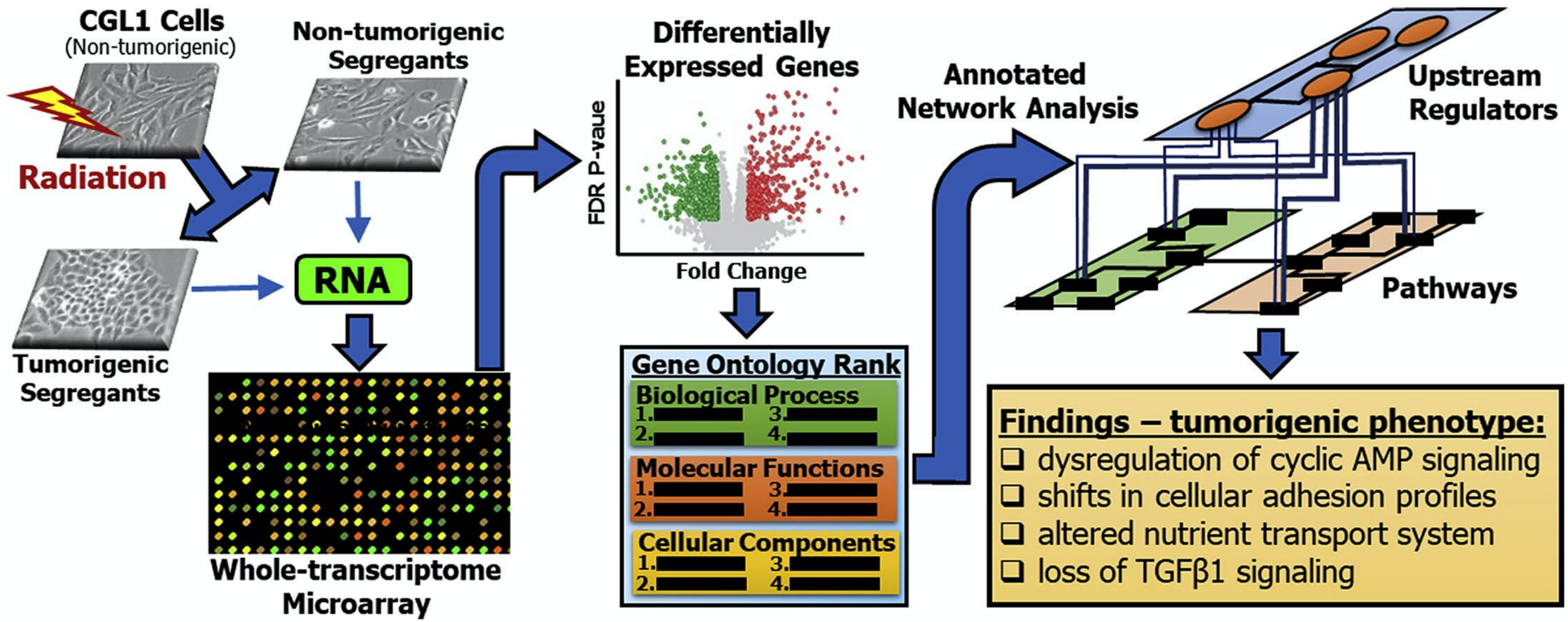




Tumorigenic cell Non-tumorigenic cell

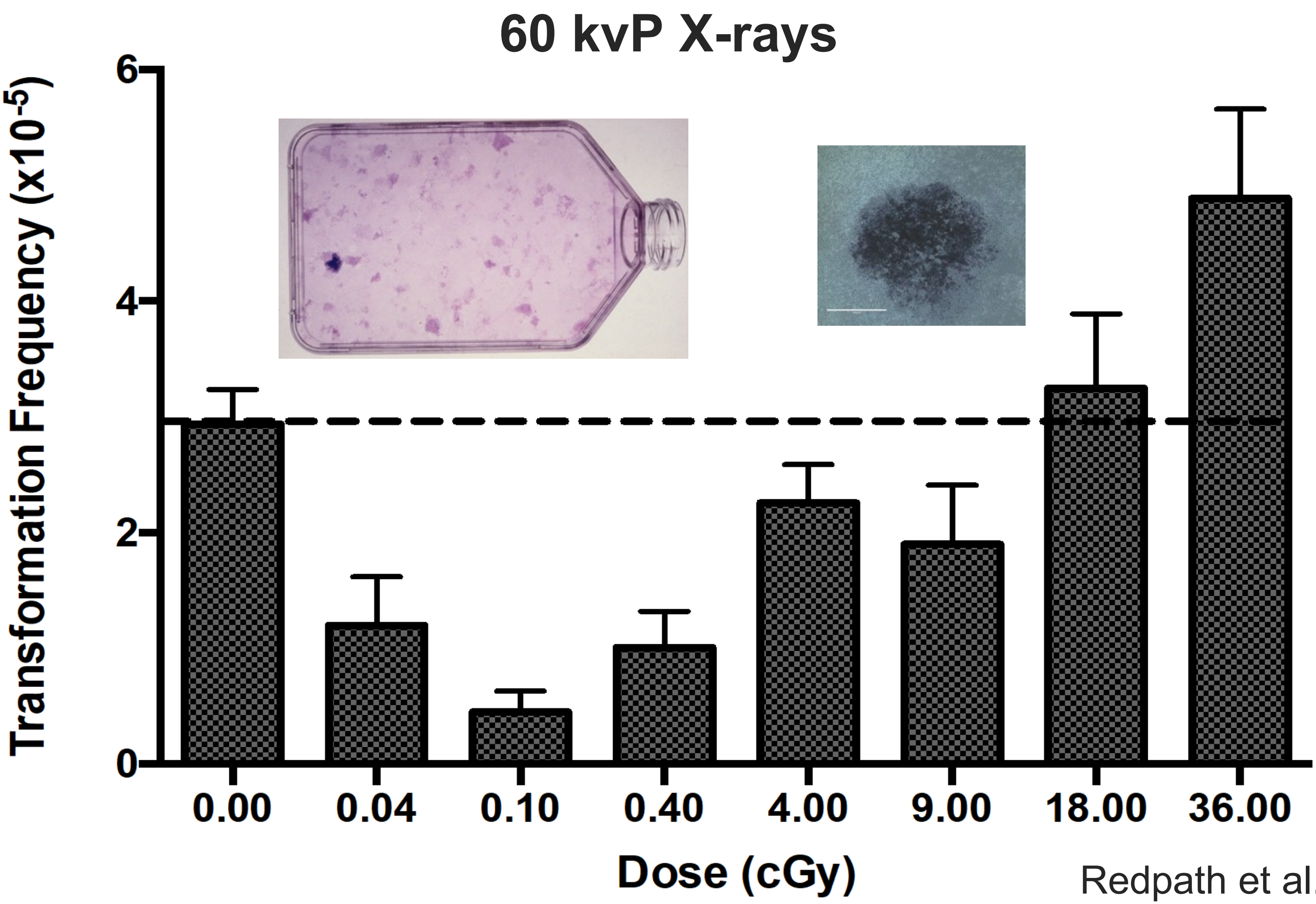
Stanbridge et al. 1982

CGL1 model system



Pirkkanen et al. Free Radic Biol Med 2019 Sep 30;145-300-311

Neoplastic transformation



Redpath et al. 2003

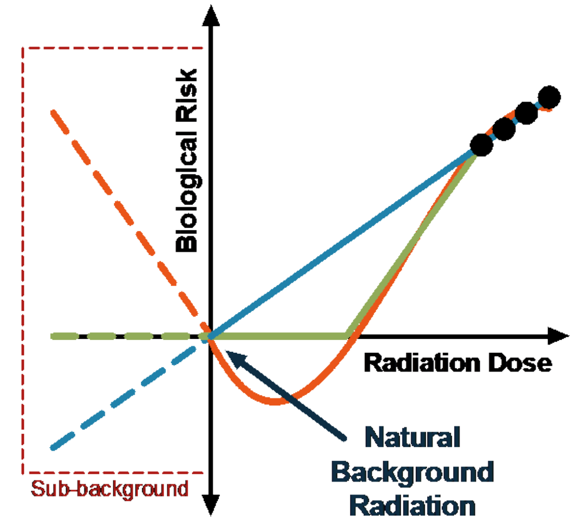
Sub-background effects

CGL1

- 1 month
- 2 month
- 3 month
- 4 month
- 5 month
- 6 month

Sub-background adapted cells

1. Baseline response
2. High dose radiation response

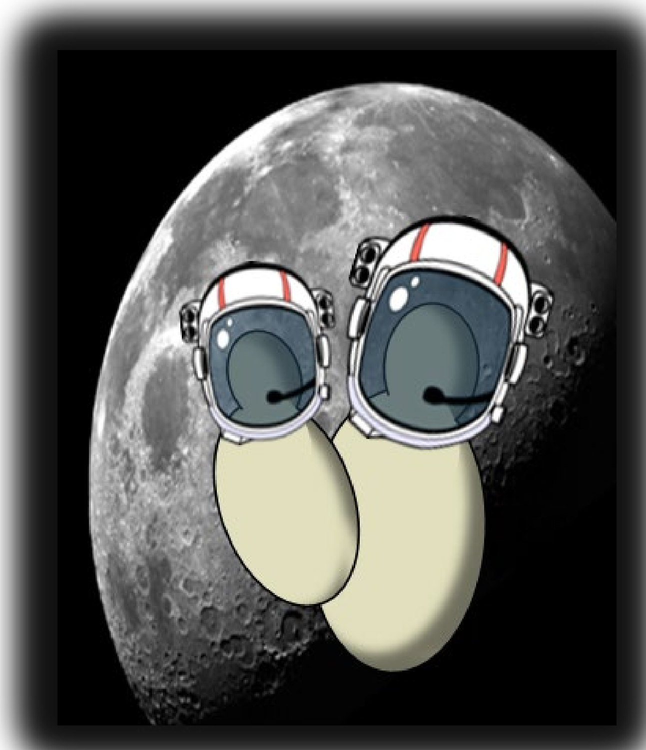


- ➢ Cell growth
- ➢ Survival
- ➢ DNA damage
- ➢ Mutation
- ➢ Transformation
- ➢ Gene expression

NASA BioSentinel Mission

NASA last launched organisms beyond low-Earth orbit (LEO) almost 50 years ago - the Apollo 17 astronauts, who reached the moon in December 1972 (< 2 weeks)

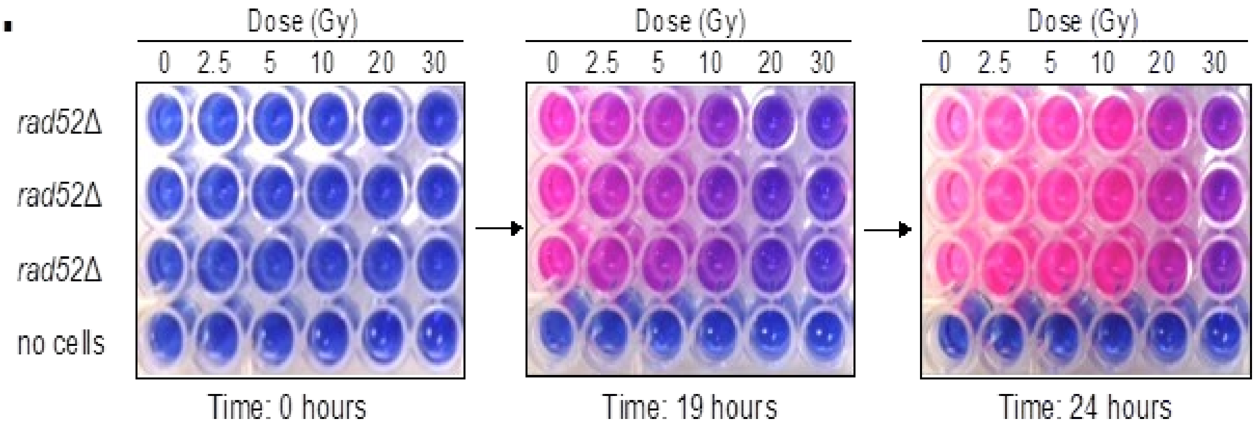
BioSentinel will gather data for 9 to 12 months and investigate the long-term effects of deep-space radiation on DNA and DNA repair



Distance to ISS:	~ 350 km
Distance to the Moon:	~385,000 km
Distance at 6 months:	~40,000,000 km

NASA BioSentinel

- Genetically engineered *Saccharomyces cerevisiae*
- Goal is to study DNA damage and repair mechanisms in the deep space radiation environment beyond LEO
- Simplistic colorimetric endpoint quantifies changes in metabolism due to accumulated DNA damage



Acknowledgements

BrucePower
Innovation at work

NSERC CRSNG

Mitacs

SNOLAB