REPAIR Project

Researching the Effects of the Presence and Absence of Ionizing Radiation

Chris Thome, Doug Boreham
Northern Ontario School of Medicine
Laurentian University

SNOLAB Future Projects Workshop
August 17, 2017

Research group

Principal Investigator

Dr. Douglas Boreham

Professor and Division Head of Medical Sciences – NOSM
Adjunct Professor – McMaster University
Principal Scientist – Bruce Power

Research Focus:

- Low-dose radiation biology
- Diagnostic imaging
- Cancer therapy

Research group

Collaborators

Dr. T.C.Tai
Professor (Physiology and pharmacology) – NOSM

Dr. Simon Lees
Associate Professor (Physiology and cell biology) – NOSM

Dr. Neelam Khaper
Associate Professor (Physiology) – NOSM

Dr. Zacharias Suntres
Professor (Pharmacology and toxicology) – NOSM

Dr. John Gunn
Professor (Aquatic biology) – Laurentian University

Dr. Joanna Wilson
Associate Professor (Aquatic biology) – McMaster University

Dr. Marc Mendonca
Professor (Radiation oncology) – Indiana University School of Medicine

Research group

Post-doctoral Fellows

Dr. Chris Thome
Dr. Suji Tharmalingam

Doctoral Students

Jake Pirkkanen
Andrew Zarnke

Technologists

Mary Ellen Cybulski
Taylor Laframboise

Funding

Bruce Power industrial support

- 2015: $85,000
- 2016-2020: $1,000,000 ($200,000 per year)

NSERC discovery

- 2015-2020: $190,000 ($38,000 per year)

Mitacs Accelerate

- 2015-2017: $330,000

NSERC CRD (under review)

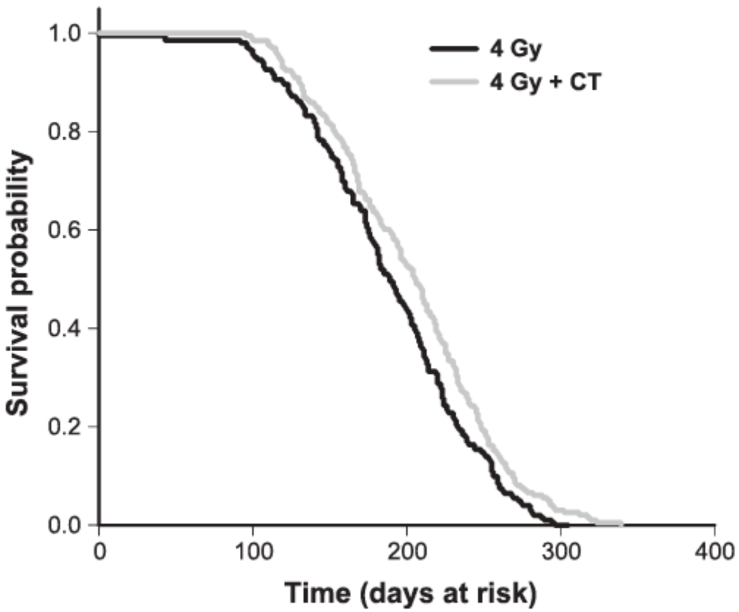
- 2017-2020: $1,000,000 ($200,000 per year)

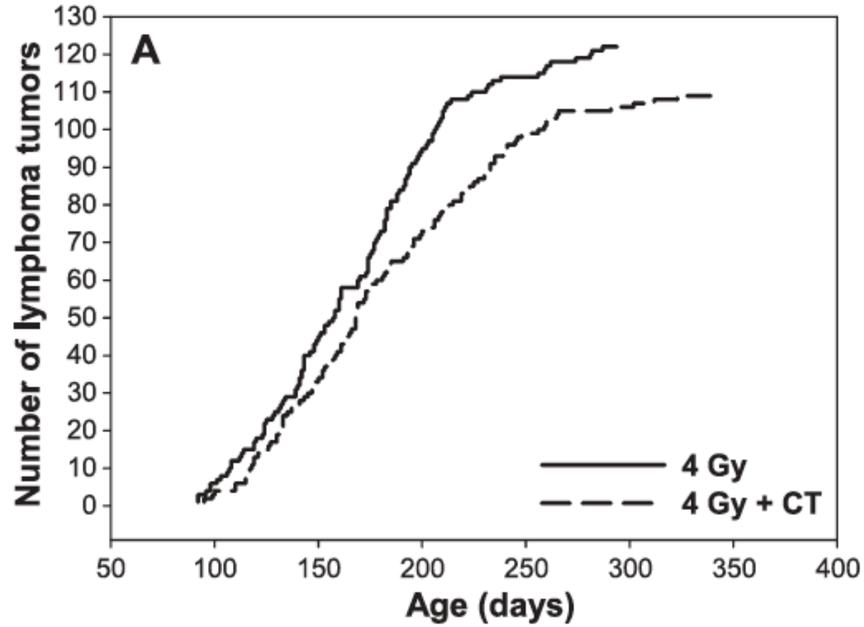
Rationale

- Ionizing radiation is ubiquitous for all living organisms on earth
- There is increasing concern over radiation exposure from medical diagnostic procedures
- The effects from these exposures still remains largely unknown
- Limited epidemiological data exists in the low-dose region (< 100 mGy)
- There is growing evidence to suggest that low-dose radiation may provide beneficial effects to living systems

Low-dose exposure

CT scan (10 mGy) increased mean survival time and increased tumor latency time in cancer prone mouse model

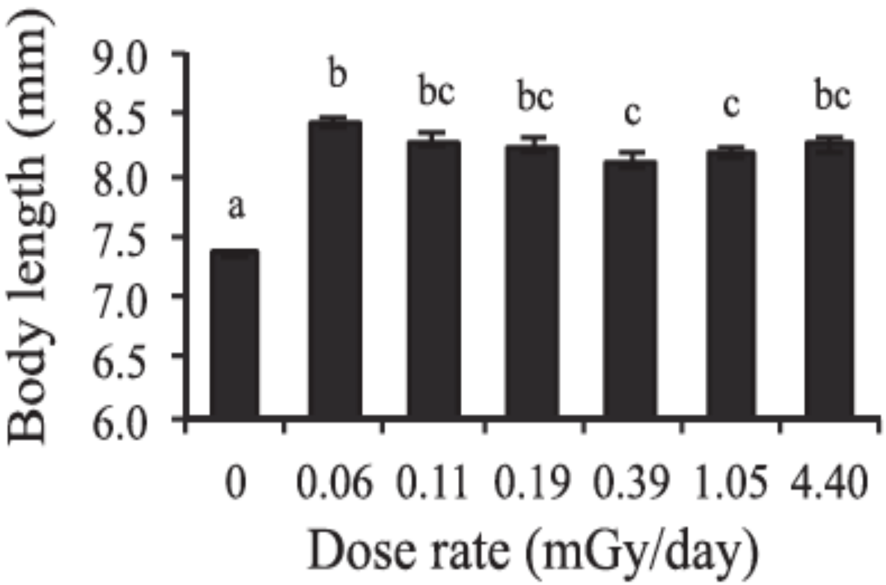


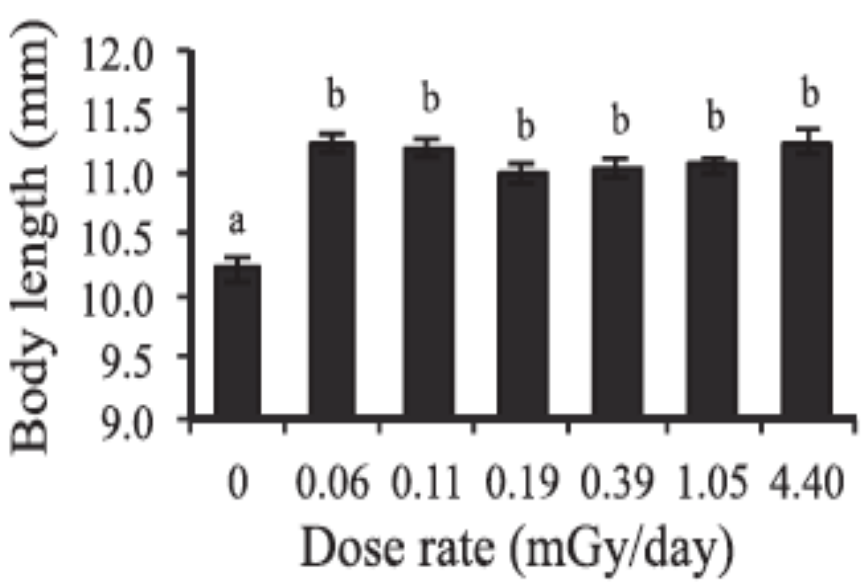


Lemon *et al* 2017, Radiat Res, 188

Low-dose exposure

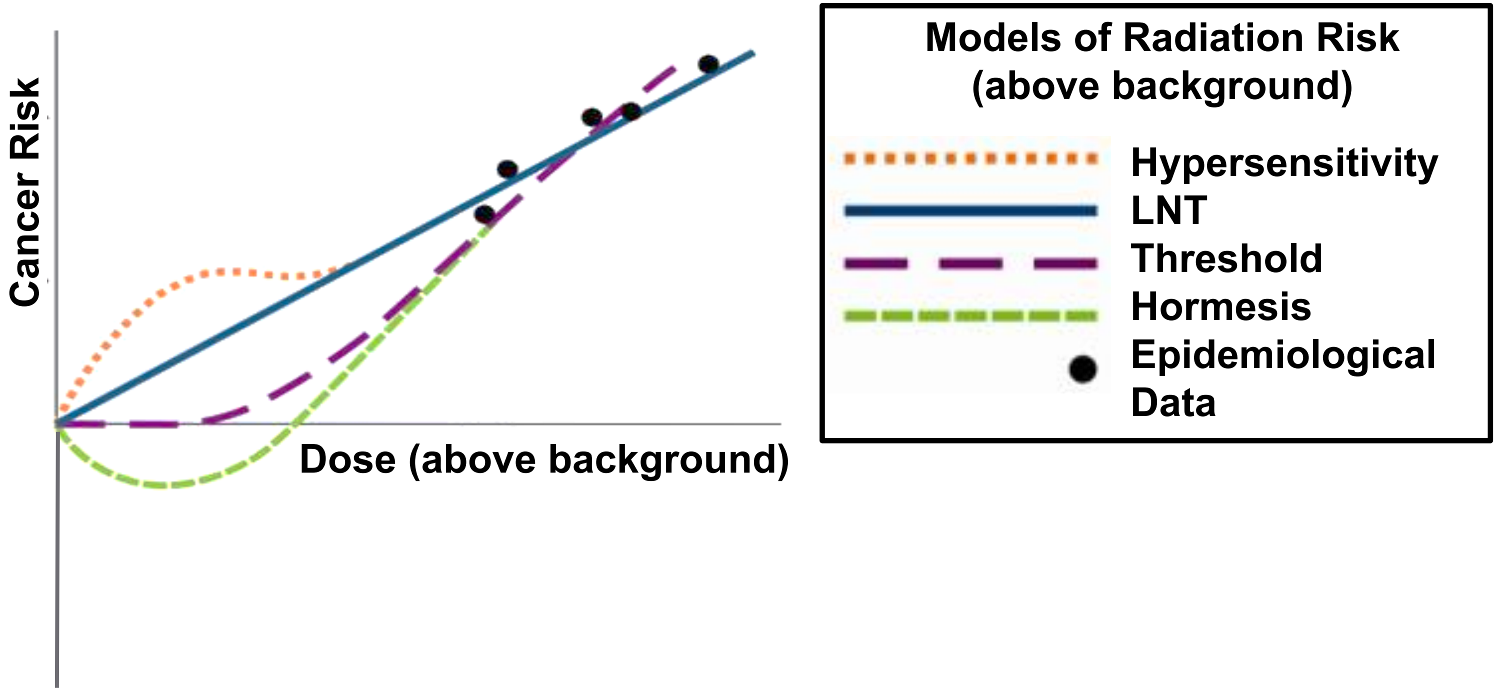
Low-dose chronic gamma ray exposure stimulated growth in developing lake whitefish embryos



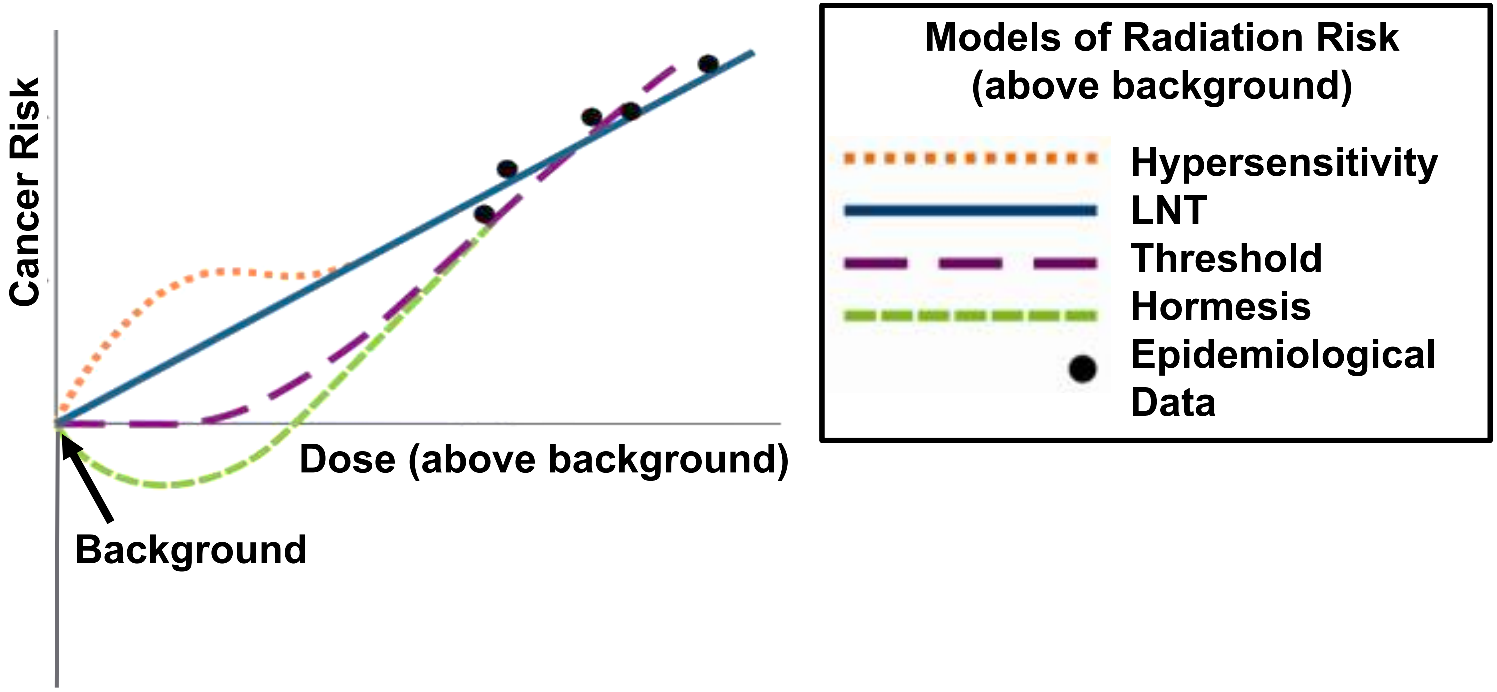


Thome *et al* 2017, Radiat Res, 188

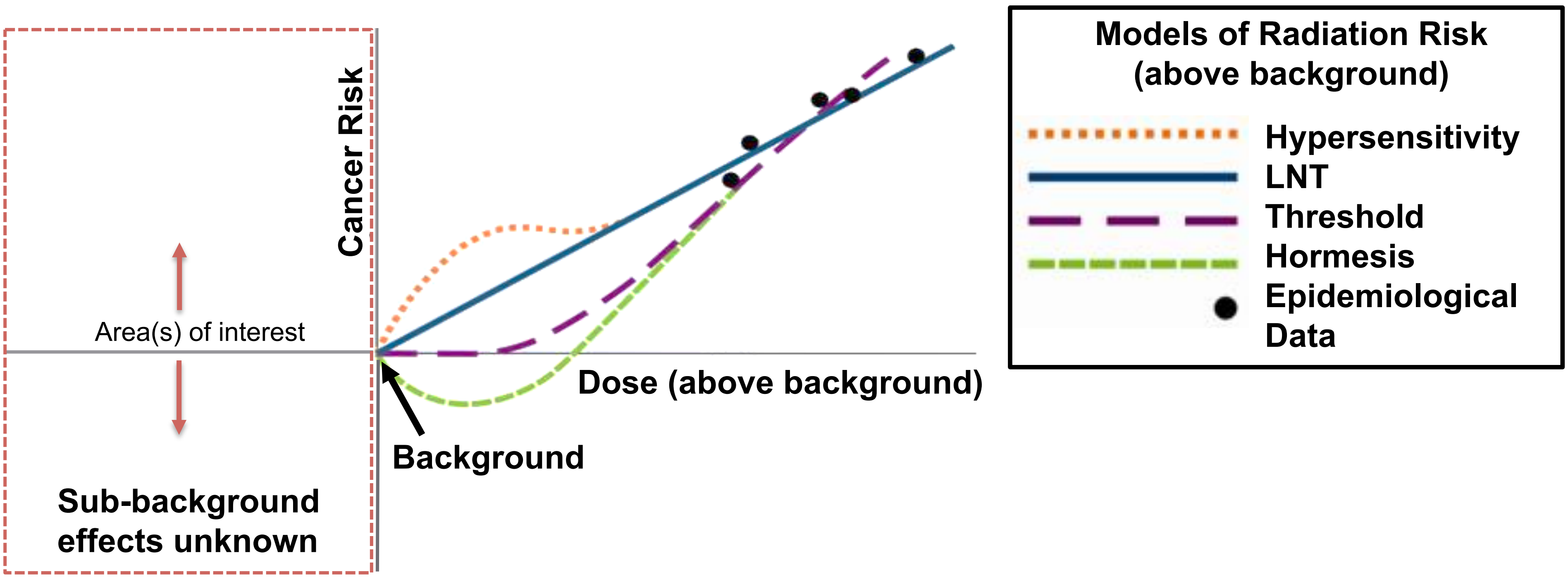
Models of risk



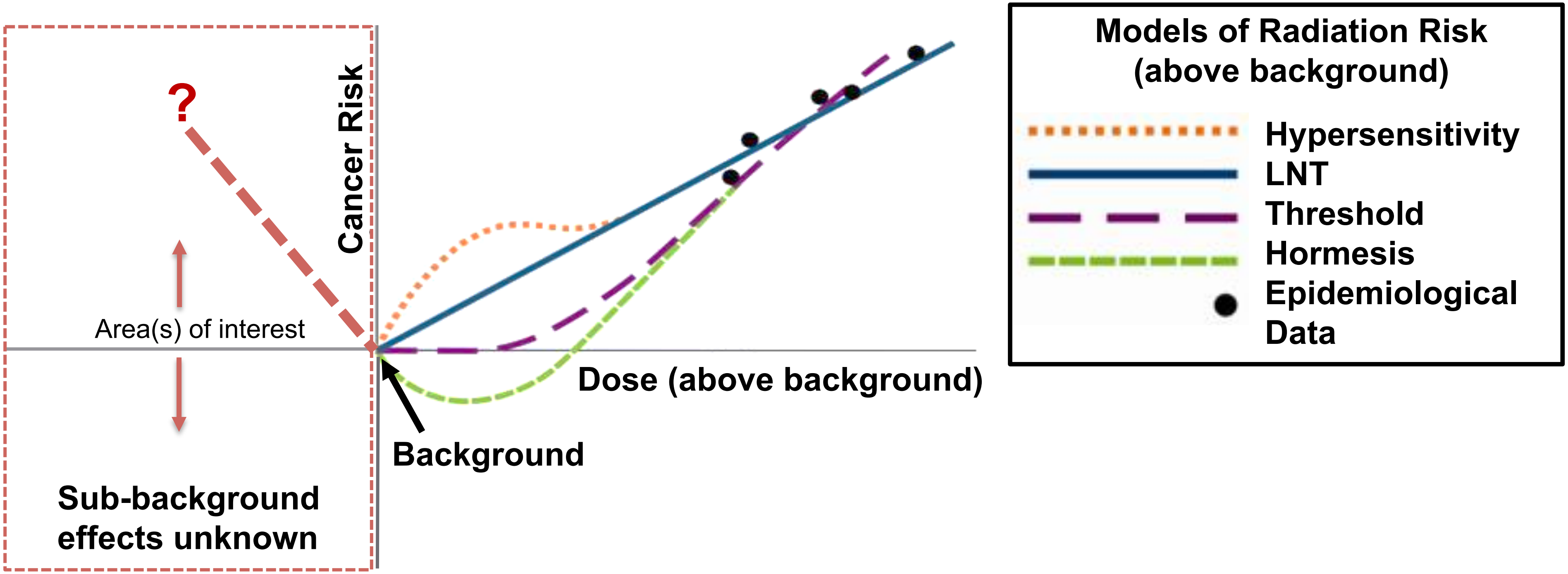
Models of risk



Models of risk



Models of risk



Sub-background exposure

1. Removal of natural background radiation impairs growth. Growth rates are restored once radiation is artificially reintroduced

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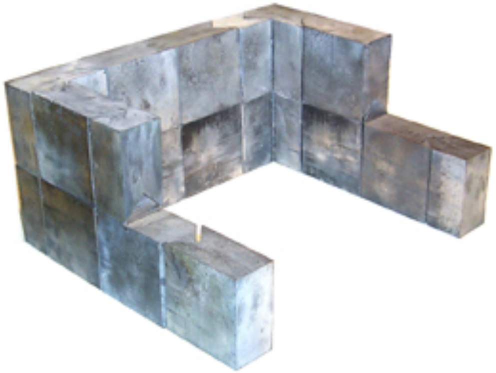

Paramecium shielded with lead (Planel *et al* 1976)

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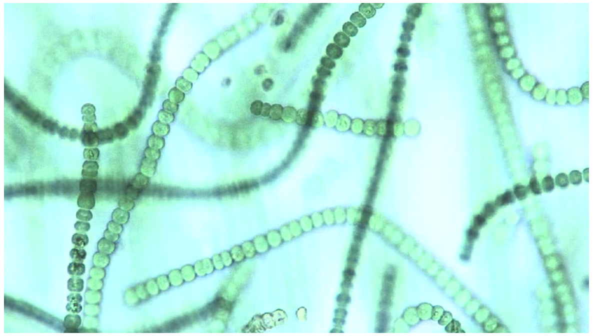

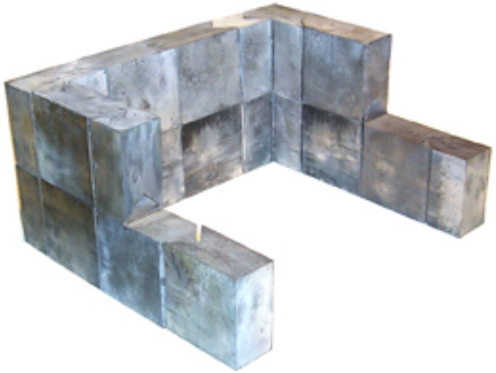

Blue-green algae (*Synechococcus lividus)* shielded with lead
(Conter *et al* 1983)

Sub-background exposure

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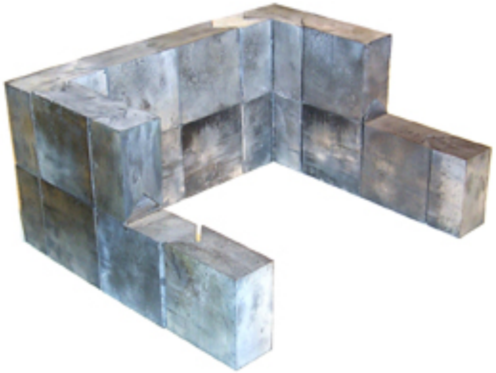

Yeast (*Saccharomyces cerevisiae*) shielded with lead/cadmium
(Gajendiran and Jeevanram 2002)

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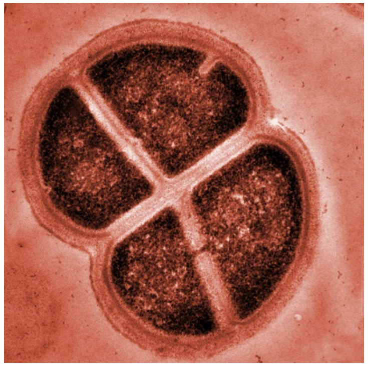

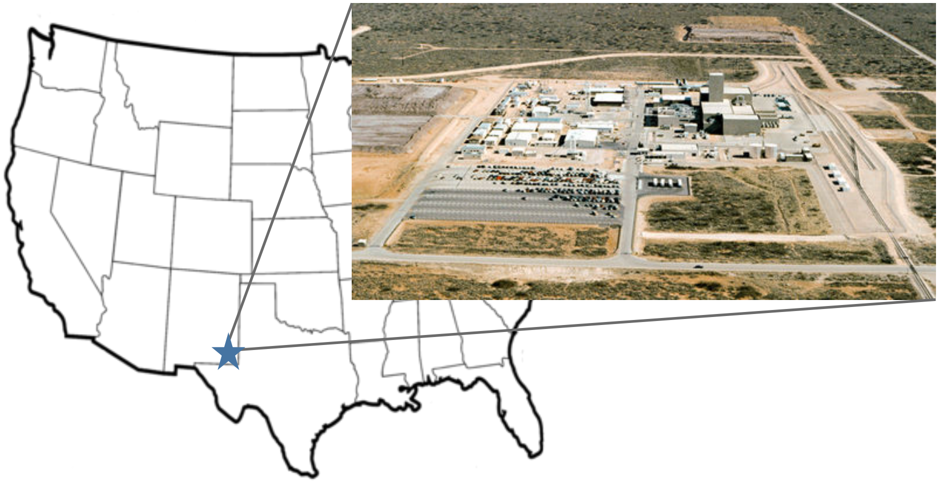

Bacteria (*Deinococcus radiodurans)* grown in Waste Isolation Pilot Plant (WIPP) (Smith *et al* 2011)

Sub-background exposure

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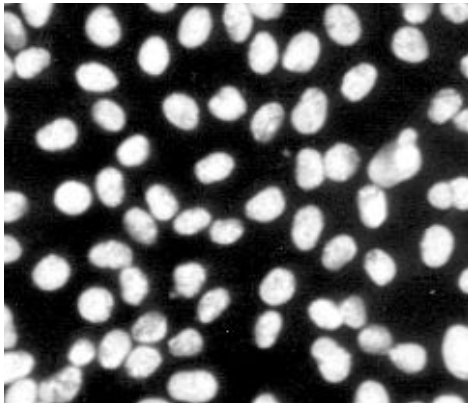

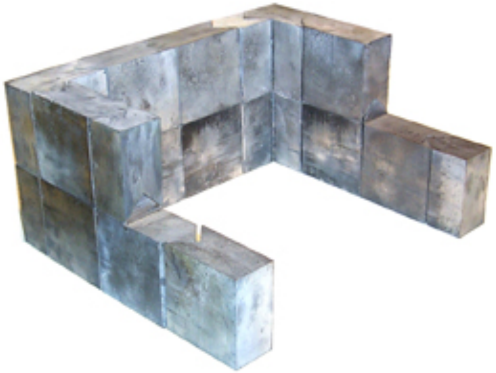

Mouse lymphoma L5178Y cells shielded with lead or iron (Taizawa *et al* 1992, Kawanishi *et al* 2012)

Sub-background exposure

2. Removal of natural background radiation reduces repair capacity towards induced damage

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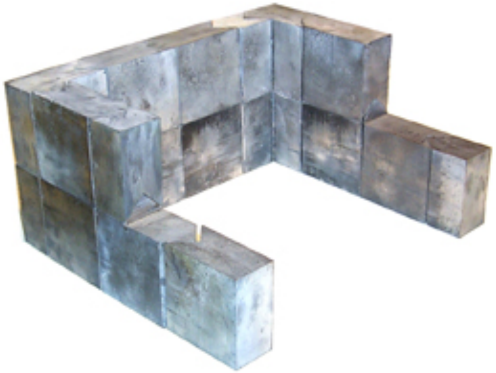
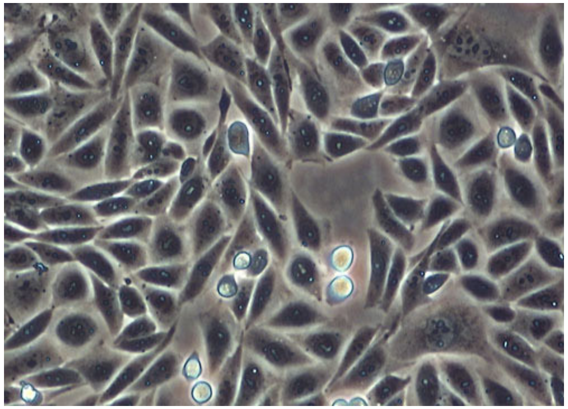
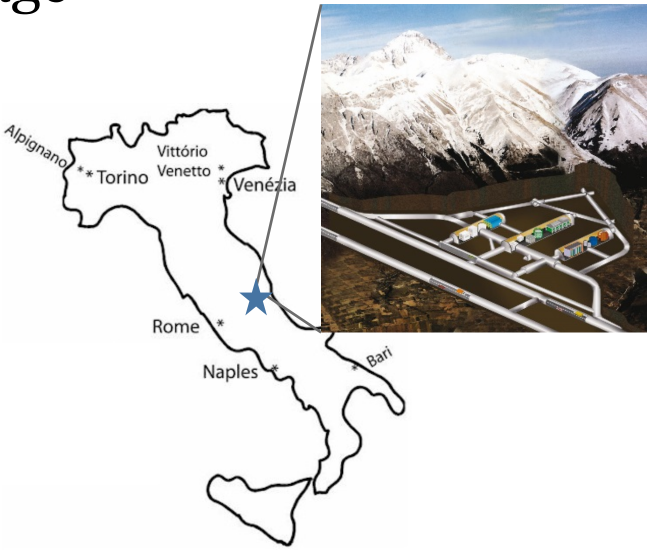


Survival fraction in yeast (*Saccharomyces cerevisiae*) shielded with lead/cadmium (Gajendiran and Jeevanram 2002)

Sub-background exposure

2. Removal of natural background radiation reduces repair capacity towards induced damage

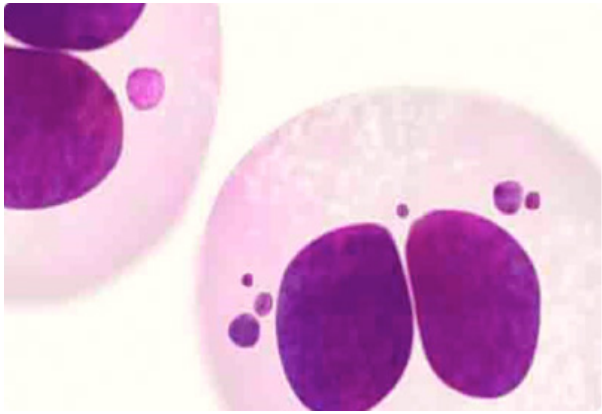


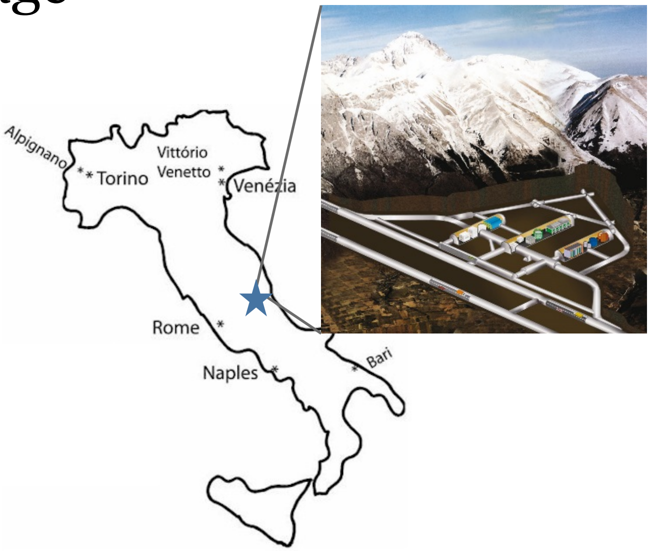


Background/induced mutation rate in Chinese hamster V79 cells grown in Gran Sasso Underground Laboratory (LNGS) (Satta *et al* 2002)

Sub-background exposure

2. Removal of natural background radiation reduces repair capacity towards induced damage





Micronuclei formation and ROS scavenging in human lymphoblastoid TK6 cells grown in LNGS (Carbone *et al* 2010)

Hypothesis and objectives

Hypothesis:

Natural background radiation is essential for life and maintains genomic stability in living organisms

Prolonged exposure to sub-background radiation environments will be detrimental to biological systems

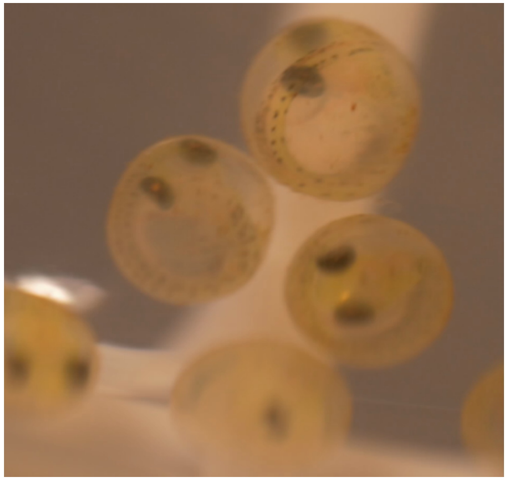
Objectives:

Examine the effects of incubation in SNOLAB compared to surface control laboratory using two model systems

- Whole organism – Lake Whitefish embryonic development
- Cell culture – CGL-1 cell line

Why lake whitefish?

- 200+ day developmental period (protracted exposure)
- Embryogenesis: sensitive to ionizing radiation exposure
- Easy to raise, low maintenance
- Clear chorion – visual markers of development rate
- Relatively non-technical endpoints (e.g. weight, morphometrics)



Experimental design

	2015-2016	2016-2017
In-vitro fertilization	December 1	November 10
Embryos transported to Sudbury	December 2	November 16
Embryos transported to SNOLAB	December 2	November 17

2015-2016

	LWL	LWL	SNO	SNO
Temperature	5°C	3°C	5°C	3°C
Dishes*	39	38	43	42
Embryos	1,950	1,911	2,150	2,100

*50 embryos per dish

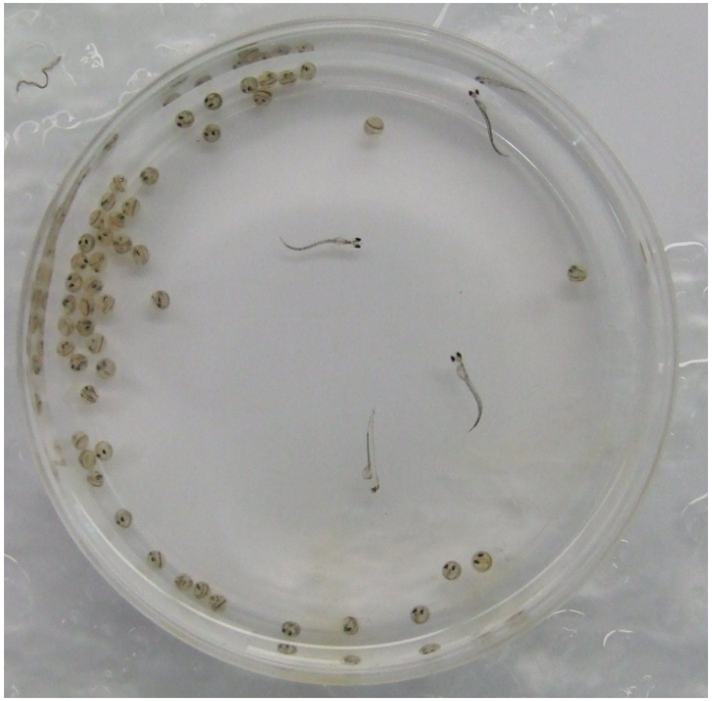
2016-2017

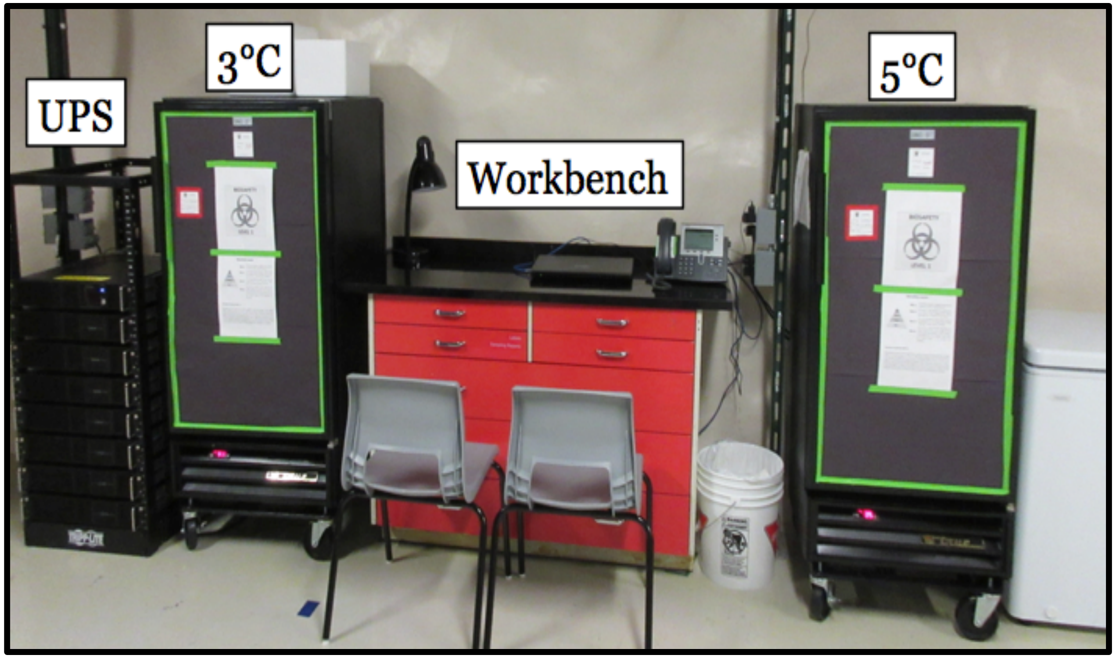
	LWL	SNO
Temperature	3°C	3°C
Dishes*	64	64
Embryos	3,200	3,200

*50 embryos per dish

Laboratory setup

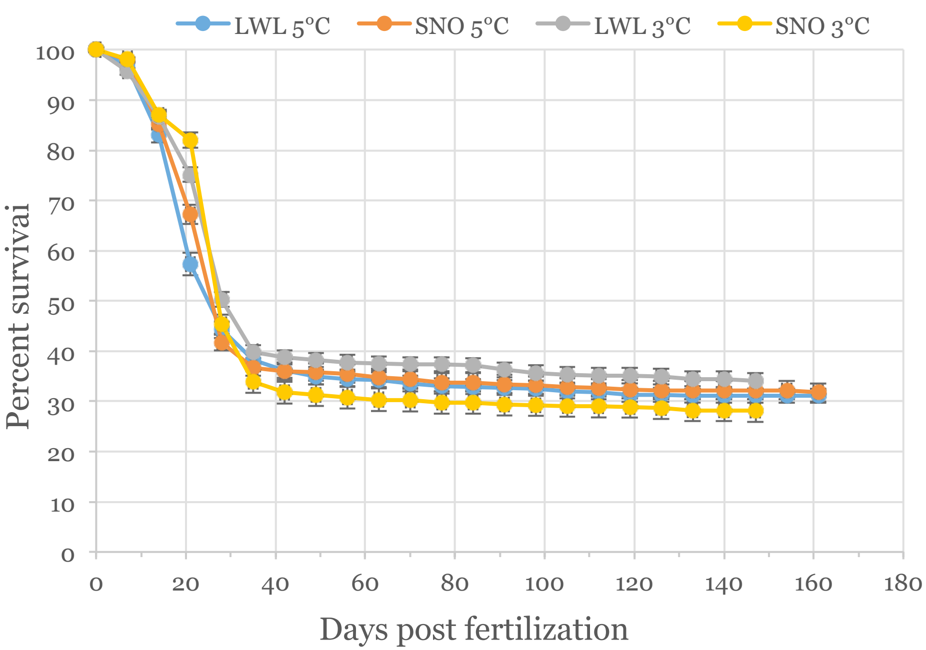
Lake whitefish
(Corgonus clupeaformis)



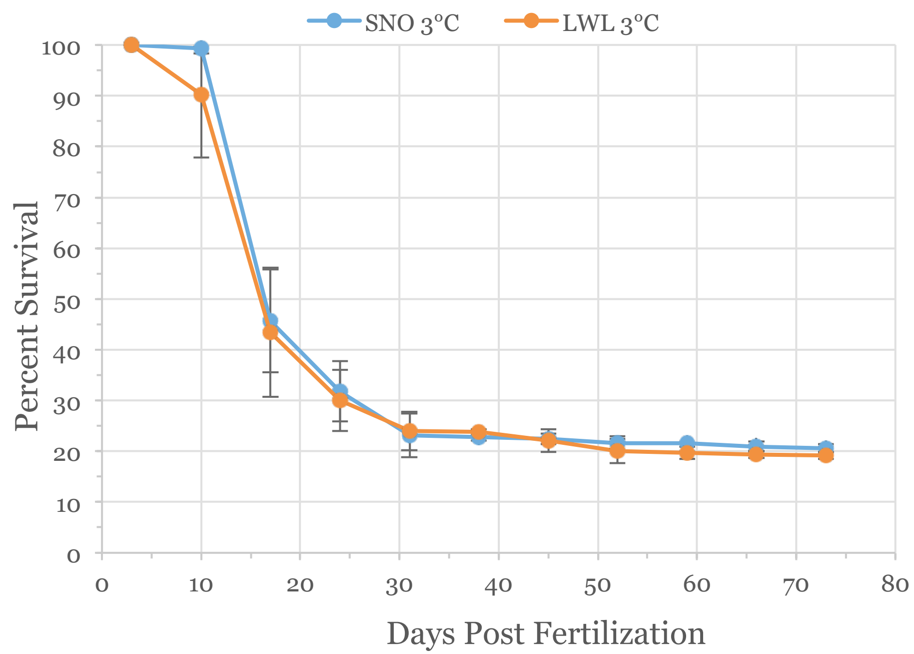


Embryo survival

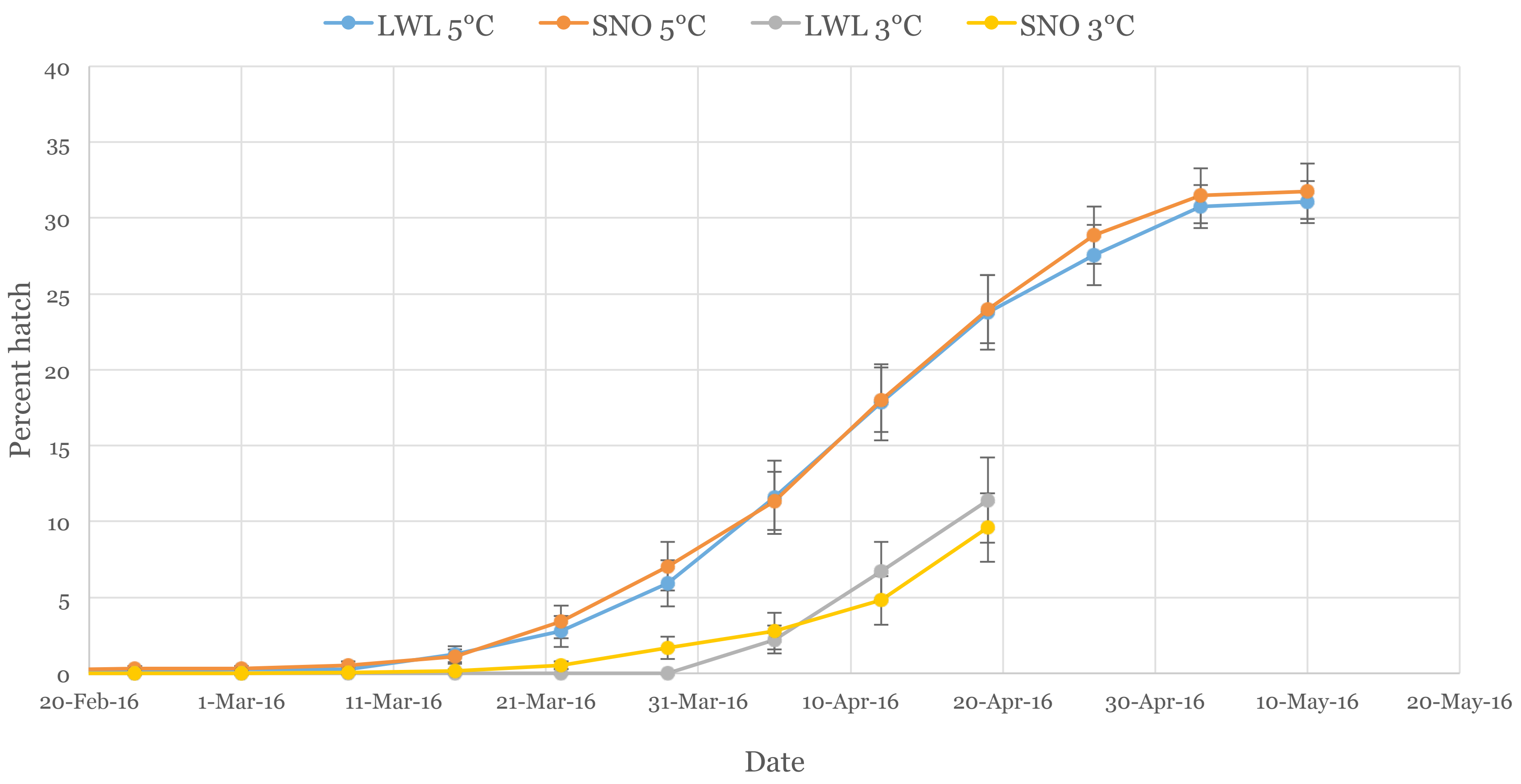
2015-2016



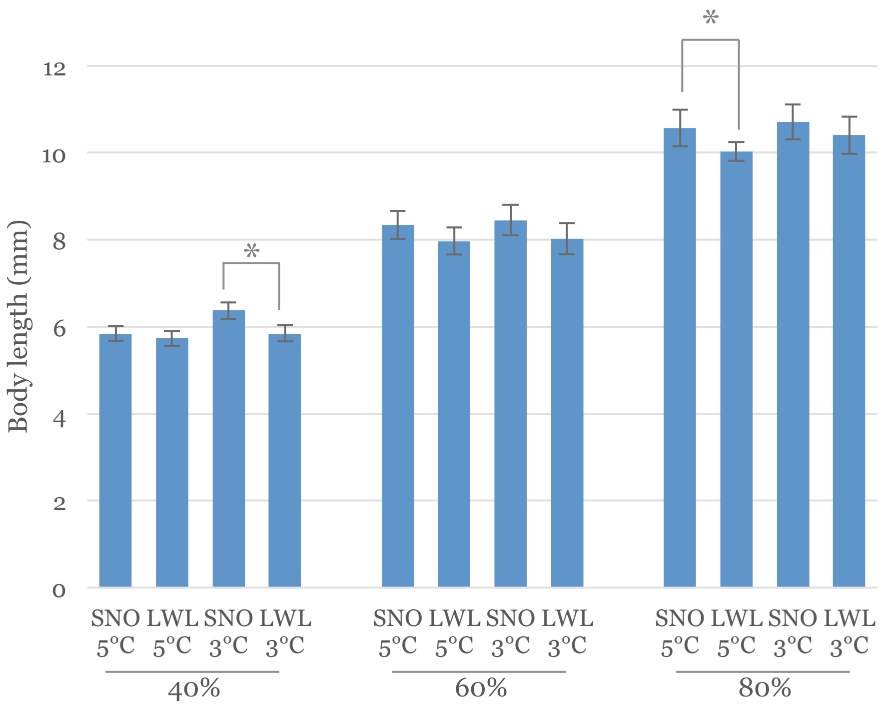
2016-2017

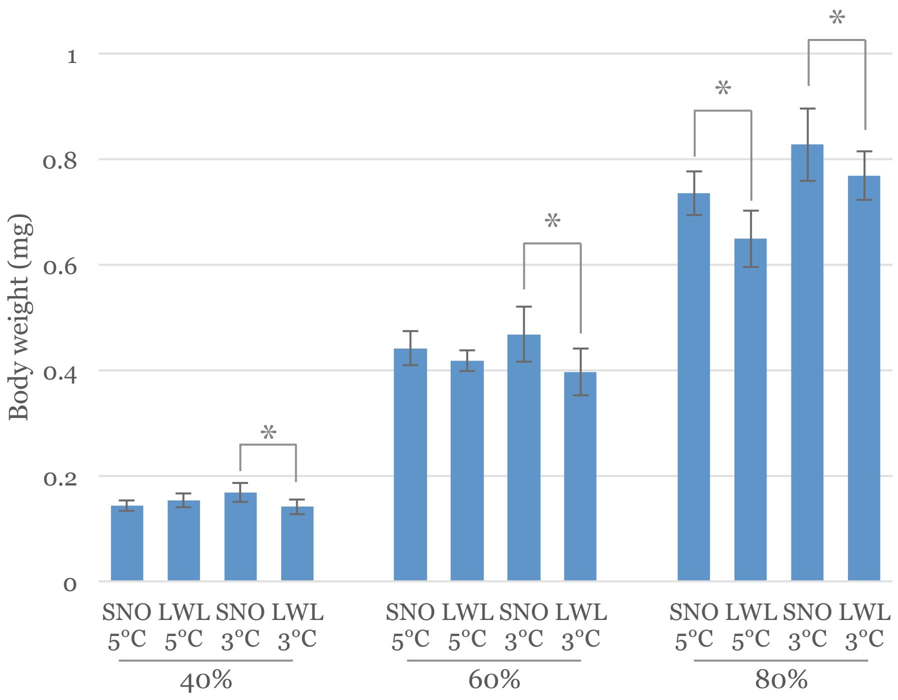


Development rate



Morphometric measurements



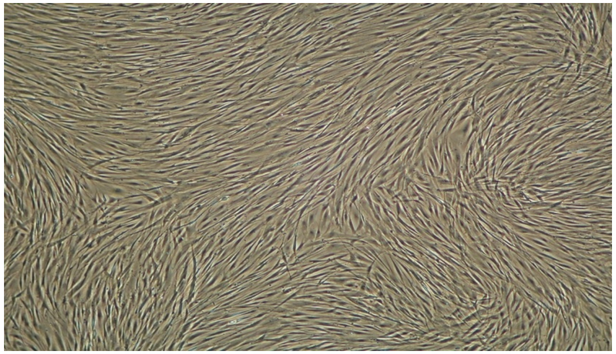


Cell culture

What is cell culture?

Individual cells are isolated from a known specimen then grown in suspension or in mono-layers on the surface of a flask in nutrient rich media.

Why do we use cell culture as a model system?



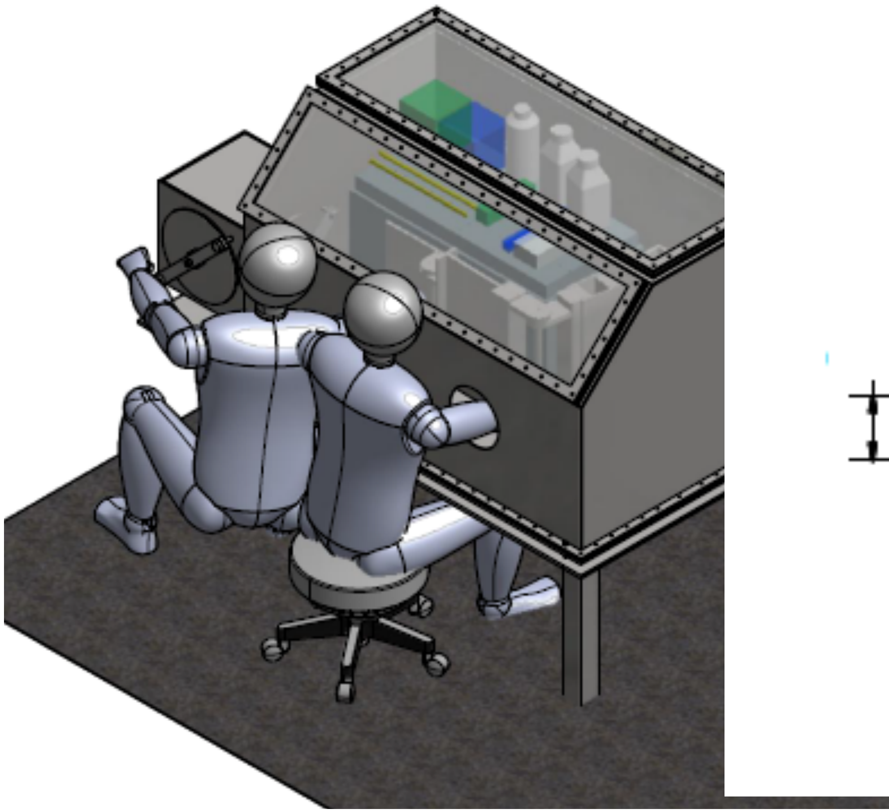
•Environmental variables are easily controlled and manipulated

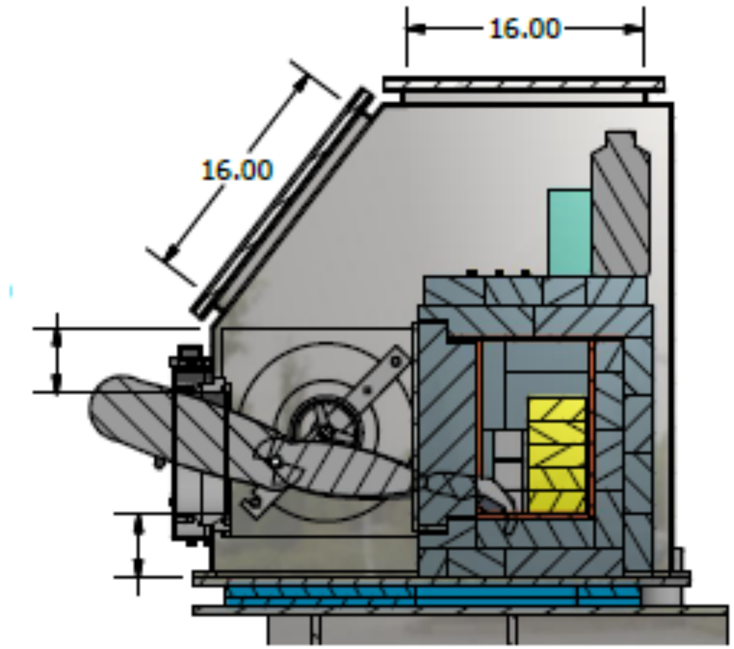
•Produces consistent and reproducible results

•Allows for a high throughput of experiments

•Specific pathways can be studied and results can be compared to the whole organism

Low radon glovebox





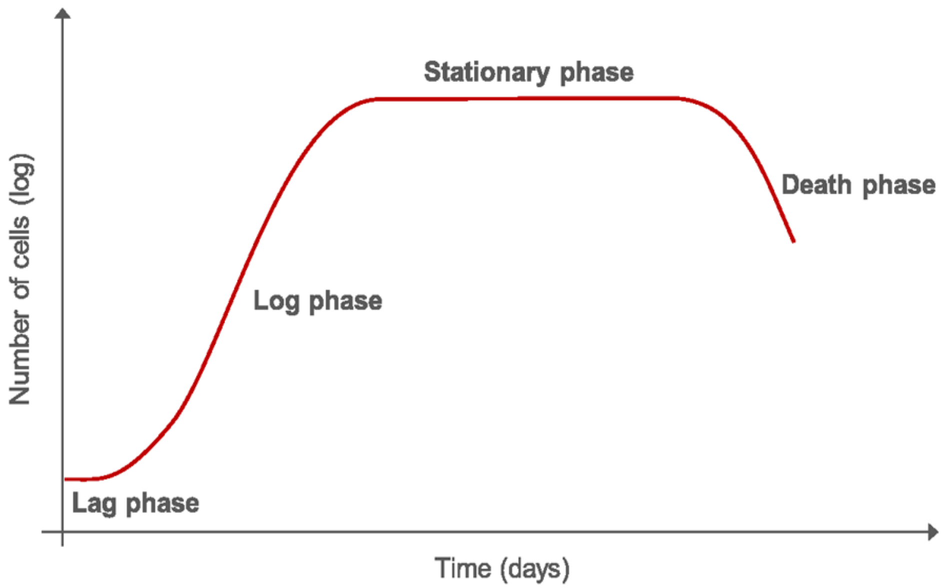
Basic growth characteristics

Growth kinetics

Growth curve analysis

•During the log phase doubling time can be calculated

•We can compare doubling time between different radiation environments

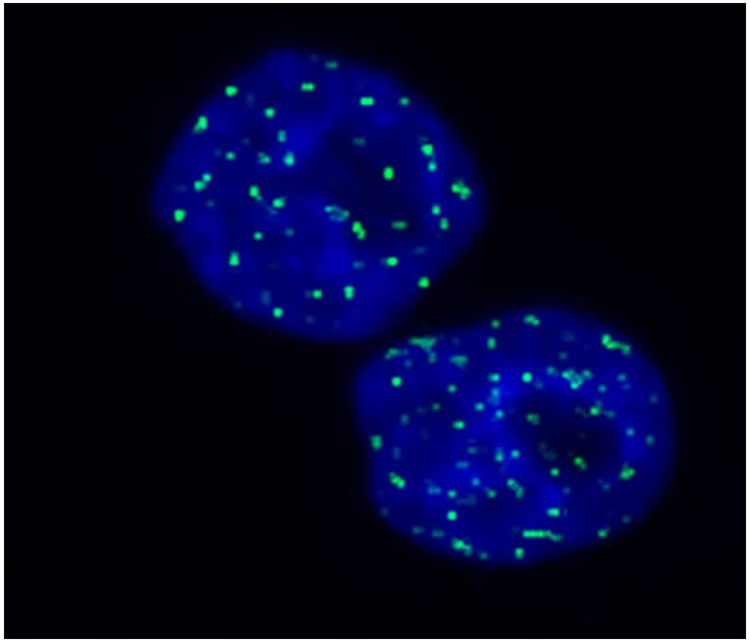


Percent survival

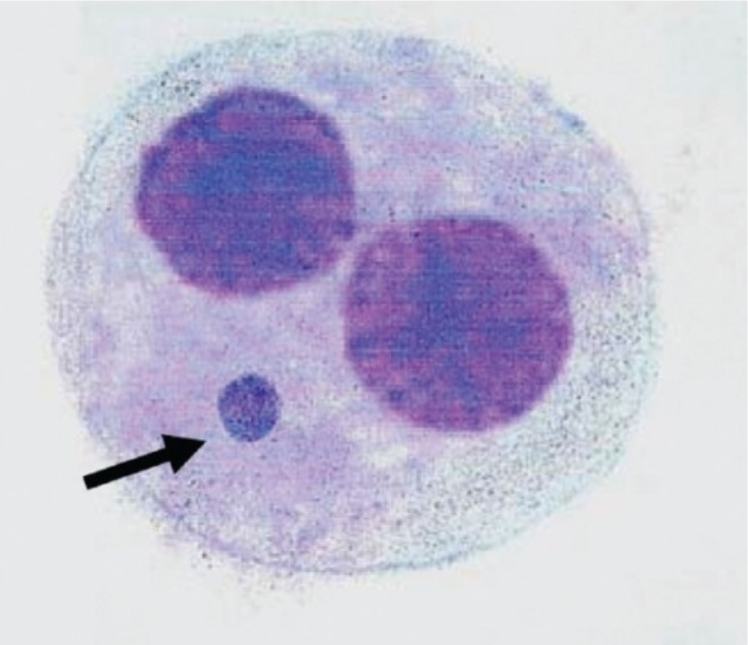
•Compare survival in different radiation environments

DNA damage

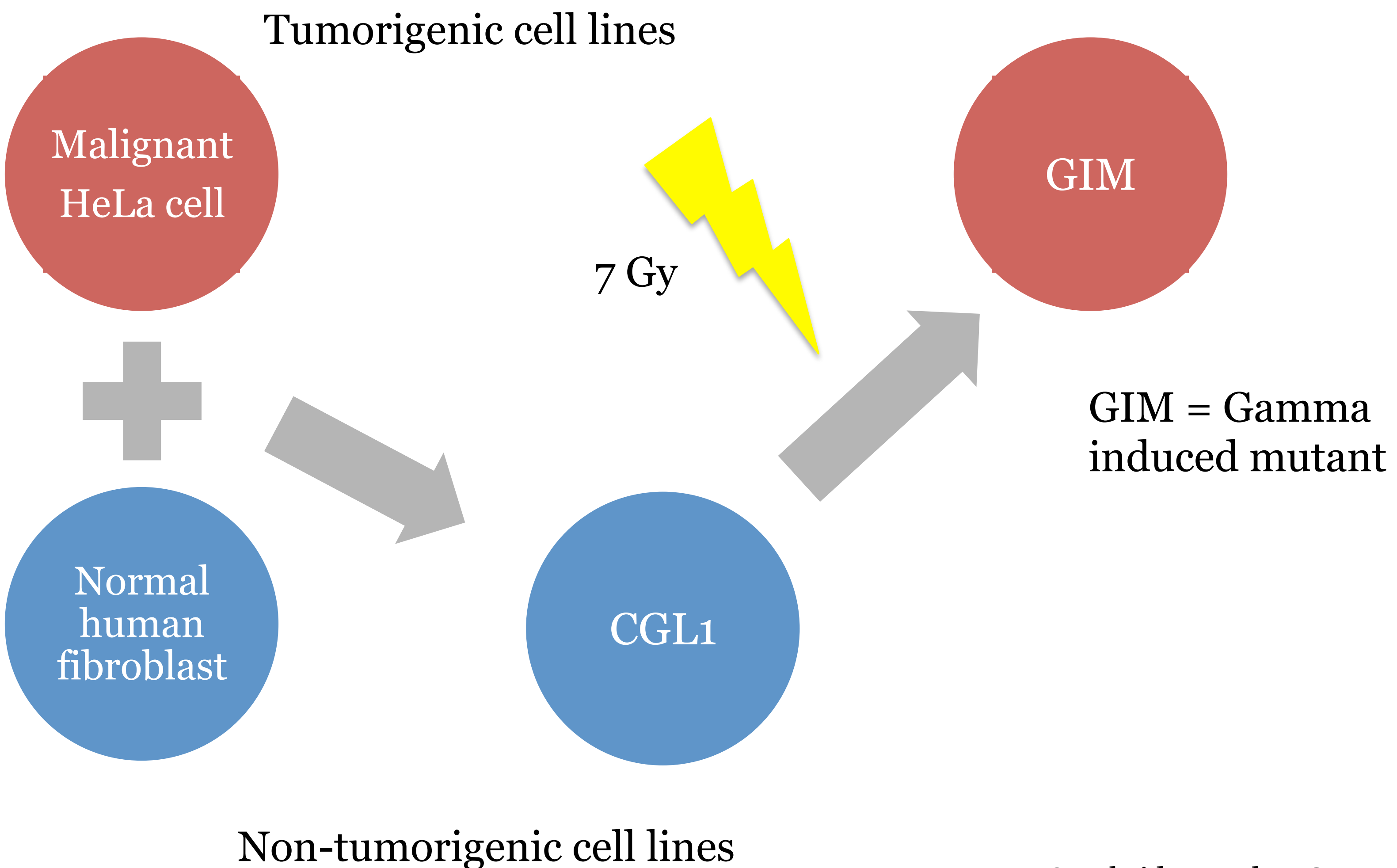
DNA damage sites



Micronucleus assay

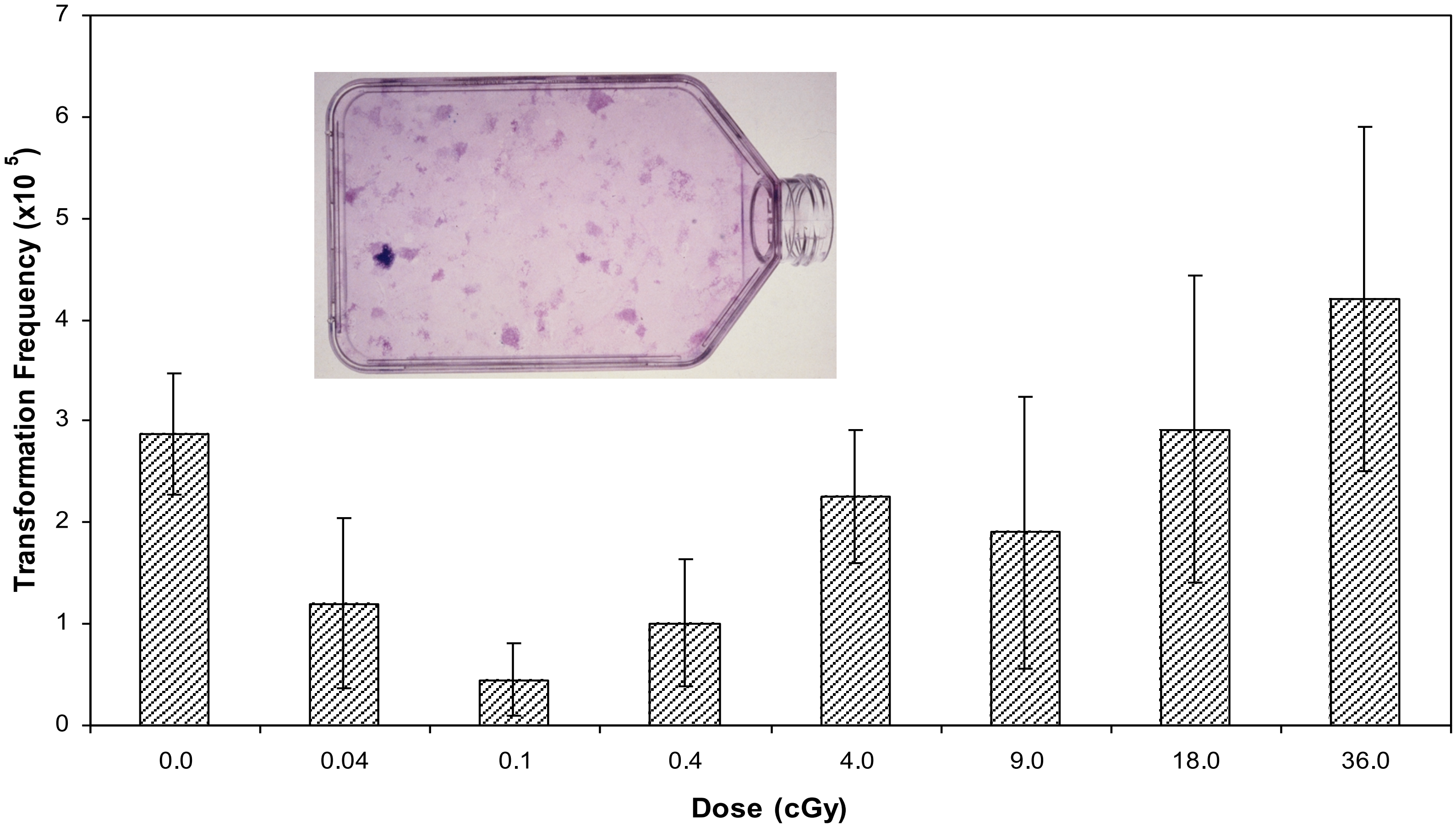


CGL1 cell line



Stanbridge et al. 1981

Transformation frequency



Redpath JL et al. 2000

Acknowledgements

Bruce Power

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NSERC
CRSNG

Mitacs

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Université Laurentienne