Northern Ontario School of Medicine
École de médecine du Nord de l'Ontario
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Laurentian University
Université Laurentienne

REPAIR Project

Researching the Effects of the Presence and Absence of Ionizing Radiation

SNOLAB Future Projects Workshop

July 15, 2019

REPAIR collaboration

Doug Boreham	Research Faculty	NOSM
Chris Thome	Research Faculty	NOSM
Simon Lees	Research Faculty	NOSM
T.C. Tai	Research Faculty	NOSM
Suji Tharmalingam	Research Faculty	NOSM
Marc Mendonca	Research Faculty	Indiana School of Medicine
Sharmila Bhattacharya	Research Scientist	NASA Ames
Sergio Santa Maria	Research Scientist	NASA Ames
Mary Ellen Cybulski	Research Manager	NOSM
Jake Pirkkanen	Post-doctoral	Laurentian
Taylor Laframboise	Technologist	Laurentian
Andrew Zarnke	PhD Student	Laurentian
Krista Currie	PhD Student	Laurentian
Konnor Kennedy	MSc Student	Laurentian

Funding

Bruce Power Industrial Support

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

NSERC CRD

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

NSERC Discovery

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

Mitacs Accelerate

- 2015 - 2017: $330,000 ($165,000 per year)
- 2019 - 2022: $165,000 ($55,000 per year)

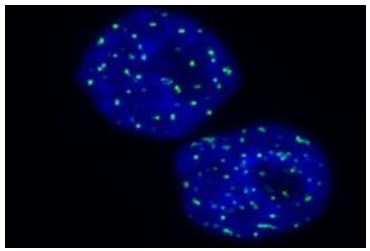
Bruce Power™ NSERC CRSNG Mitacs

Radiation response

Normal Cell

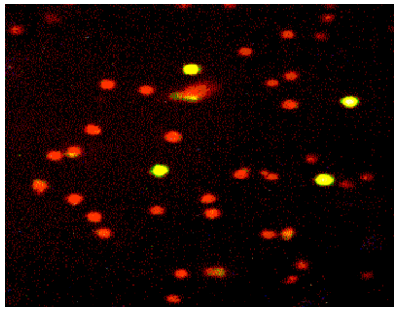
Error free repair

DNA Damage



Error prone repair

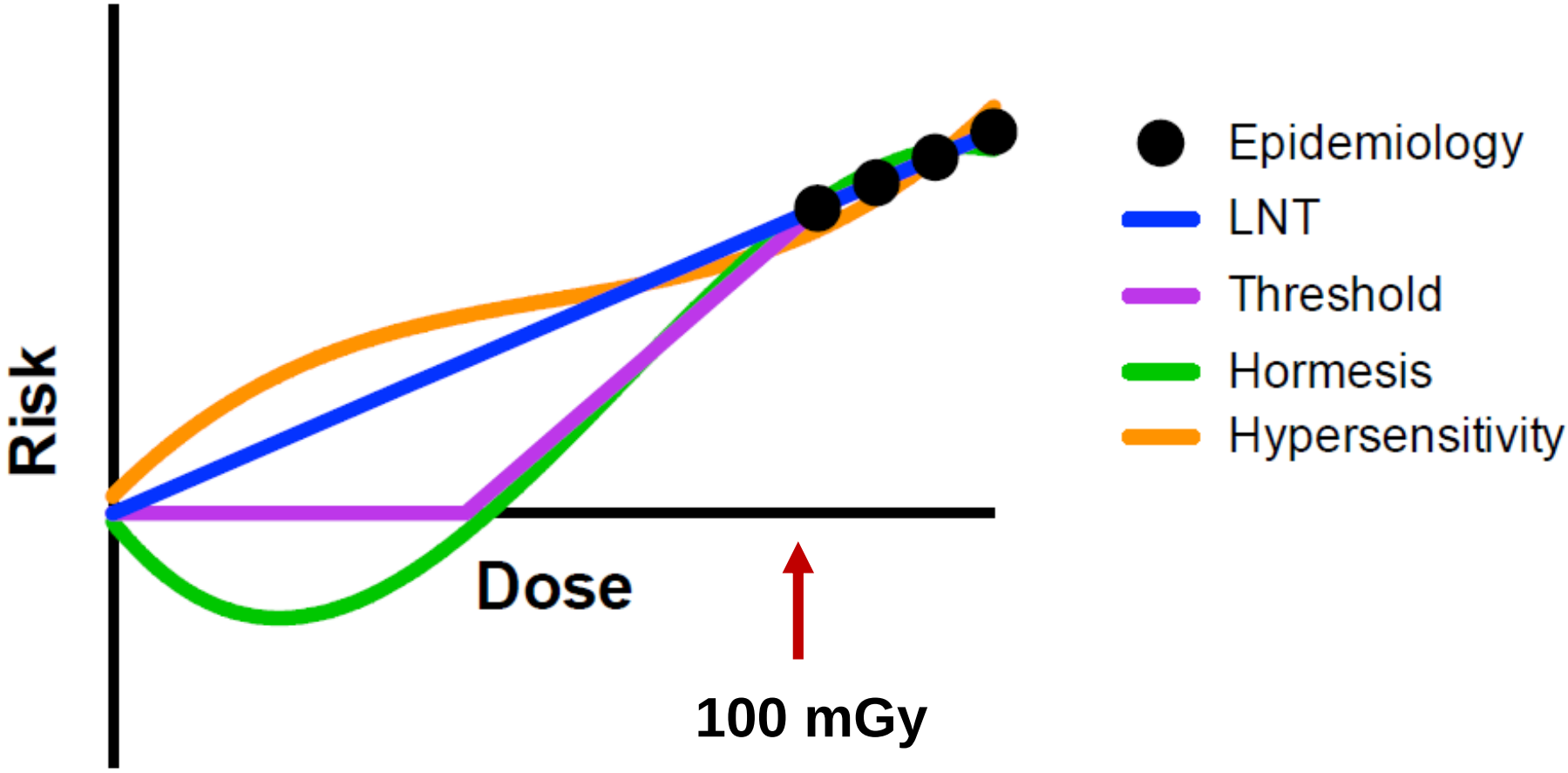
Cell death



Mutations

Cancer

Models of radiation risk



Diagnostic radiation

Lemon et al. 2017

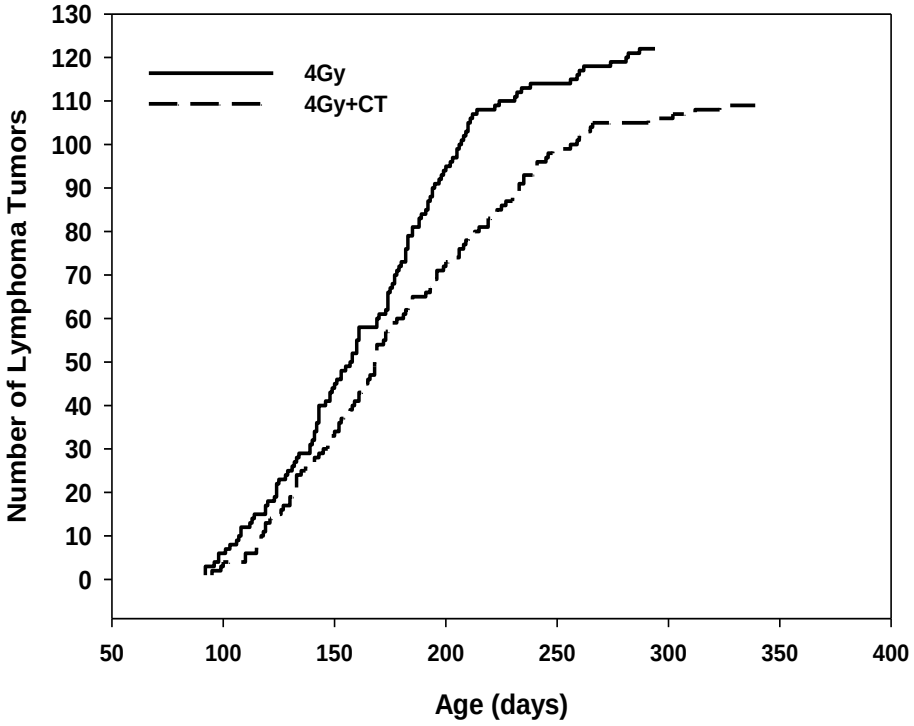
Trp53$^{+/-}$ mice

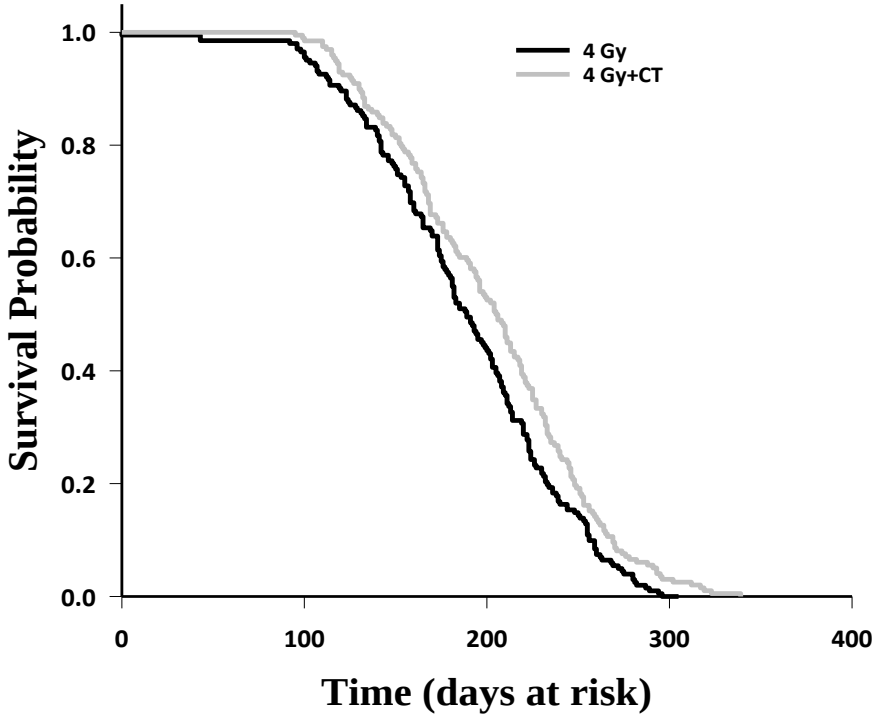
7-8 wks

4 Gy

3 wks

Weekly 10 mGy CT scan



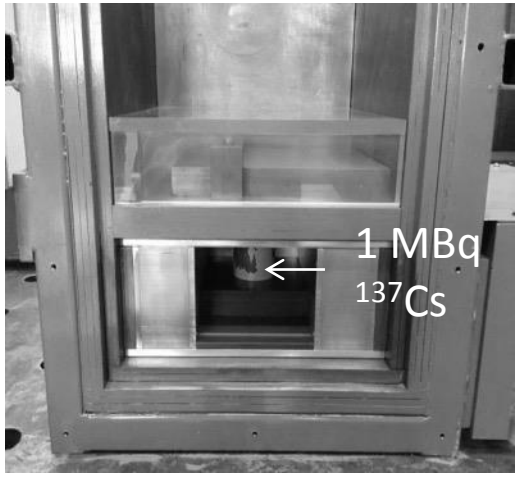


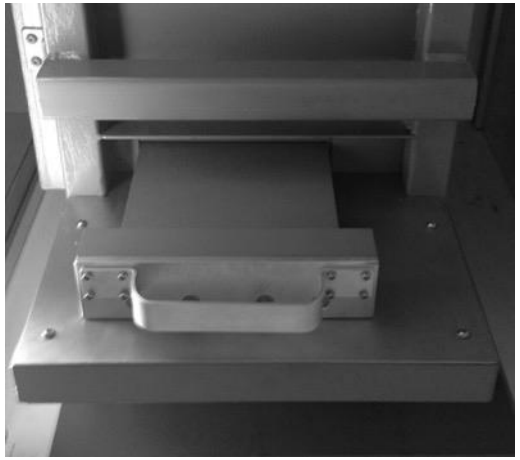
Embryonic development

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

Thome et al. 2017





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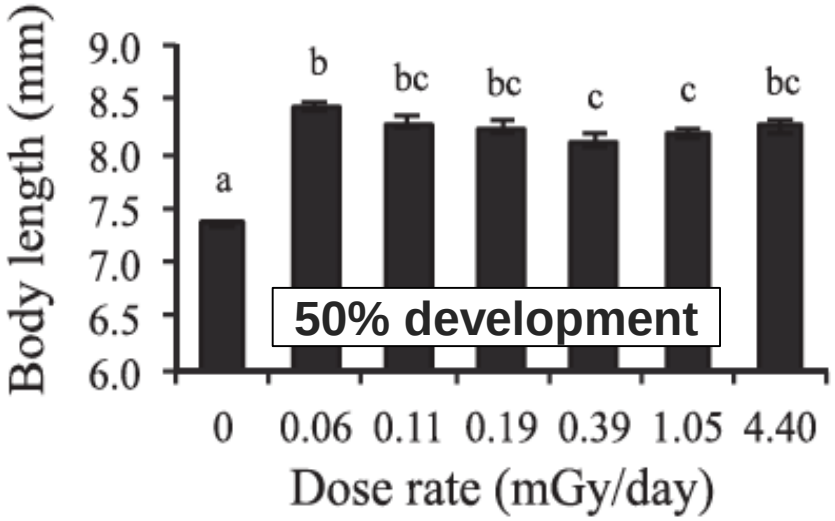
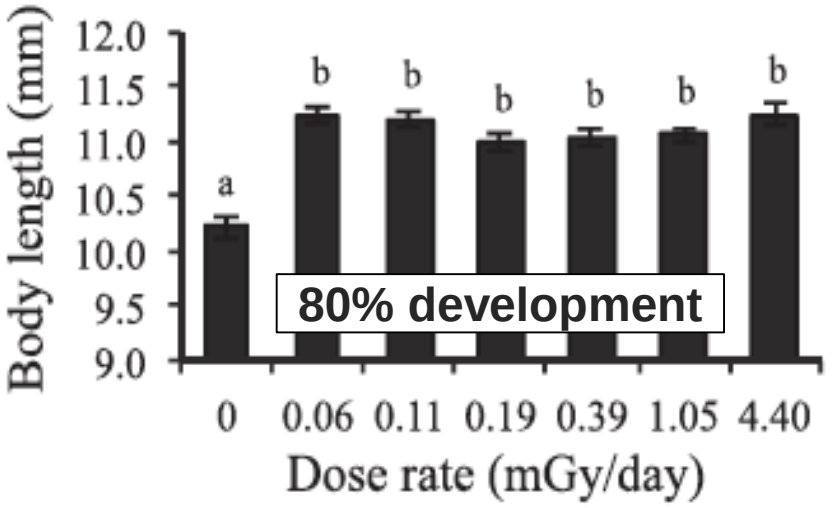
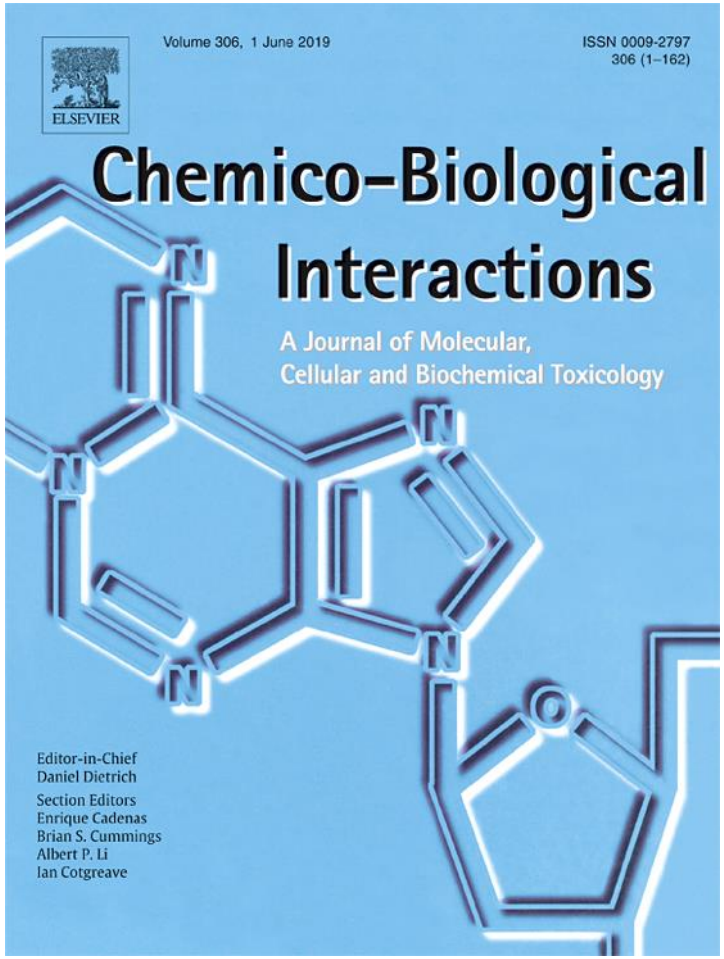




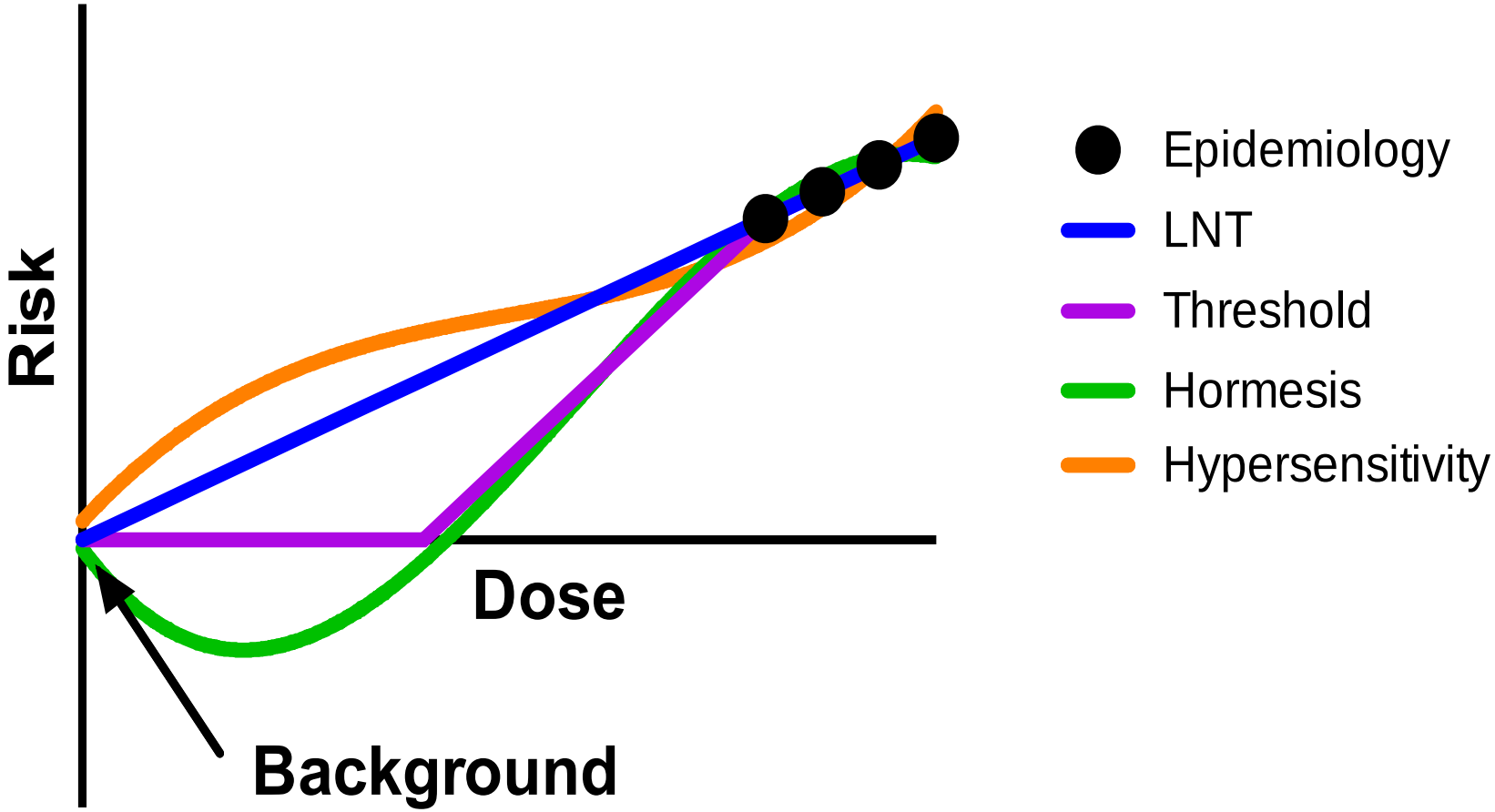
Chemico-Biological Interactions

Volume 301, March 2019

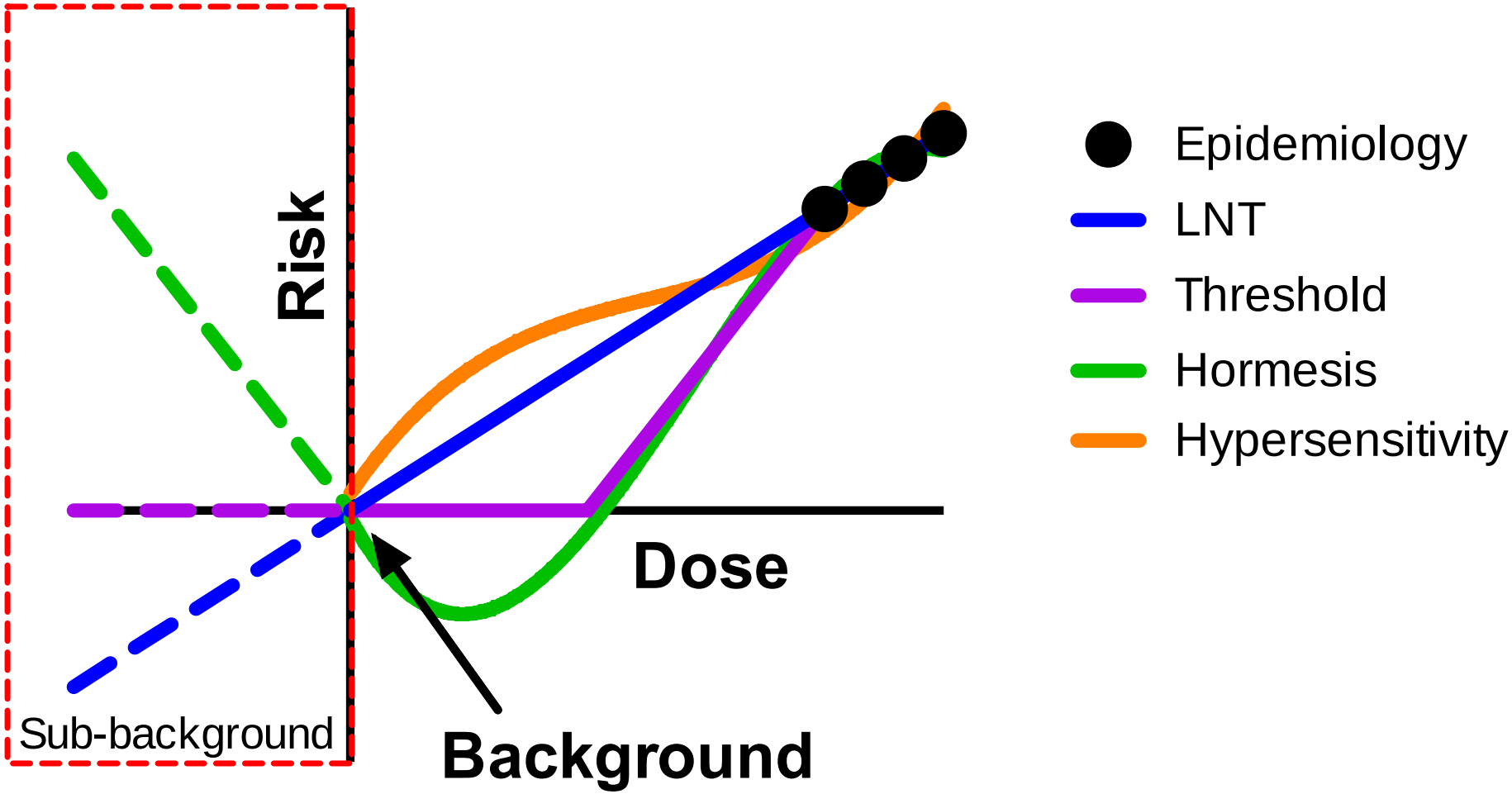


- Tharmalingam, S., Sreetharan, S., Brooks, A. L., and Boreham, D. R. 2019. Re-evaluation of the Linear No-threshold (LNT) Model Using New Paradigms and Modern Molecular Studies. *Chemico-Biological Interactions. 301: 54-67*
- Zarnke, A. M., Tharmalingam, S., Boreham, D. R., and Brooks, A. L. 2019. BEIR VI Radon: The Rest of the Story. *Chemico-Biological Interactions. 301: 81-87.*
- Ricci, P. F., and Tharmalingam, S. 2019. Ionizing Radiations Epidemiology Does Not Support the LNT Model. *Chemico-Biological Interactions. 301: 128-140*
- Scott, B. R., and Tharmalingam, S. 2019. The LNT Model for Cancer Induction is Not Supported by Radiobiological Data. *Chemico-Biological Interactions*. 301:34-53.

Models of risk



Models of risk



Sub-background effects

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

   Paramecium (Planel *et al* 1976), Blue-green algae (Conter *et al* 1983), *S. cerevisiae* (Gajendiran and Jeevanram 2002), *Deinococcus radiodurans* (Smith *et al* 2011), Mouse lymphoma L5178Y cells (Taizawa *et al* 1992, Kawanishi *et al* 2012).

2. Removal of natural background radiation reduces repair capacity:

   Survival fraction (Gajendiran and Jeevanram 2002), Background/induced mutation rates (Satta *et al* 2002), Micronuclei formation and ROS scavenging (Carbone *et al* 2010).

Sub-background laboratories

1. Gran Sasso

- Yeast: *Saccharomyces cerevisiae* (Satta et al 1995)
- Fruit flies: *Drosophila melanogaster* (Morciano et al 2018)
- Cell culture: Chinese hamster ovary, Human lymphoblast (Satta et al 2002, Antoneli 2008, Fratini 2015, Carbone 2009, 2010)

2. WIPP

- Bacteria: *Deinococcus radiodurans, Shewanella oneidensis* (Smith et al 2011, Castillo et al 2015)

3. CJEM, Jinping

- Cell culture: Chinese hamster ovary, Human thyroid (Liu et al 2018)

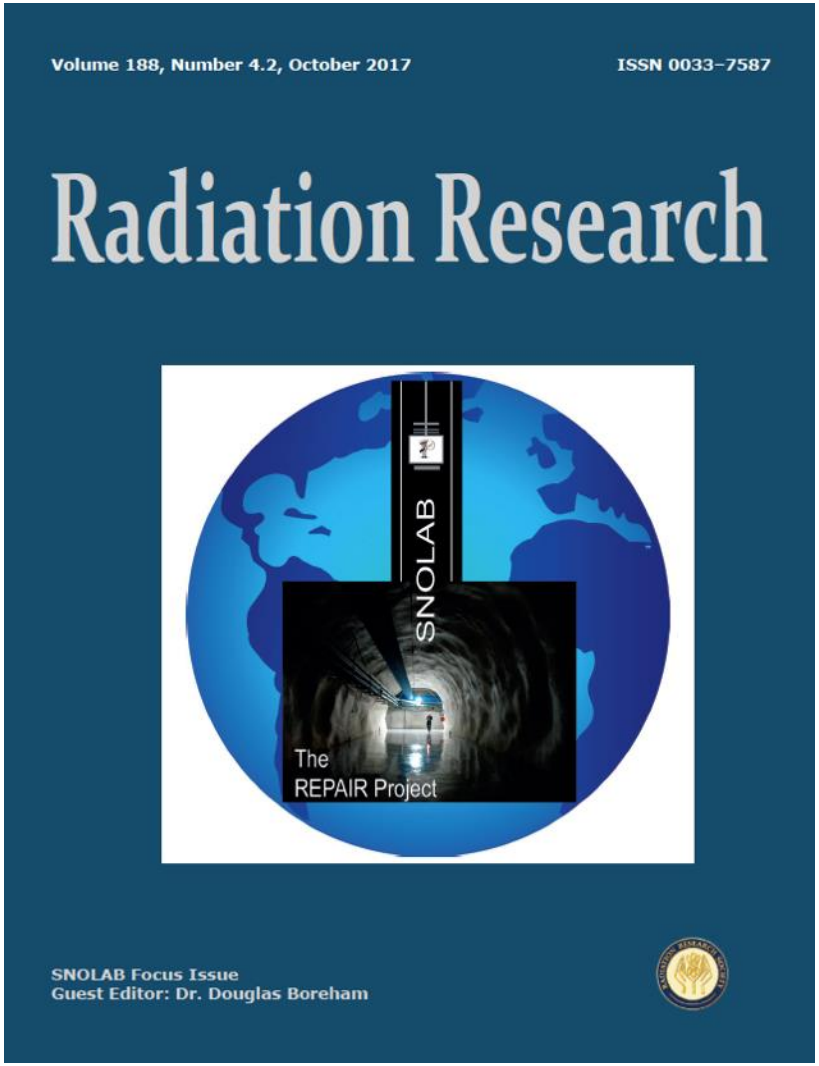
Hypothesis

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

Radiation Research

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 cell model for examining survival, DNA damage and carcinogenesis

Lake whitefish

Embryos were reared at 2 temperatures:

- 5ºC, 3ºC

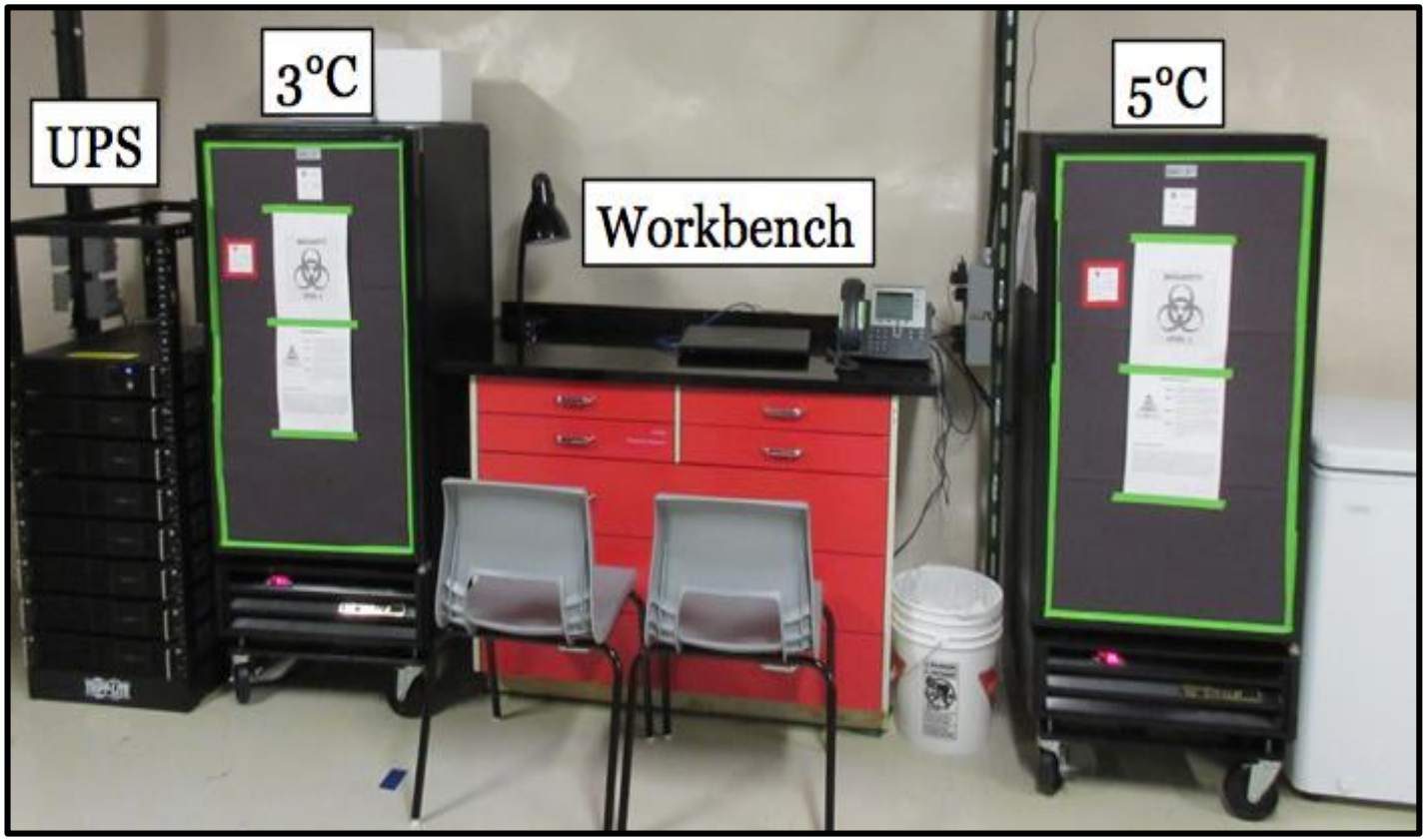
Embryos were analyzed at three timepoints:

- 40%, 60%, 80% development

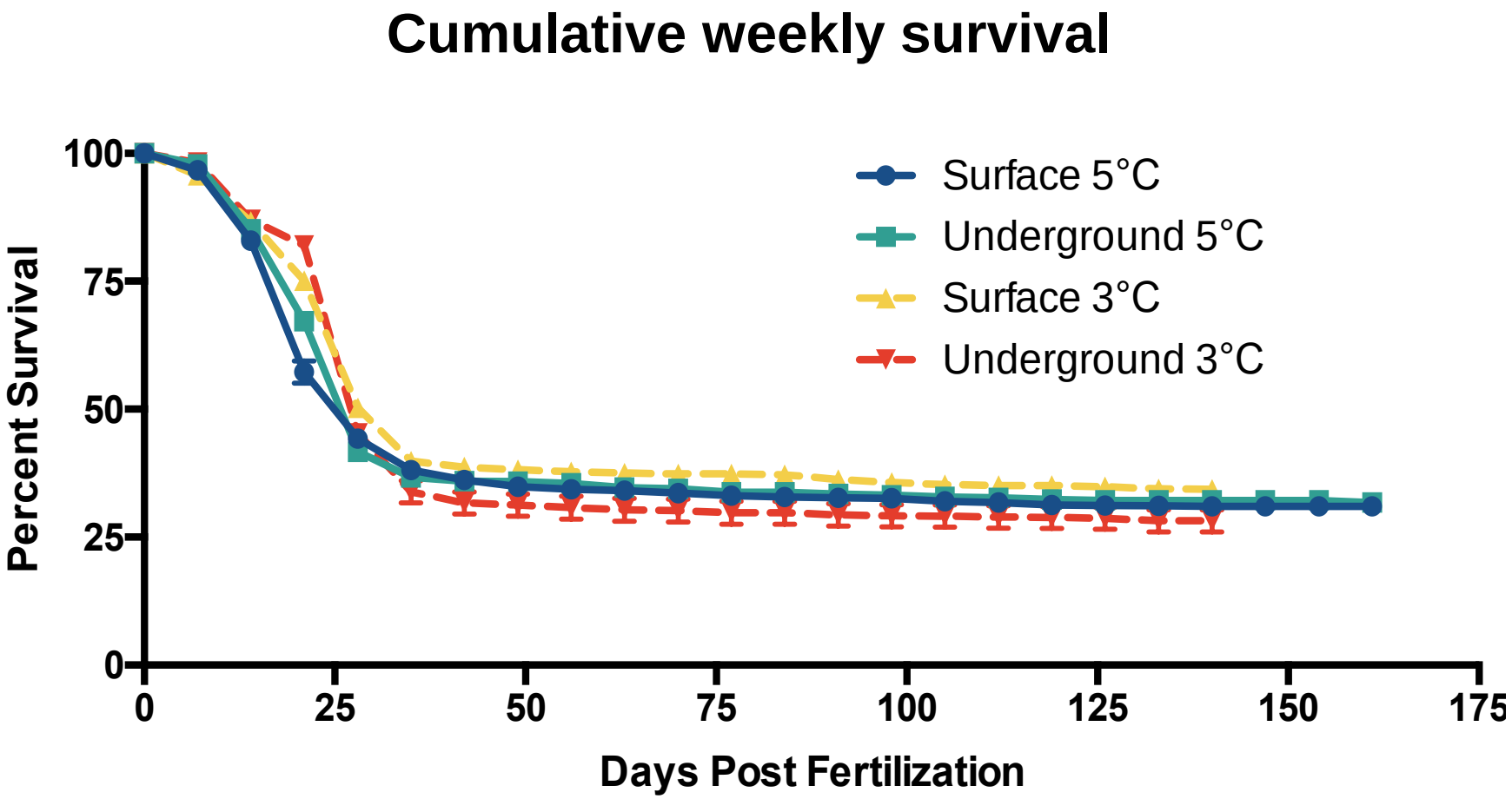
	Temperature (°C ± SD)	Dishes	Embryos	Sampling timepoint (dpf*)		
				40%	60%	80%
Surface 5°C	4.7 ± 0.2	39	1,950	38	58	79
Underground 5°C	4.6 ± 0.3	43	2,150	38	58	79
Surface 3°C	3.3 ± 0.4	38	1,900	50	73	101
Underground 3°C	3.4 ± 0.2	42	2,100	50	73	101

Lake whitefish

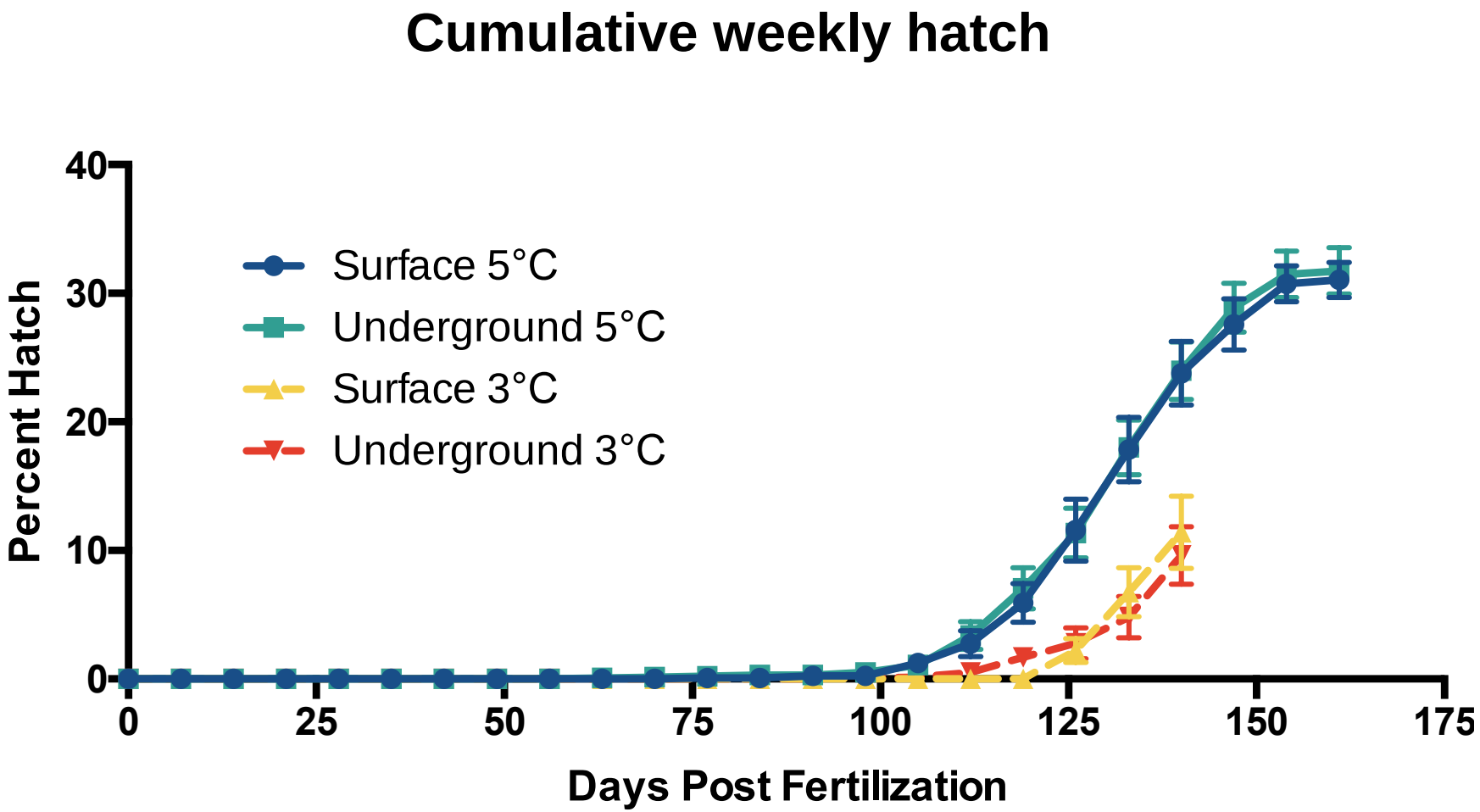
Chemistry/life sciences laboratory
2015 - 2017



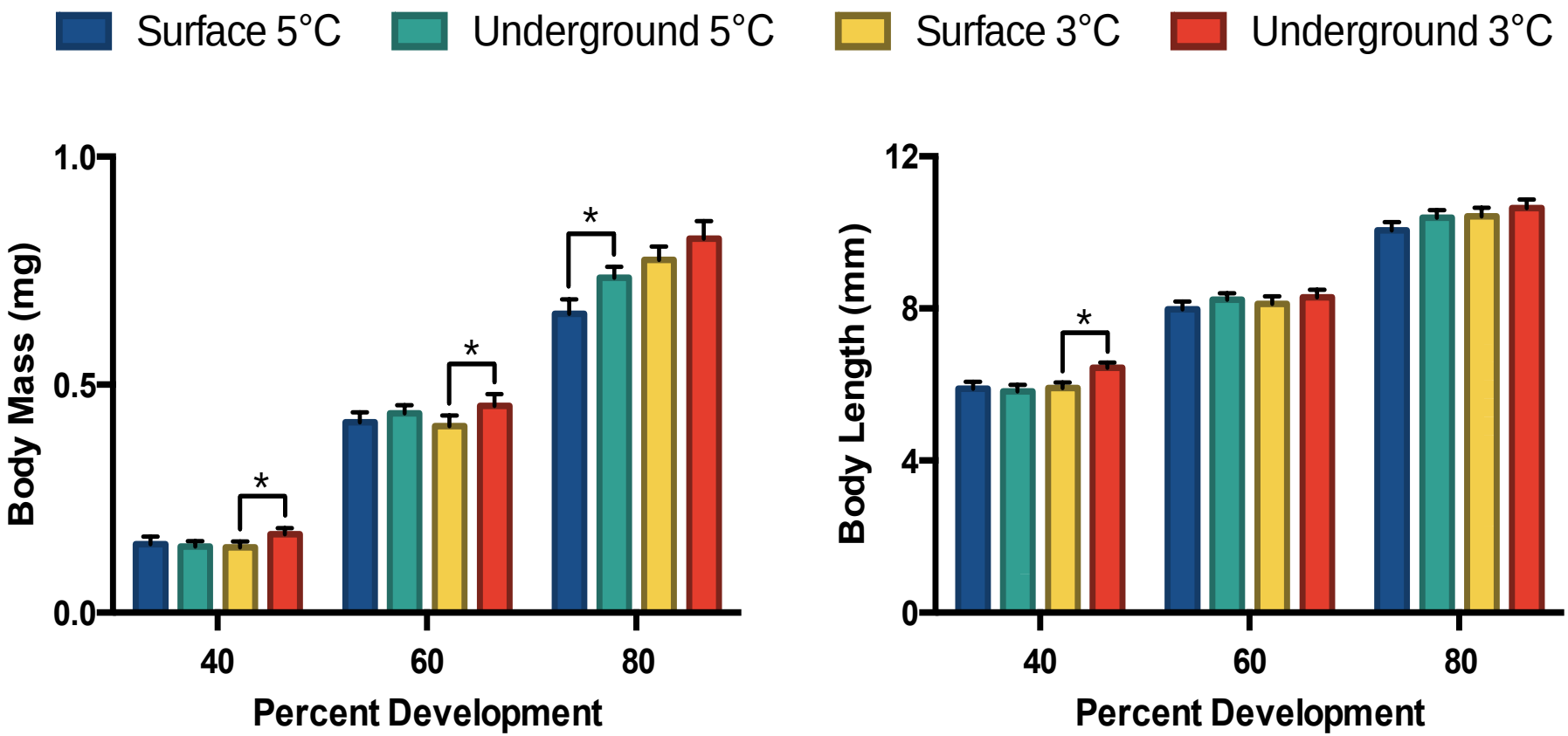
Lake whitefish



Lake whitefish



Lake whitefish

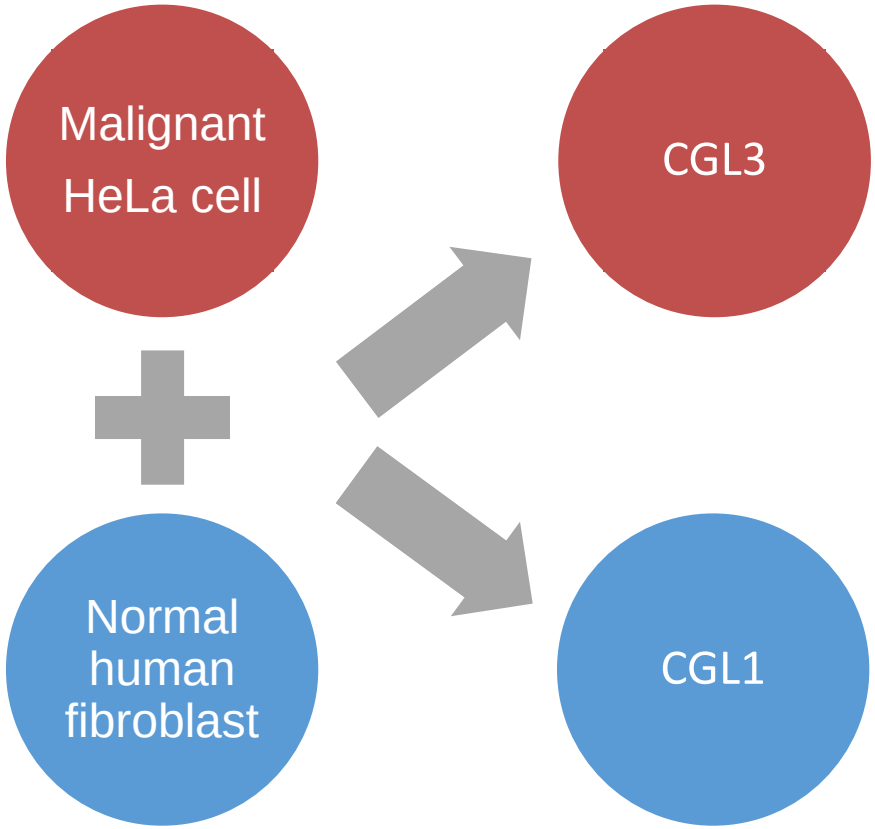


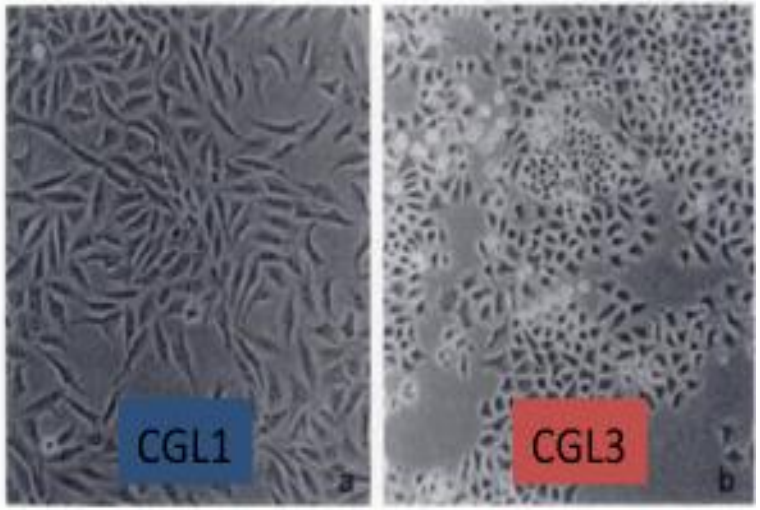
Cell culture

Chemistry/life sciences laboratory

2019

CGL1 model system



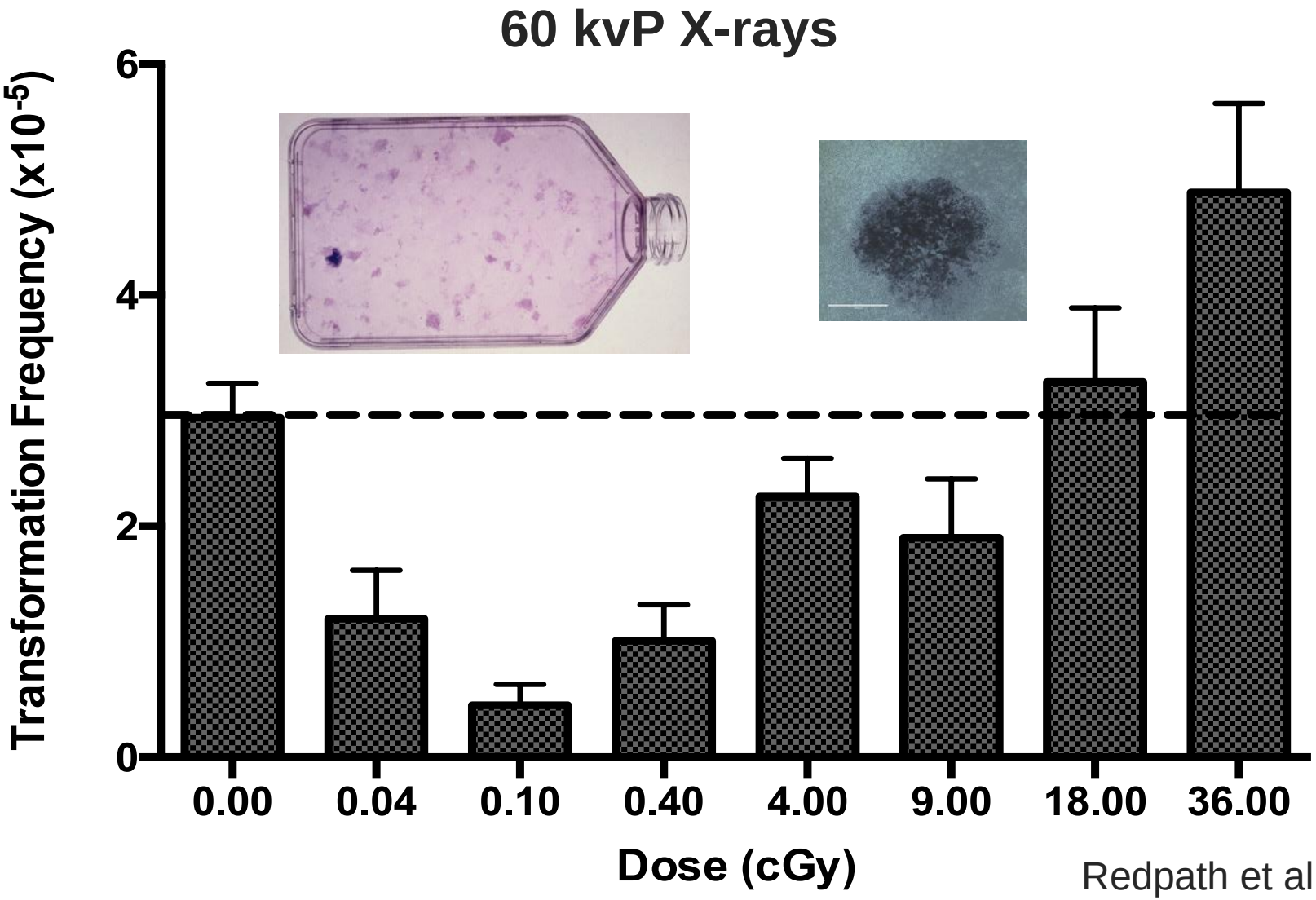


Tumorigenic cell

Non-tumorigenic cell

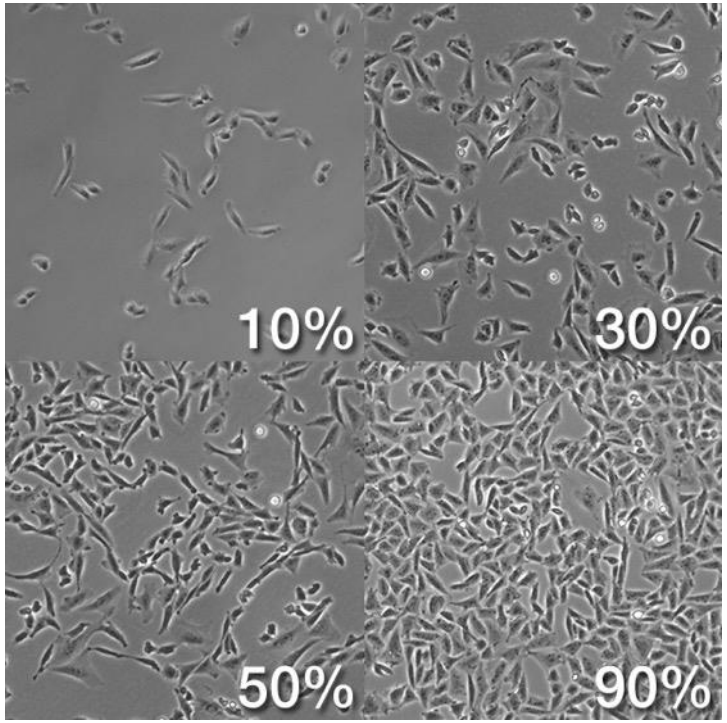
Stanbridge et al. 1982

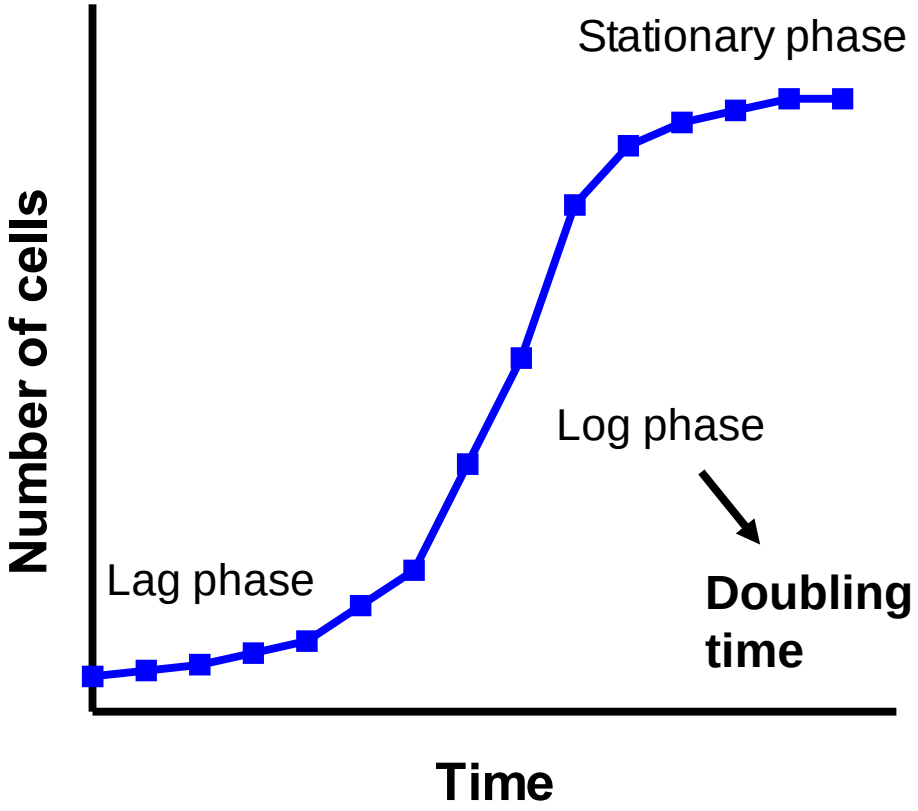
Neoplastic transformation



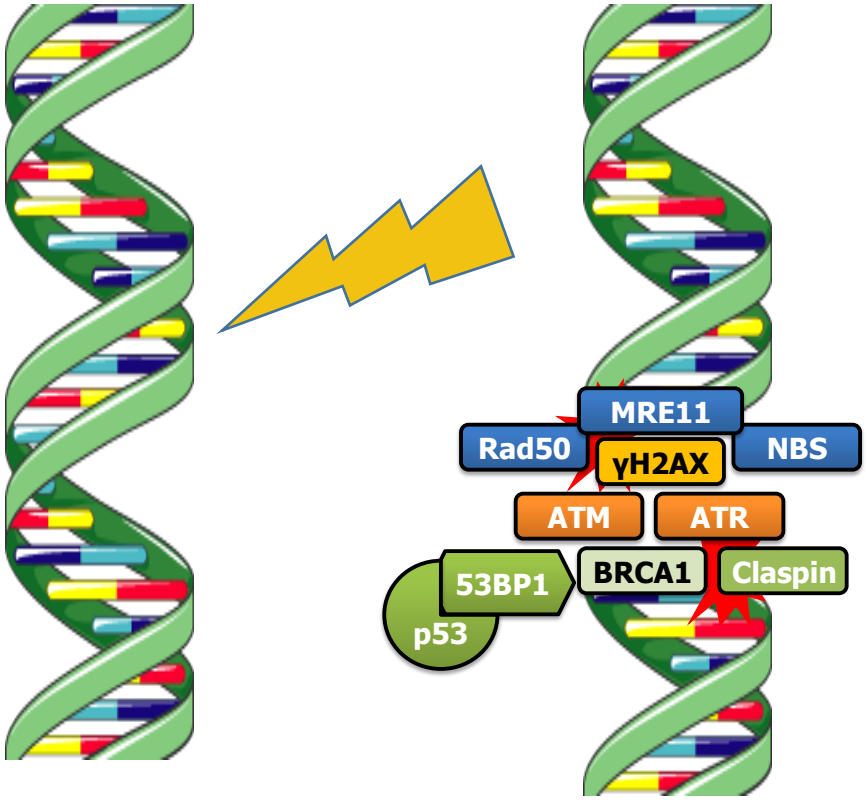
Redpath et al. 2003

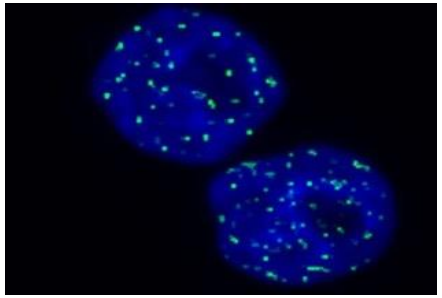
Cell growth

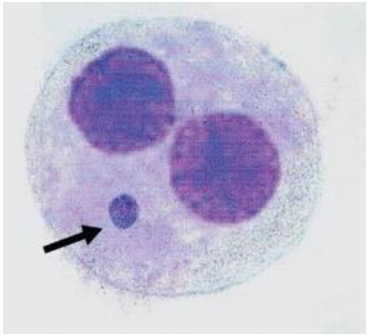

10%
30%
50%
90%

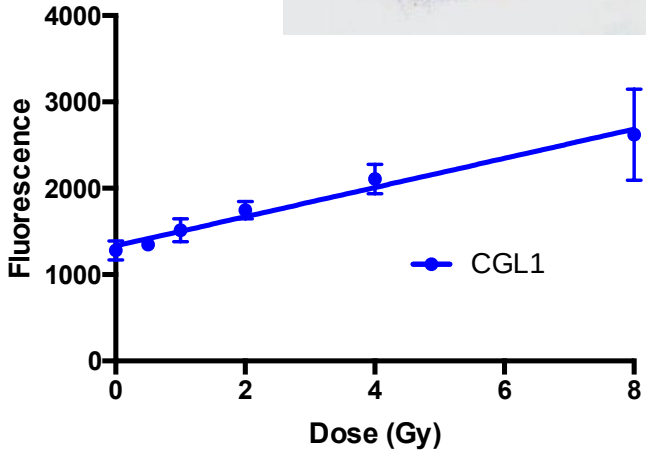

Stationary phase
Number of cells
Log phase
Lag phase
Doubling time
Time

DNA damage and mutation

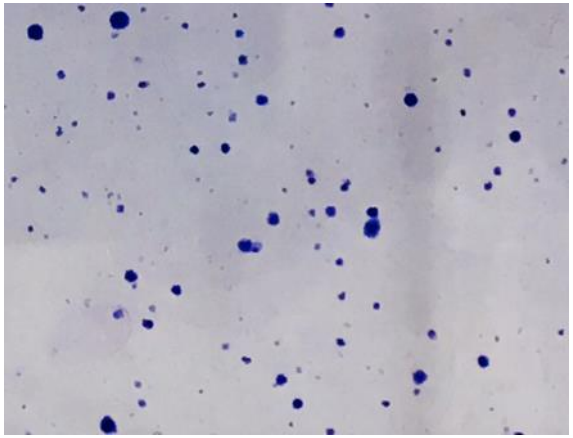


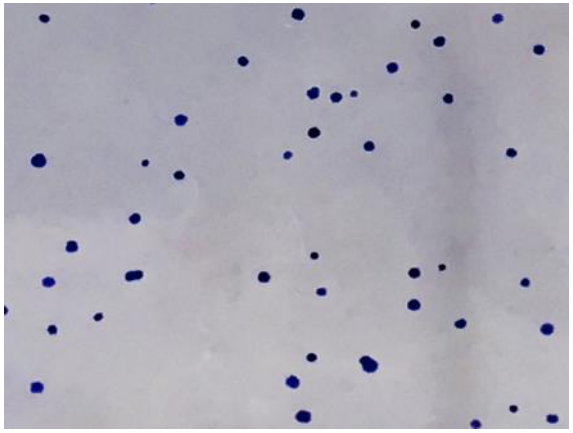


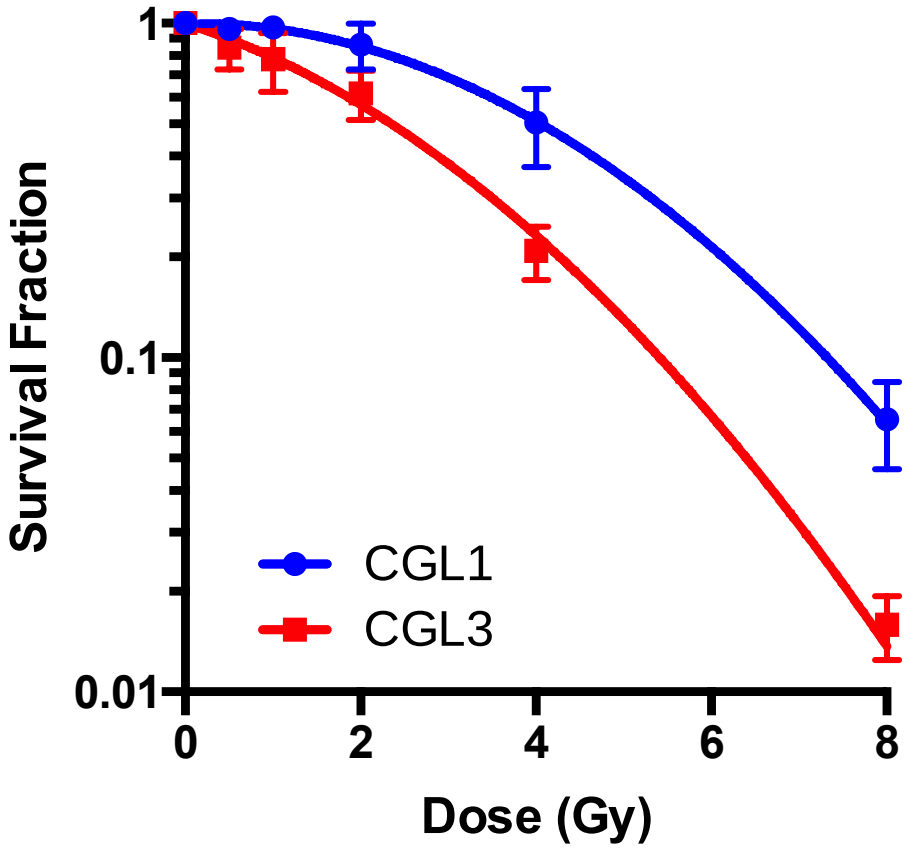




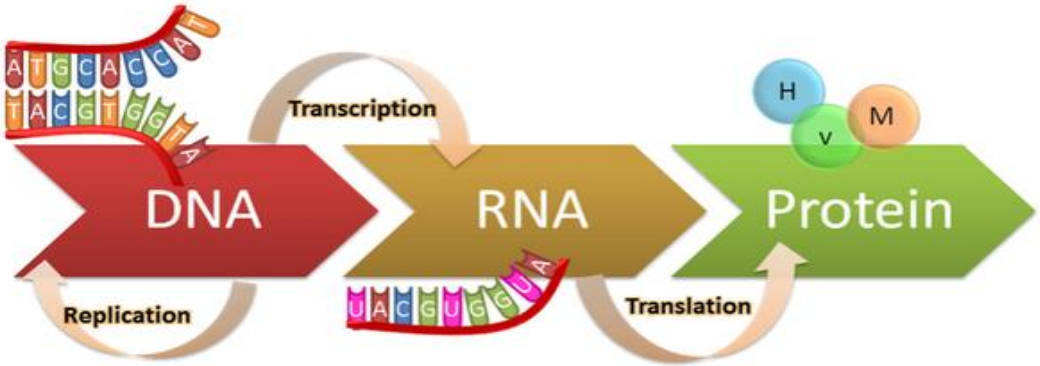
Cell survival

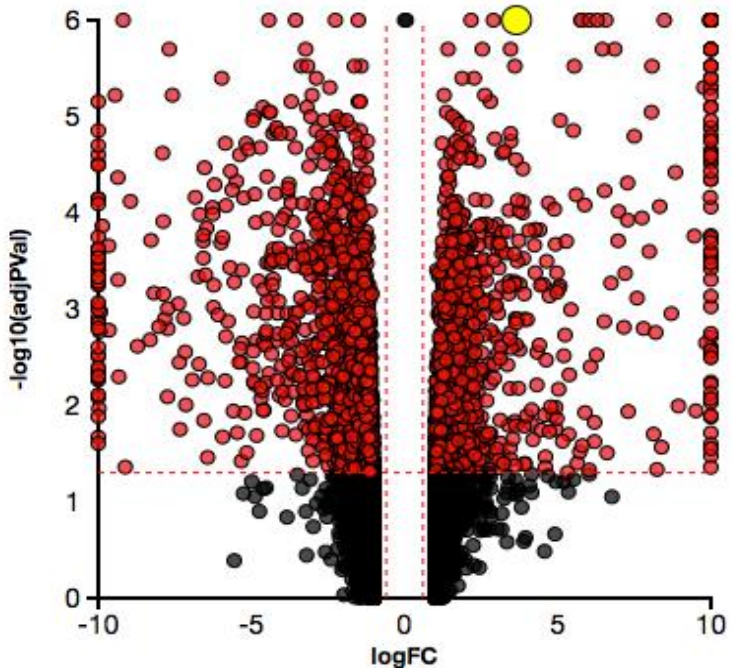






Gene expression





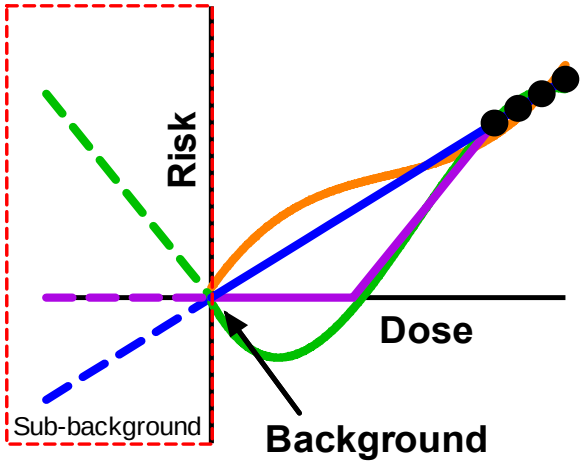
Sub-background effects

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

Questions?