Northern Ontario School of Medicine
École de médecine du Nord de l'Ontario

Examining the biological effects of ultra-low background radiation exposure within SNOLAB

Dr. Douglas Boreham
Chris Thome, Jake Pirkkanen, Andrew Zarnke

DULIA-BIO workshop
October 14, 2015

Research group

Dr. Douglas Boreham

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

Research interests:

- Low-dose radiobiology
- Diagnostic imaging
- Cancer therapy

Chris Thome

Post doctoral researcher - NOSM

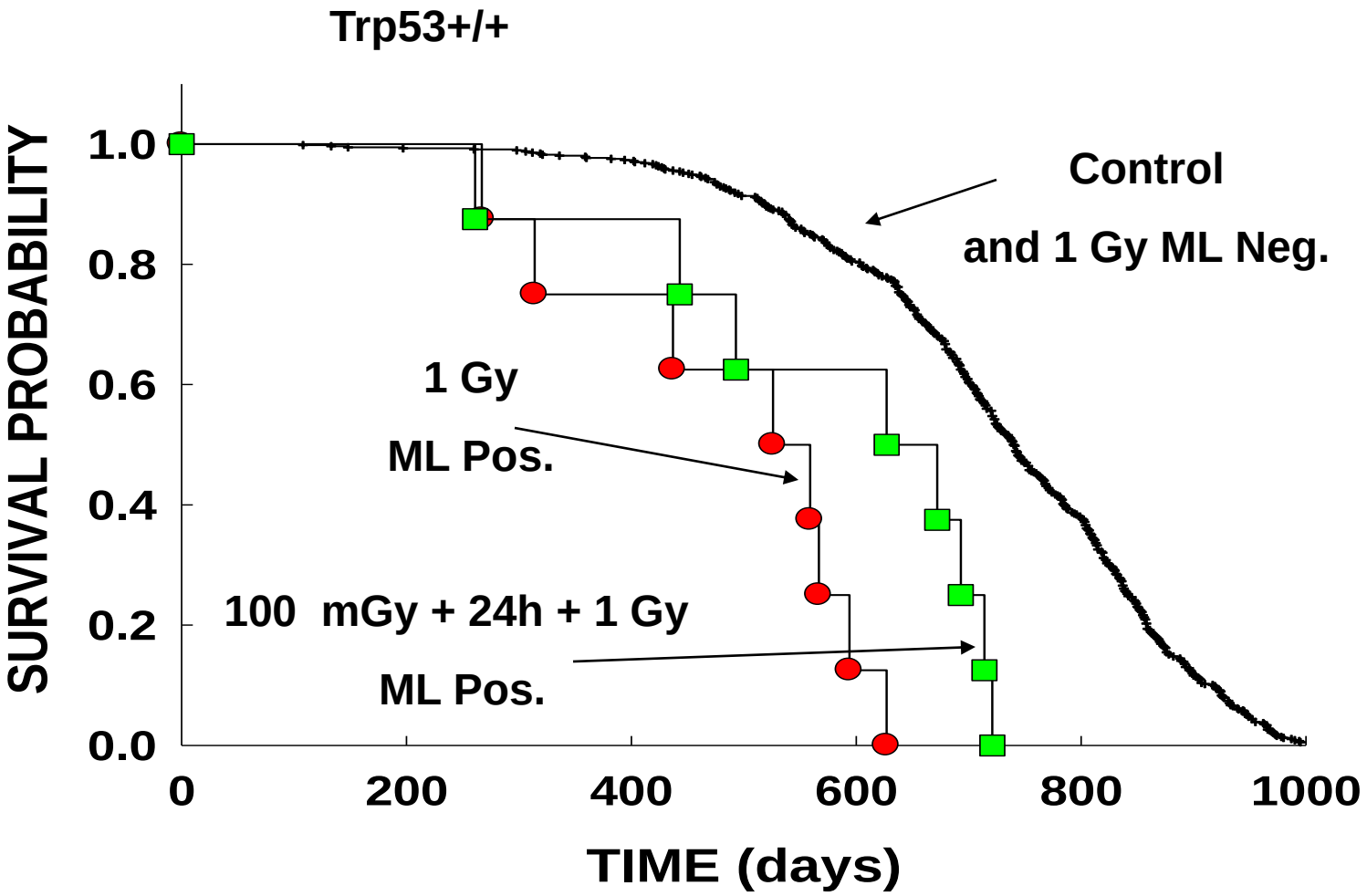
Jake Pirkkanen

Graduate student – Laurentian University

Andrew Zarnke

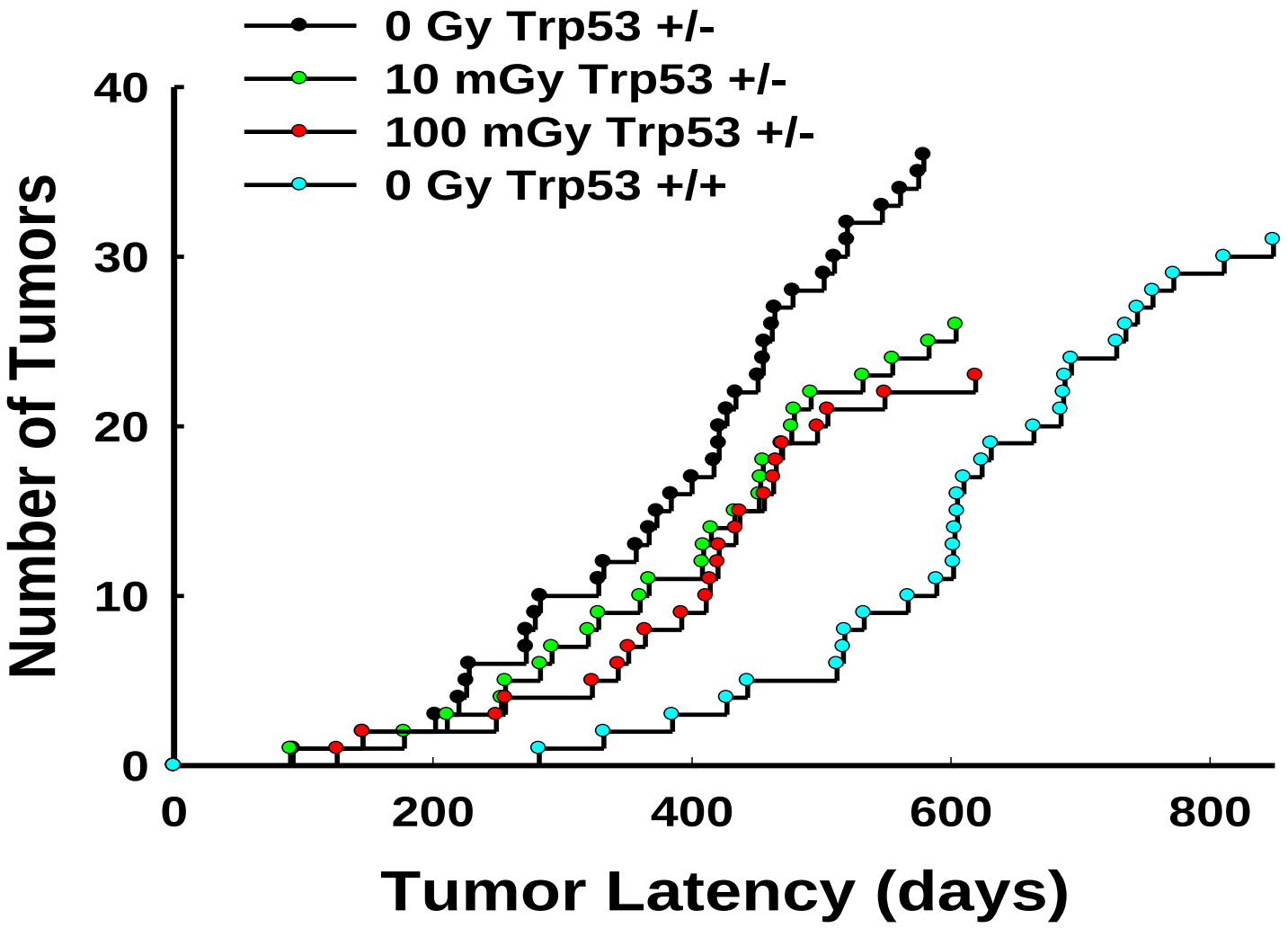
Graduate student – Laurentian University

Low Dose Radiation Improved Survival of Myeloid Leukemia in Genetically Normal Mice



Mitchel, Jackson, McCann and Boreham, Radiat. Res. 152:273-279 (1999)

Lymphoma Latency



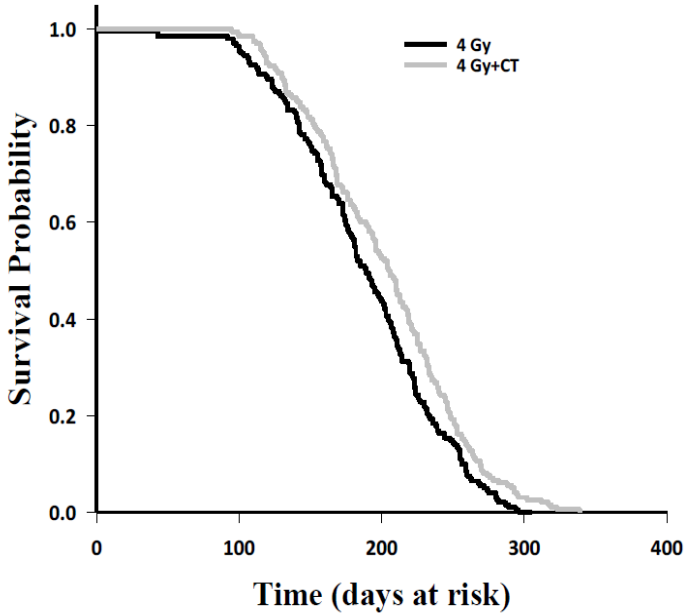
Mitchel, Jackson, Morrison and Carlisle, Radiat. Res. 159:320-327 (2003)

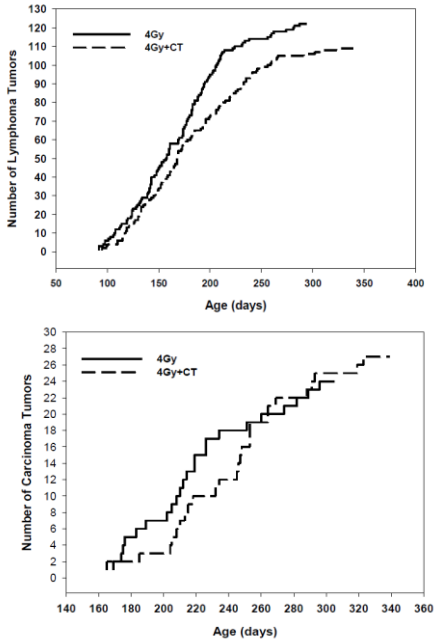
Diagnostic imaging

Northern Ontario School of Medicine
École de médecine du Nord de l'Ontario

CT Scan

- Increased mean survival time
- Increased latency of lymphomas and carcinomas





Phan *et al*

PET Scan

- Reduction in kidney disease

Table IV. Number of *Trp53*+/– mice with tissue-specific lesions

Treatment	Kidneys	Bladder	Heart	Reproductive organs
Control	32	3	0	28
10 mGy γ-rays	23	6	0	20
10 mGy PET	15[a]	0	0	27
4 Gy γ-rays	25	0	0	38
10 mGy PET + 4 Gy γ-rays	32	0	0	36

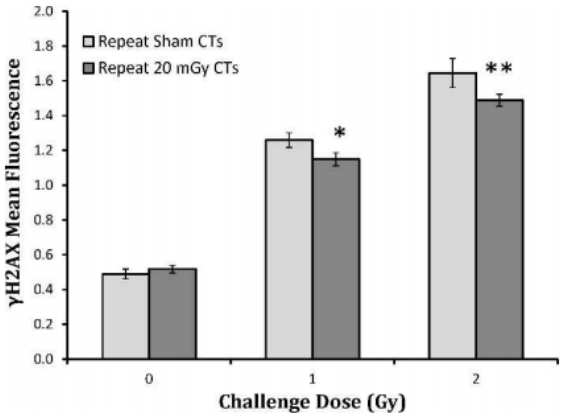
[a] $P < 0.021$ relative to unirradiated control mice.

Taylor *et al* 2014

Adaptive response

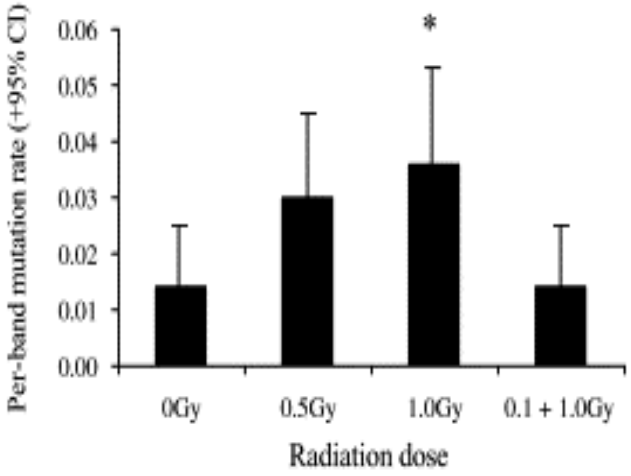
Low-dose radiation exposure can protect against a future high-dose exposure

DNA DSB formation



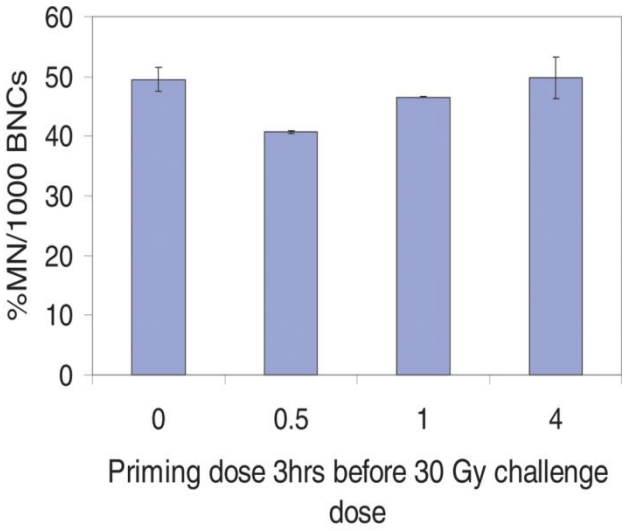
Phan *et al* 2012

Mutation rate



Somers *et al* 2004

Micronuclei formation



Cassidy *et al* 2007

Hypothesis and objectives

Hypothesis:

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

Prolonged exposure to ultra-low radiation environments will be detrimental to biological systems

Objectives:

1. Establish a functional biological research laboratory within SNOLAB
2. Examine the effects of incubation in SNOLAB compared to surface control laboratory using several simple model systems
   - Mammalian cell culture – C3H 10T1/2 cell line
   - Whole organism – Lake Whitefish embryonic development
   - Microorganism - Yeast

SNOLAB

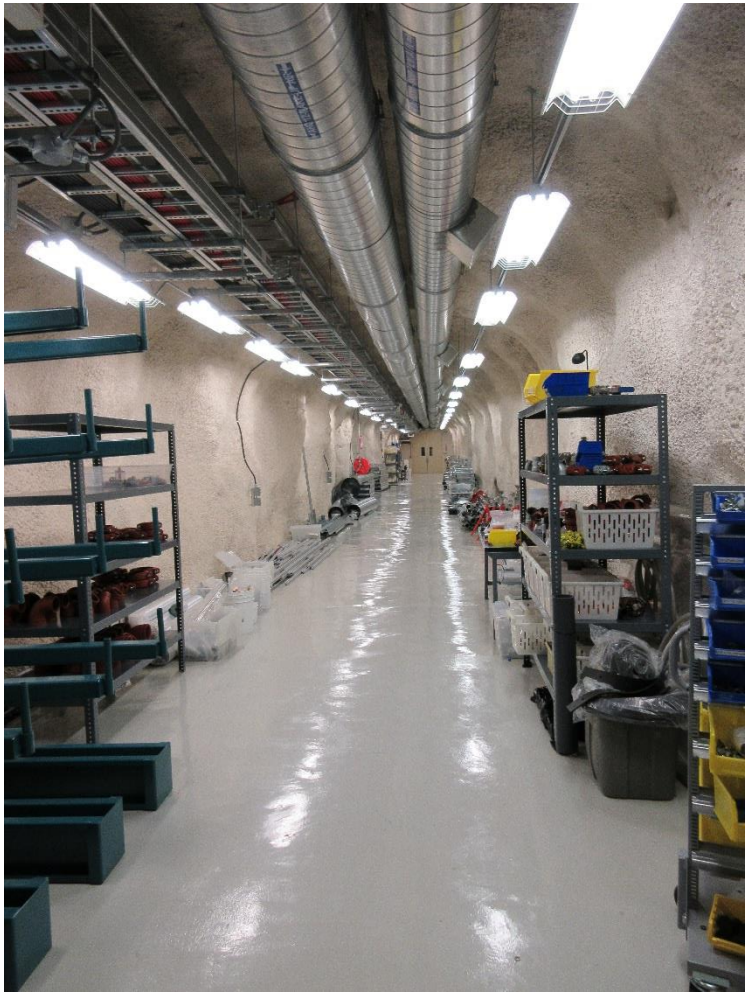
- Located within an active nickel mine in Sudbury, Ontario
- 6,800 ft (2 km) underground
- Class 2000 clean room

Compared to surface:

- 50 million times less cosmic radiation
- 100 million times less radiation
- Polymer coated walls and continuous air exchange to reduce radon

SNOLAB

SNOLAB

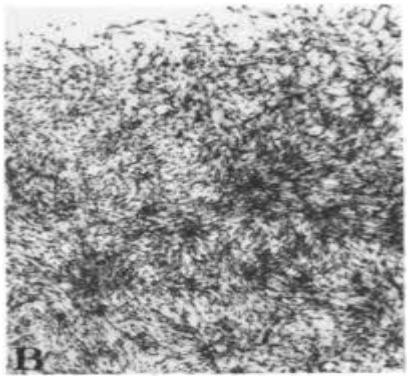


C3H 10T1/2 cell line

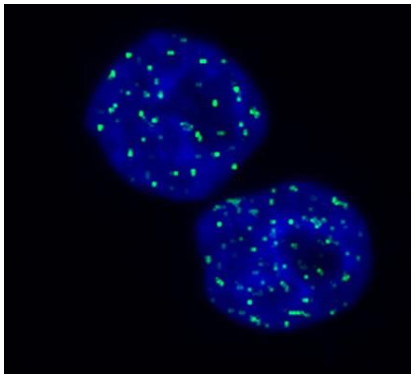
Northern Ontario School of Medicine
École de médecine du Nord de l'Ontario

Radiobiological endpoints

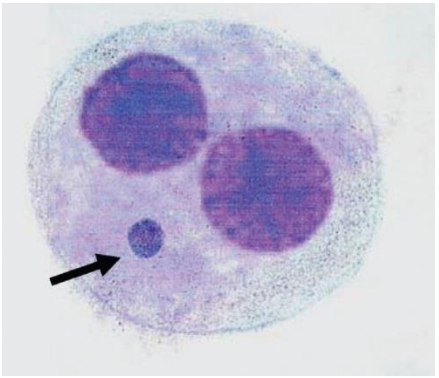
Transformation frequency



DNA DSB formation



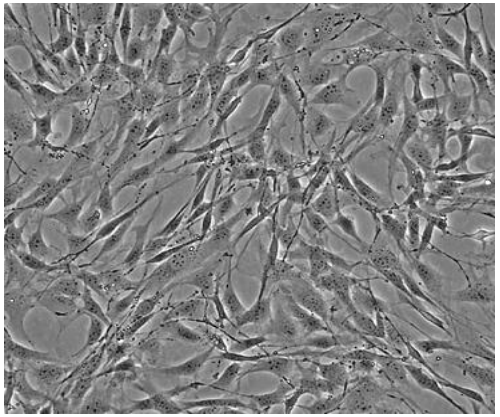
Micronuclei formation



C3H 10T1/2 cell line

Collaboration with Dr. Edouard Azzam – Rutgers New Jersey Medical School

- Mouse embryonic stem cell line
- Pre-carcinogenic
- High spontaneous transformation rate
- Sensitive to low-dose ionizing radiation

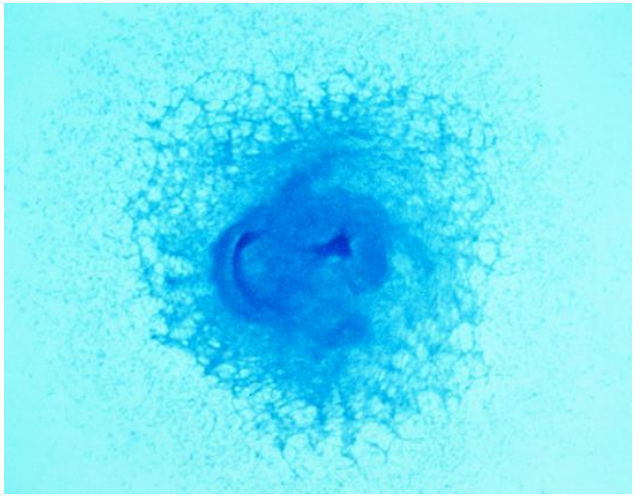


Previous findings:

A single low-dose of radiation (1 mGy to 100 mGy) can decrease transformation frequency below spontaneous levels (Azzam *et al* 1996)

Chronic adapting low-doses of radiation (0.1 Gy, 0.65 Gy or 1.5 Gy) can protect against an acute challenge dose of 4 Gy (Azzam *et al* 1994)

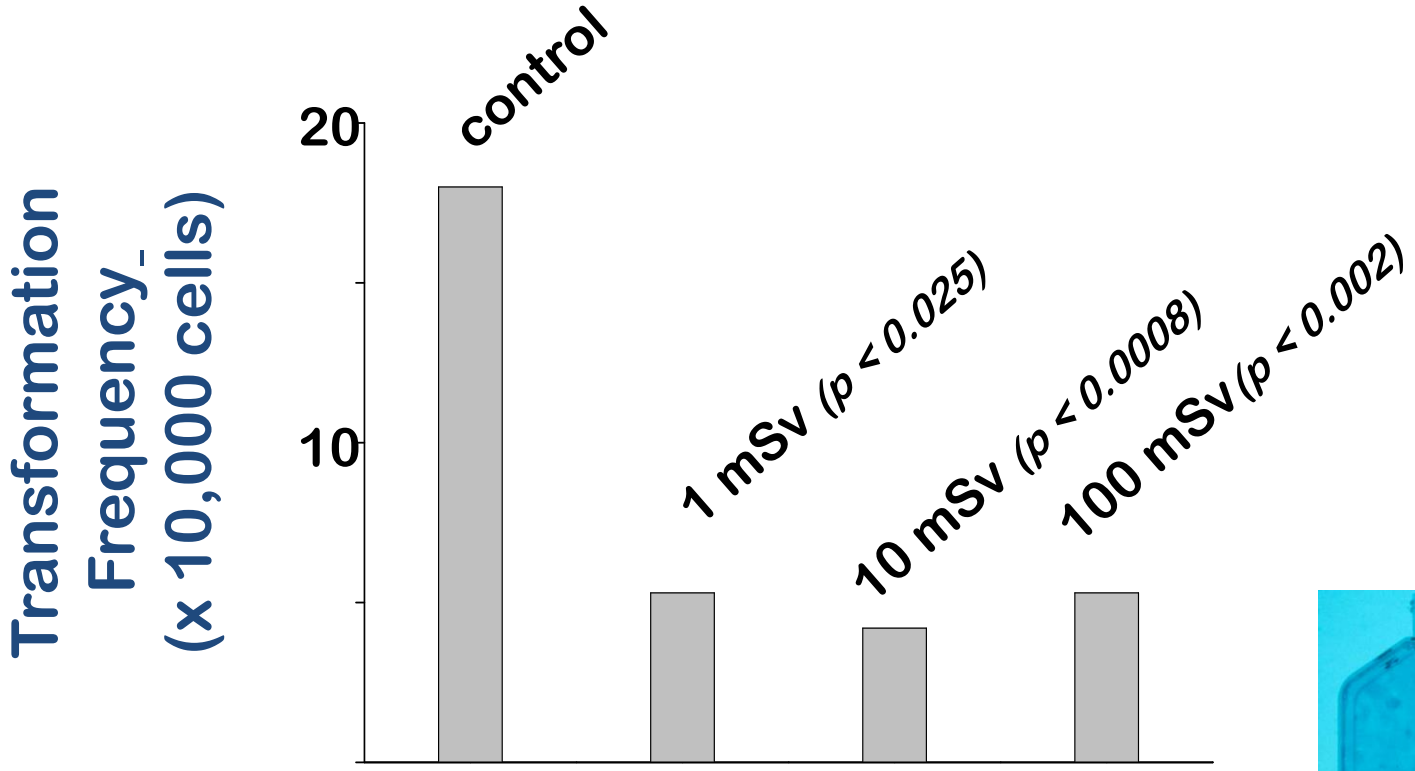
C3H-10T1/2 Cell Transformation Assay



Type III Foci

Azzam, de Tolido, Raaphorst and Mitchel, Radiat. Res. 146:369-373 (1996)

Low Dose γ-Rays Reduces the Spontaneous Transformation Frequency in Mouse Embryo Cells



Azzam *et al.*, *Radiat. Res.* (1996)

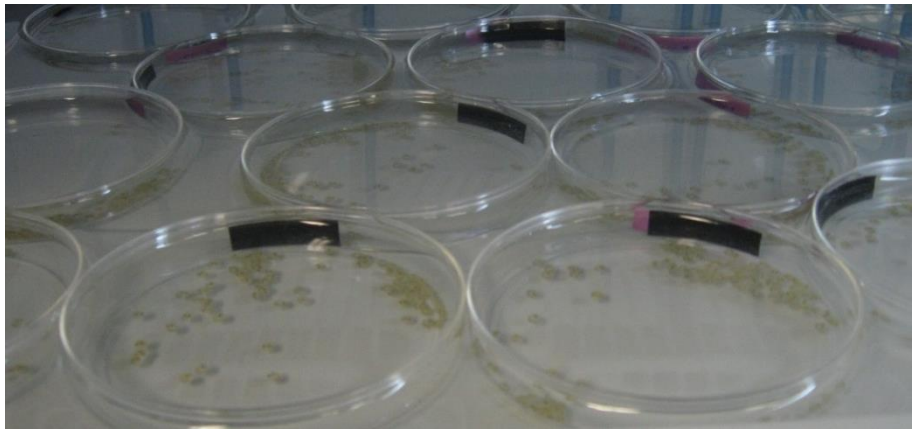
C3H 10T1/2 cell line

- Cells will be cultured within SNOLAB and the surface control lab
- Glove box incubators enable matching conditions by controlling air, temperature and pressure
- Cells will be cultured for multiple passages and at periodic intervals tested for:
  - Spontaneous transformation frequency
  - Background levels of DNA DSB and micronuclei
- The dose-response for induced damage will be examined in low-background adapted cells

Lake Whitefish

Good model organism for examining radiological effects

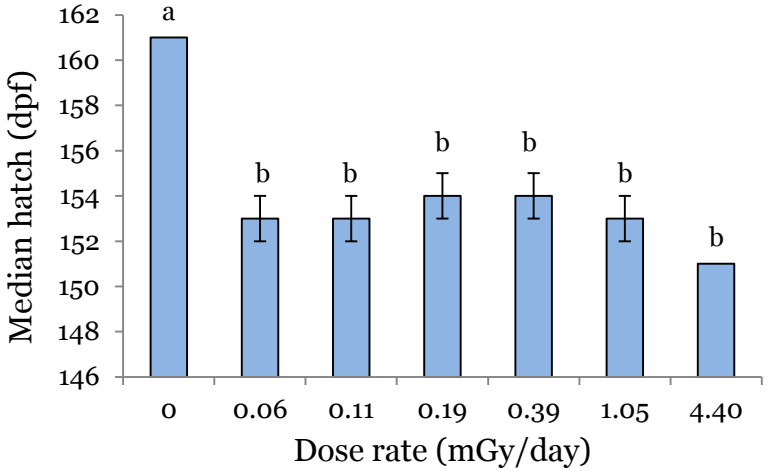
- Embryogenesis one of the most sensitive life stages to radiation
- Long development period (> 200 days)
  - Extended low-dose chronic exposures
  - Accurate targeting of specific development stages
- Can accurately quantify development rate, growth, metabolic efficiency
- Easy to raise and low maintenance

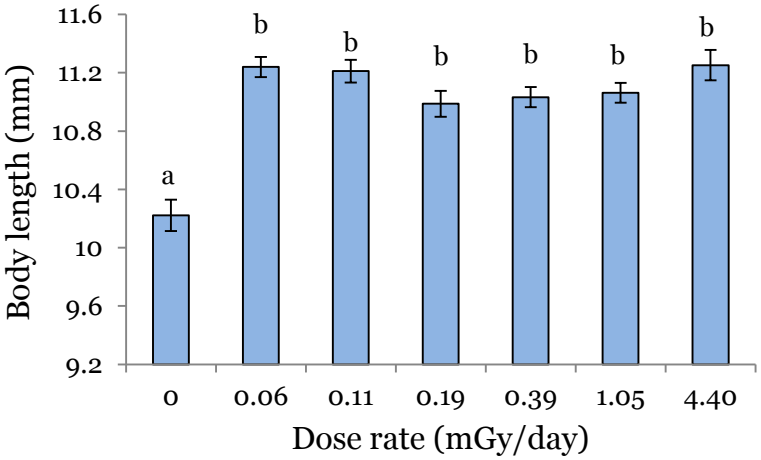


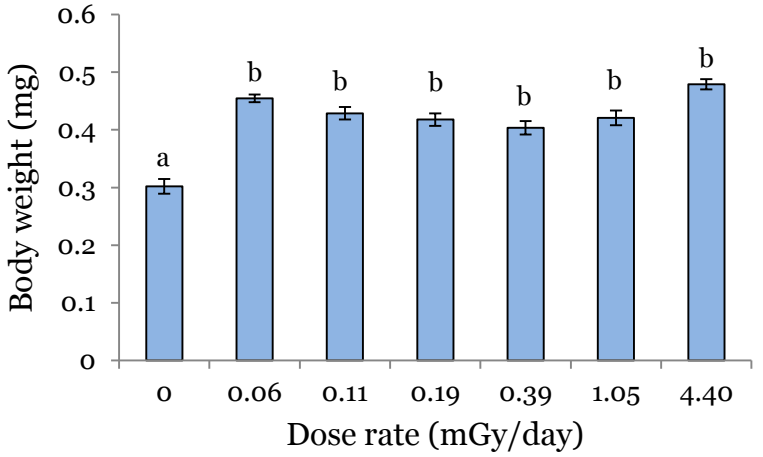
Lake Whitefish

Chronic low dose ^{137}Cs gamma ray exposure

- Accelerated development – earlier time to median hatch
- Stimulated growth – larger body length and weight







Lake Whitefish

- Lake Whitefish embryos will be reared within SNOLAB and the surface control lab
- Embryos will be raised from fertilization to hatch within standard refrigeration units
- At multiple stages embryos will be analyzed for:
  - Mortality
  - Development rate
  - Size
  - Growth efficiency
- The response to acute thermal or chemical stress will be examined in low-background adapted embryos

Yeast

- Yeast colonies will be grown in SNOLAB and in the surface control laboratory
- The genes involved in the ultra-low background response will be examined using Yeast Gene Deletion Sets
  - ~4500 gene deletion mutants
  - Plated in quadruplicate over 14 plates