

Adaption by Low Dose **Radiation Exposure :**

A Look at Scope and Limitations for Radiation Protection

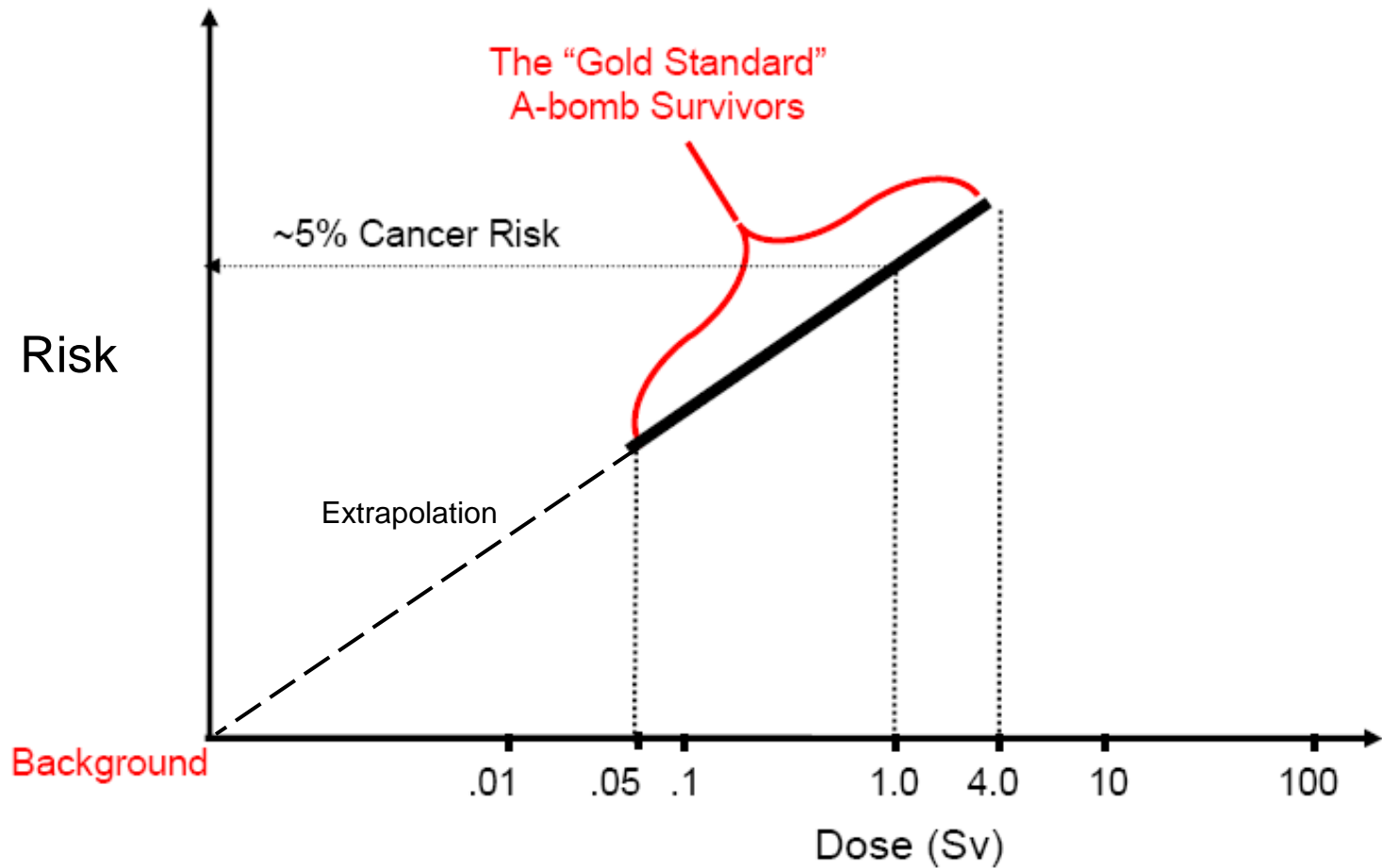
Ron Mitchel

Atomic Energy of Canada Limited

Chalk River, ON, Canada

mitchelr@aecl.ca

Linear No-Threshold Hypothesis



Radiation Protection: LNT Hypothesis

- **Assumed to be true for humans and all other organisms**
 - **Basis for all human and environmental radioprotection**

Linear No Threshold Hypothesis Implies:

- 1. Risk is determined by the physics**
- 2. Biological inputs to the risk are either constant with dose or irrelevant at all doses**

Adaption to radiation shown in:

- Single cell organisms
- Insects
- Plants
- Lower vertebrates
- Mammalian cells including human
- Mammals

***This is an Evolutionarily
Conserved Response***

MAJOR PROTECTIVE MECHANISMS INDUCED IN CELLS

- **DNA REPAIR**
- **APOPTOSIS**
- **IMMUNE SURVEILLANCE**
- **BYSTANDER EFFECTS**

ADAPTION IN THE IMMUNE SYSTEM

The Percentage of Human T-Lymphocytes
Expressing IL-2 Receptors
24 h After Stimulation

Control Cells	Irradiated Cells (10 mGy)	50% Control Cells + 50% Irradiated Cells
7.7 ± 4.1	17.8 ± 3.3 p<0.01	22.6 ± 4.8 p<0.01

Xu, Greenstock, Trivedi and Mitchel. *Radiat. Environ. Biophys.* 35, 89-93 (1996)

The Influence of Low Doses On the Risk of Spontaneous Neoplastic Transformation

<u>Treatment</u>	<u>Transformation Frequency</u> (x 10 ⁻³)
Control	1.8
1.0 mGy	0.53
10 mGy	0.42
100 mGy	0.53

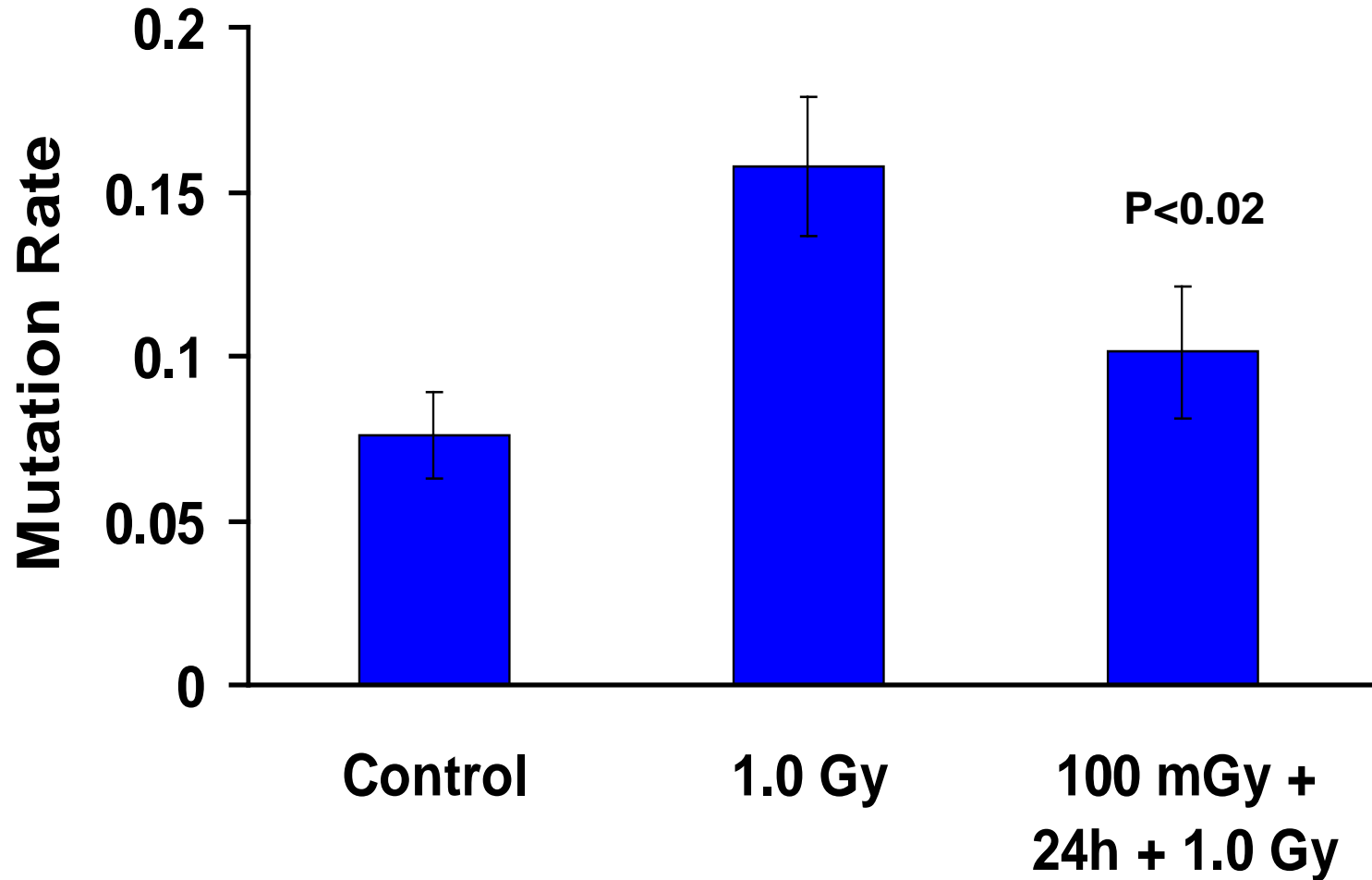
**DO ADAPTIVE RESPONSES
REDUCE RISK *in vivo*?**

SCOPE OF RISK?

HOW DO WE MEASURE HUMAN RADIATION RISK?

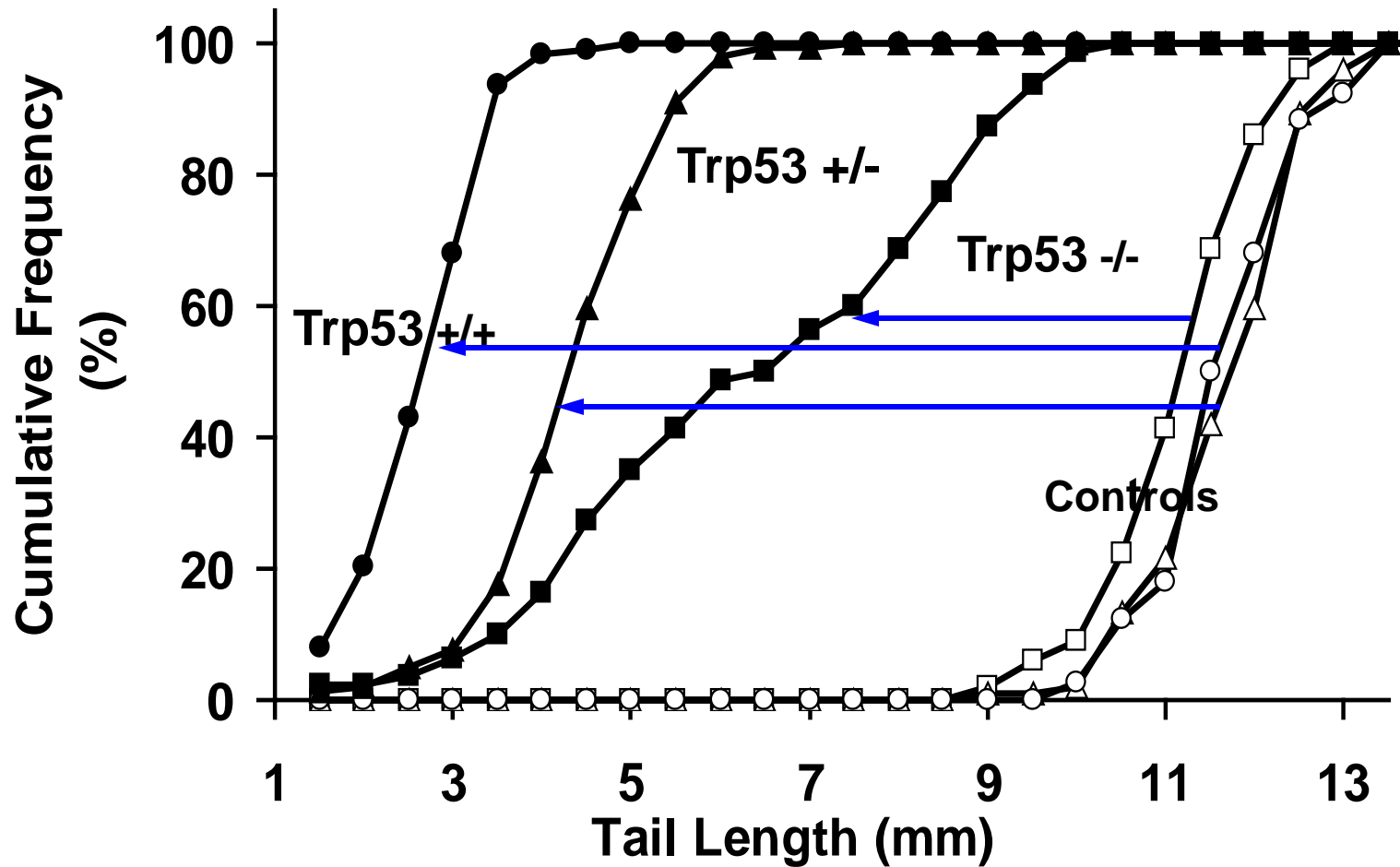
- **Cancer**
- **Teratogenesis**
- **Non-cancer diseases**
- **Heritable mutations**

GERMLINE MUTATION (ESTR loci) IN MICE

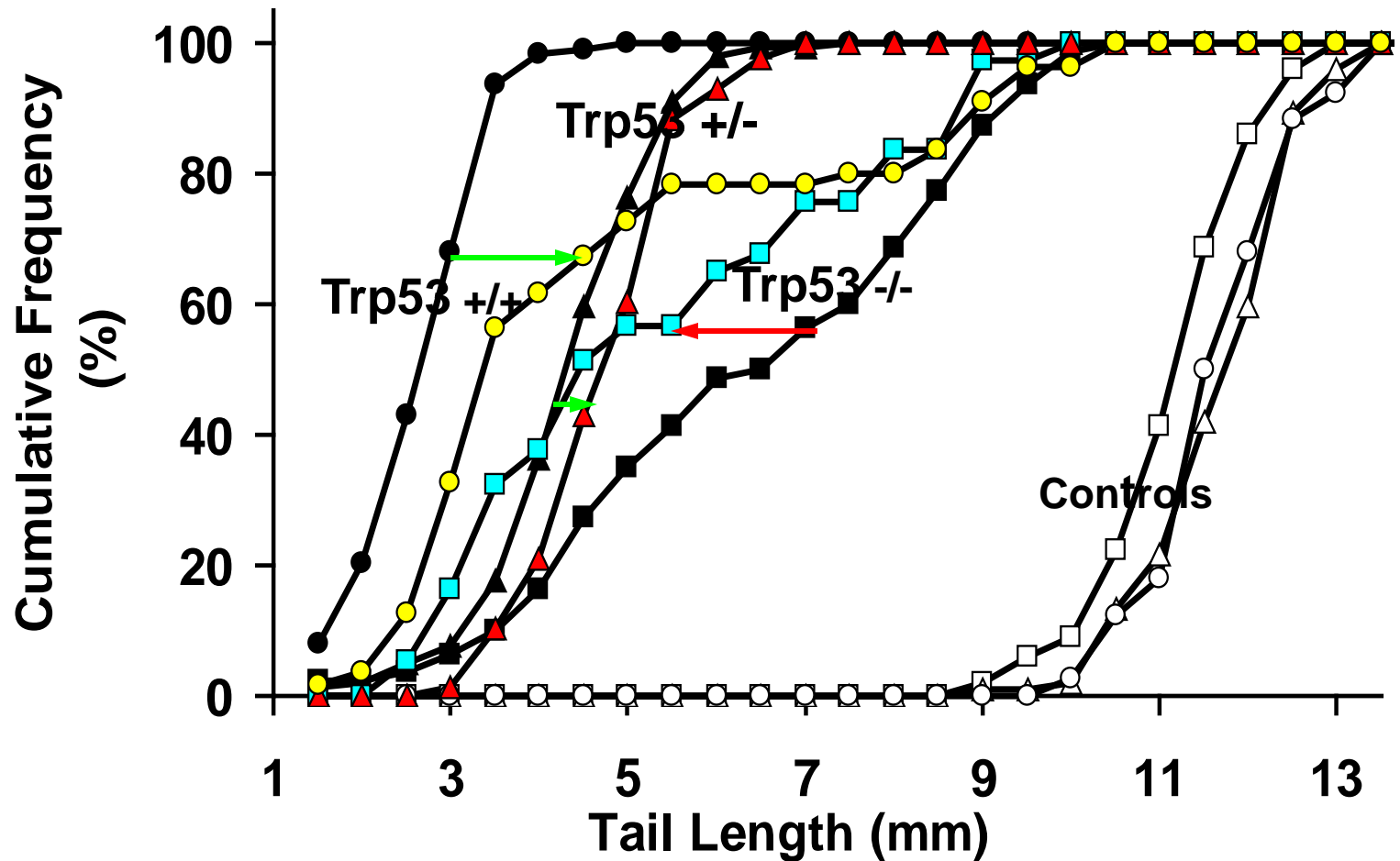


Somers CM, Sharma R, Quinn JS, Boreham DR
Mutat Res 568:69-78 (2004)

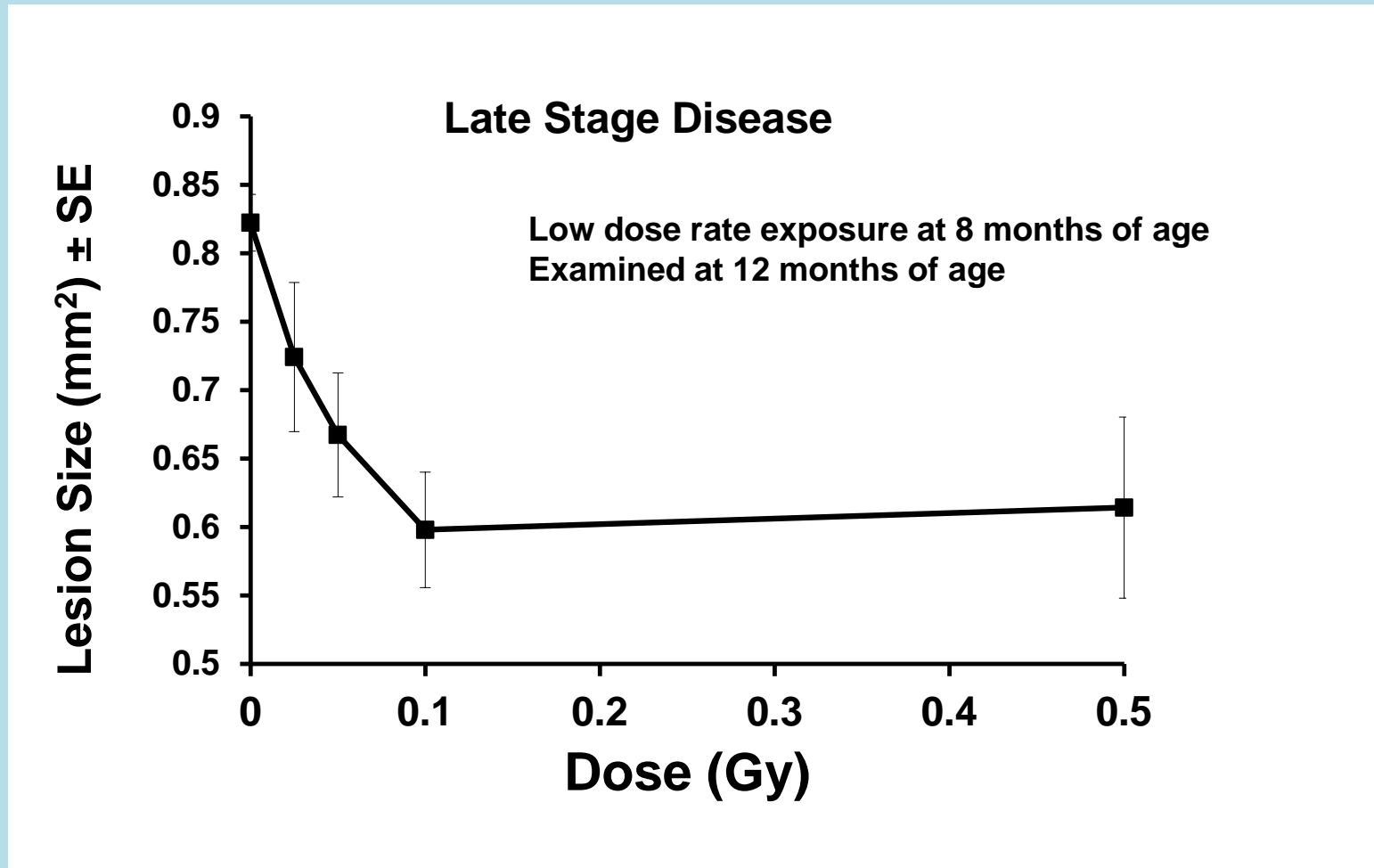
The Effect of 4 Gy on Fetal Day 11



Teratogenesis: 300 mGy + 24h + 4 Gy on Fetal Day 11



Low Dose Reduction in Aortic Root Atherosclerotic Lesion Size in ApoE^{-/-} Mice



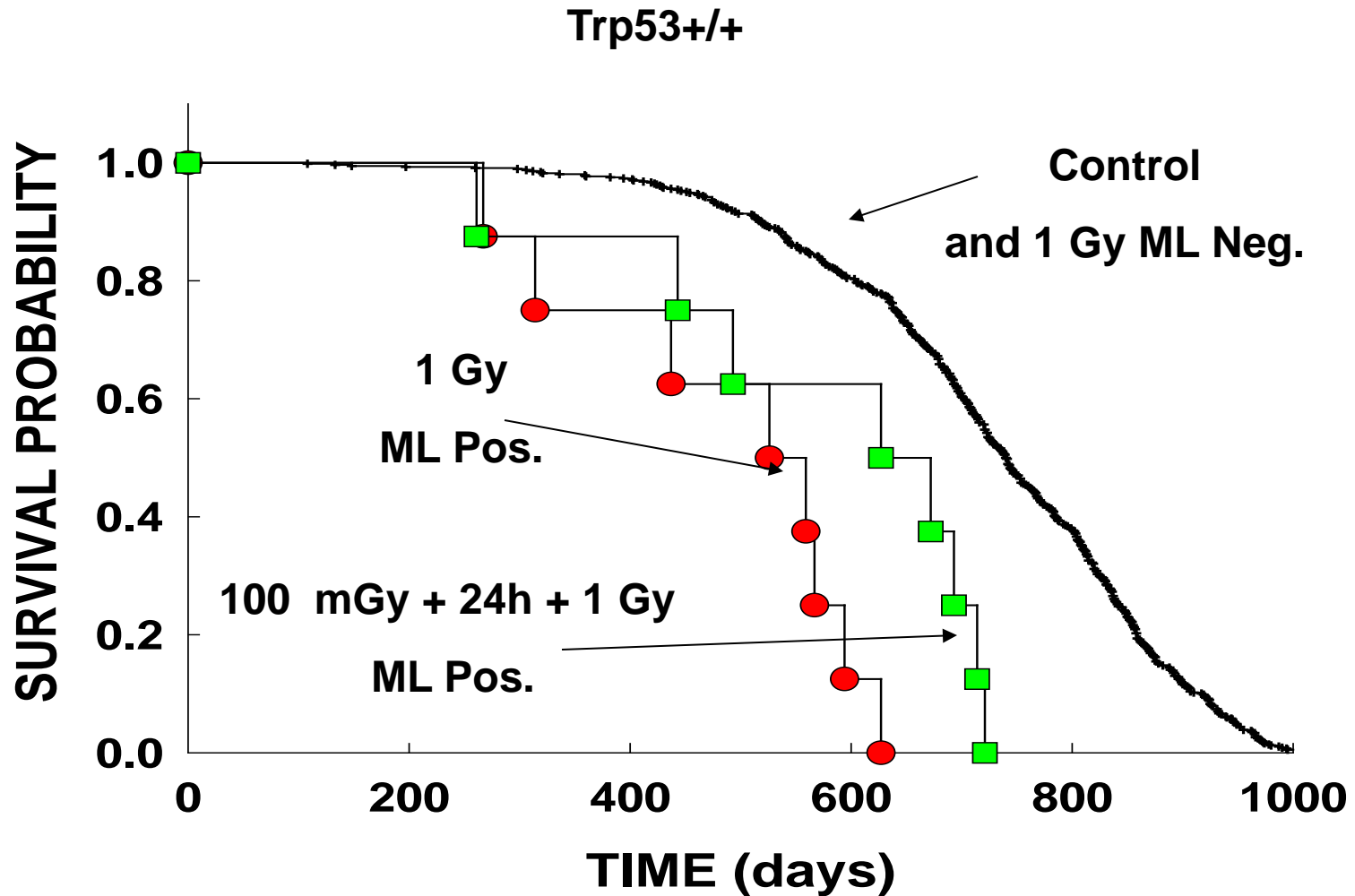
Mitchel et al. Radiat. Res. 175; 665, 2011

CHEMICAL-INDUCED **SKIN TUMORS IN MICE**

Protection by Radiation Against Chemical Tumor Initiation

<u>Initiation Treatment</u>	<u>Tumors per Animal</u>
MNNG	2.04
Beta Radiation (0.5 Gy)	0
Beta + 24h + MNNG	0.39

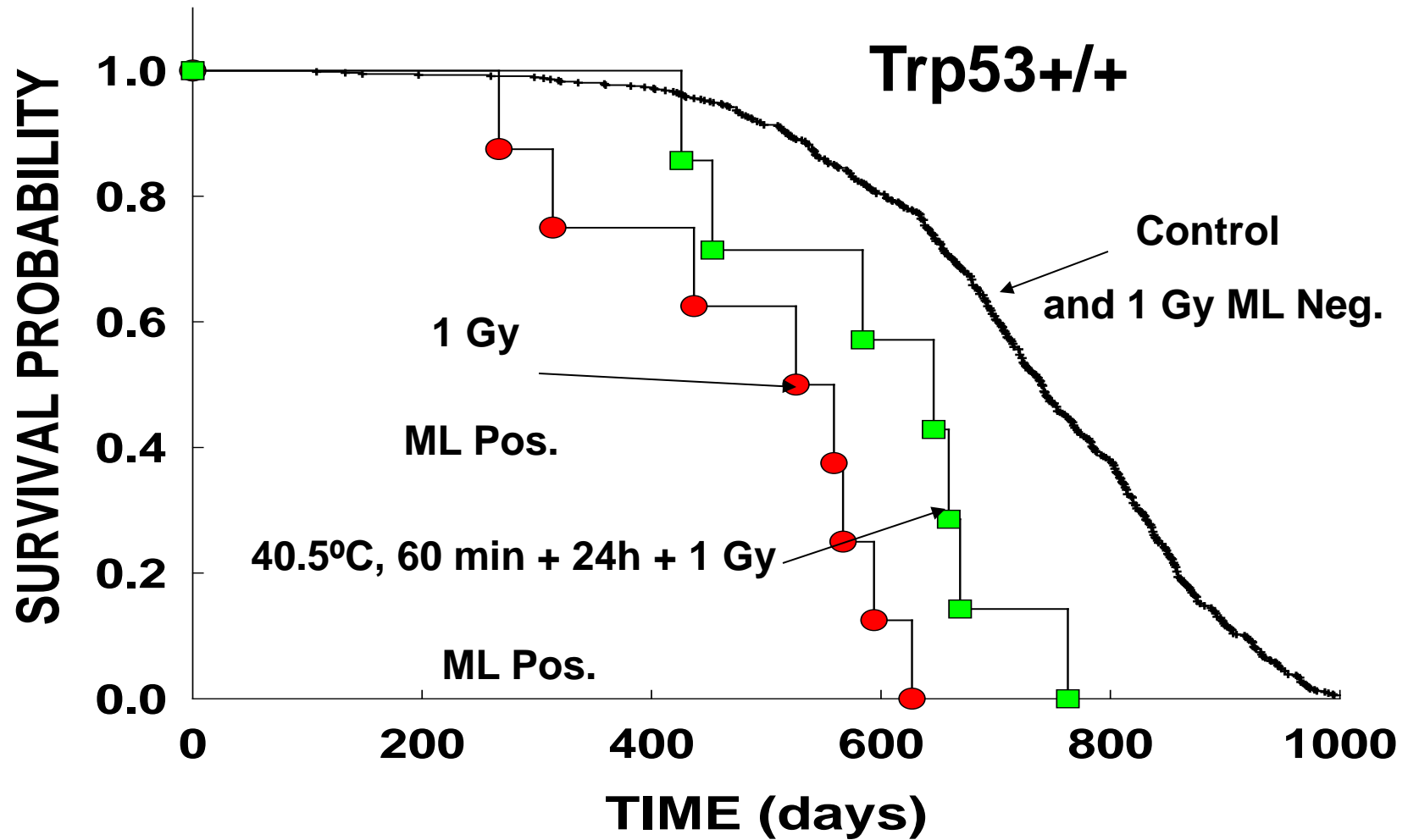
Myeloid Leukemia in Genetically Normal Mice



STRESS RESPONSES

- **Adaptive response to radiation is part of a general stress response**
- **Other stress can modify radiation risk, and visa versa**

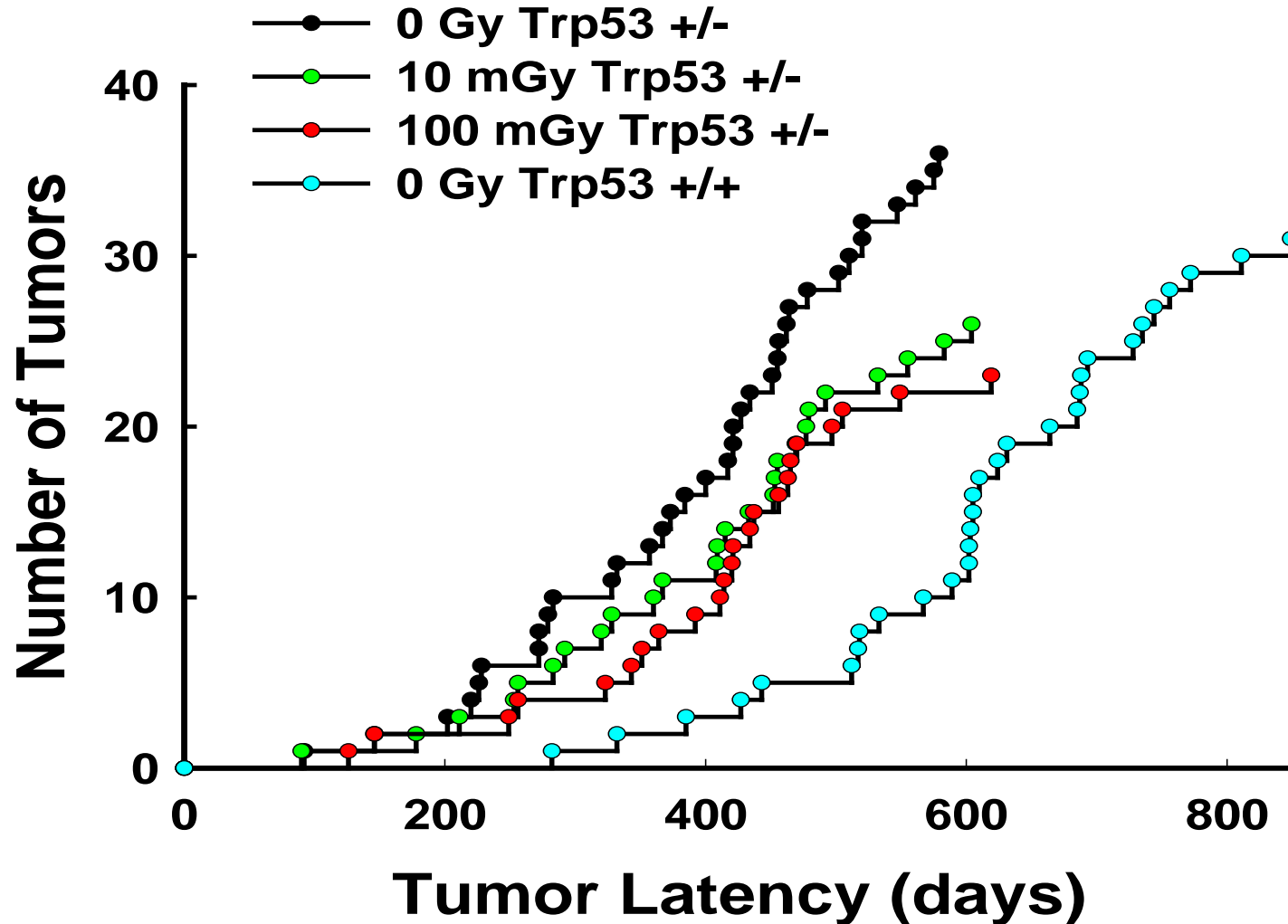
Myeloid Leukemia in Genetically Normal Mice



**ARE THERE UPPER
LIMITS (THRESHOLDS)
FOR PROTECTIVE
EFFECTS??**

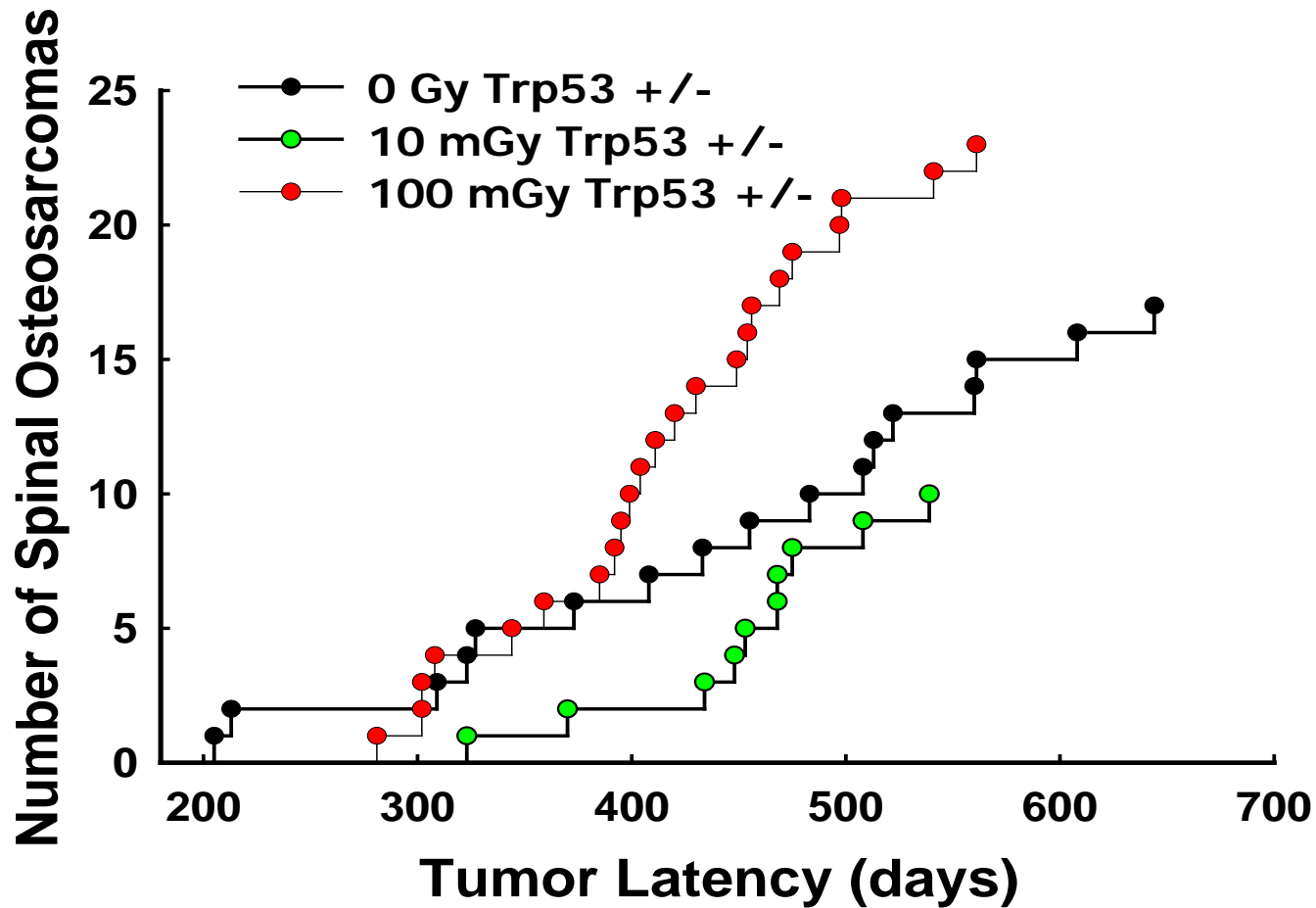
(and what influences them??)

Lymphoma Latency



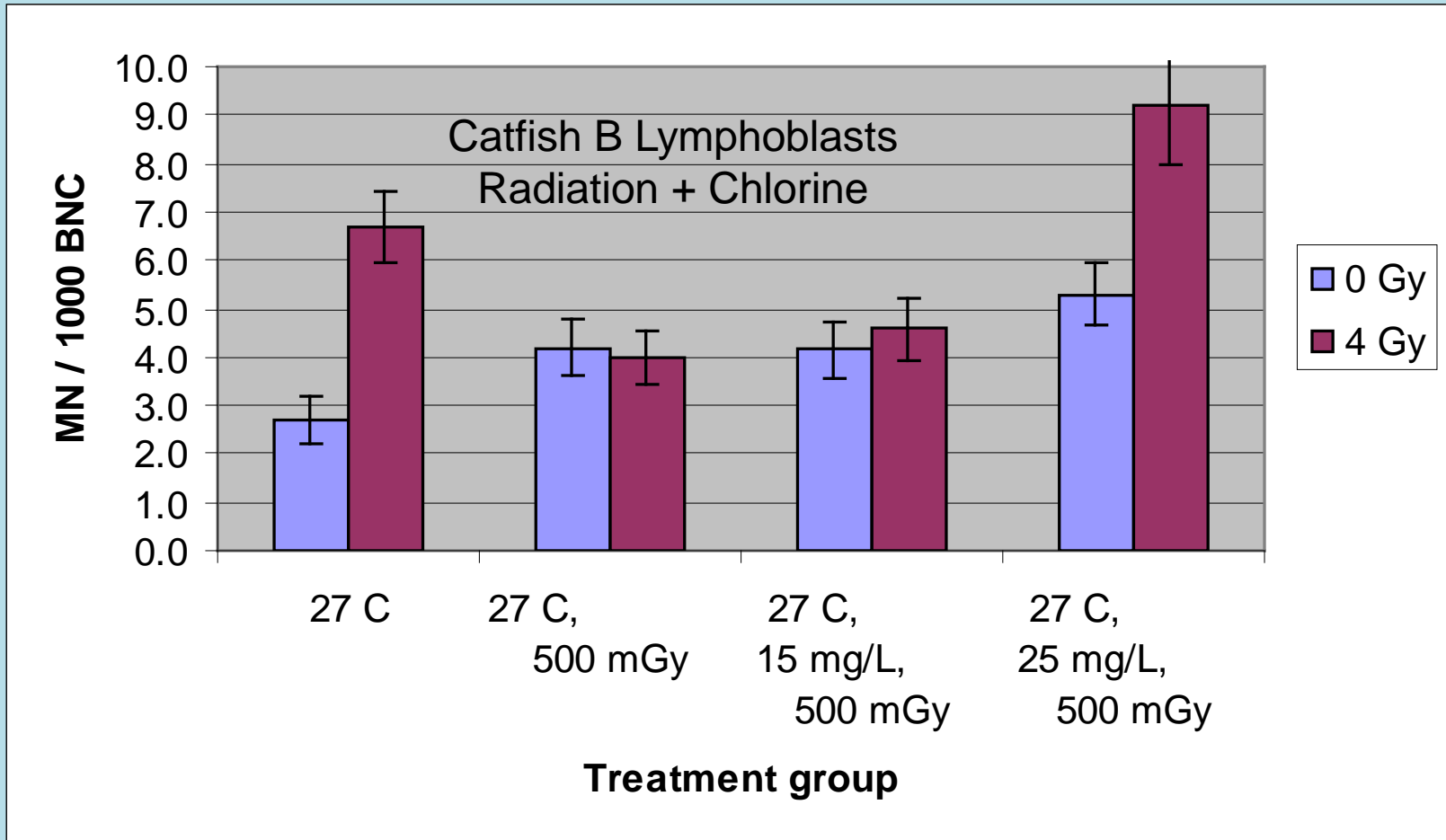
Mitchel, Jackson, Morrison and Carlisle, Radiat. Res. 159:320-327 (2003)

Spinal Osteosarcomas in Trp53+/- Mice



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

Multiple Low Stresses Accumulate to Exceed the Upper Stress Threshold

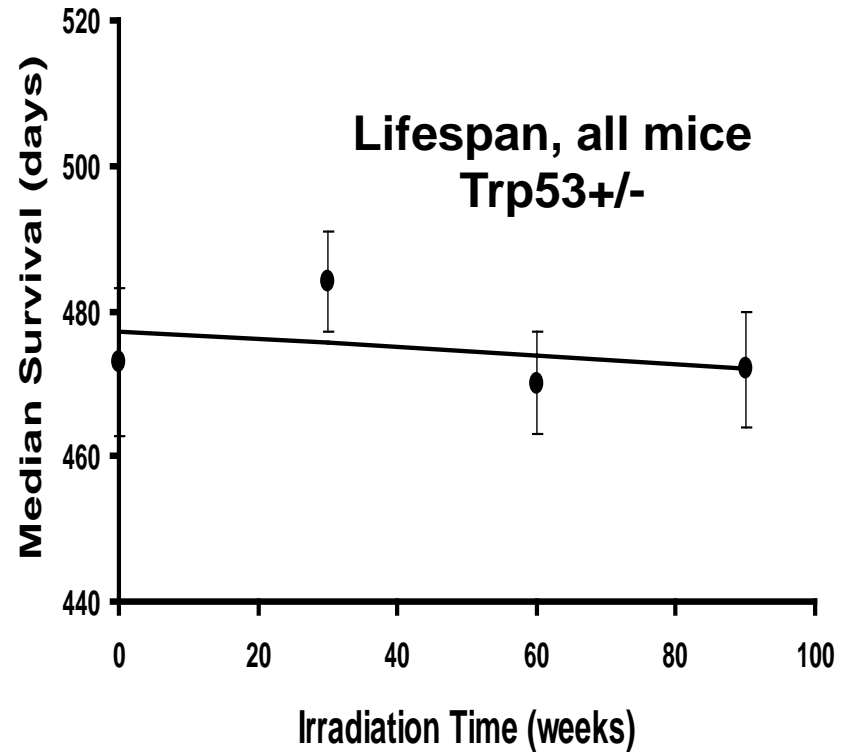
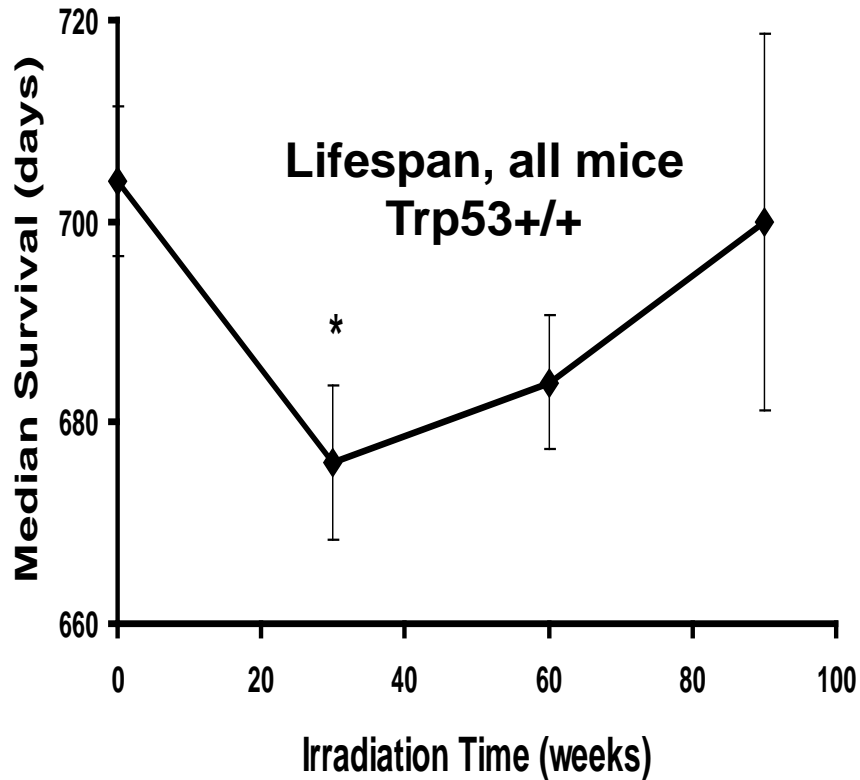


M. Audette-Stewart AECL, unpublished

**ARE THERE LOWER
LIMITS (THRESHOLDS)
FOR PROTECTIVE
EFFECTS??**

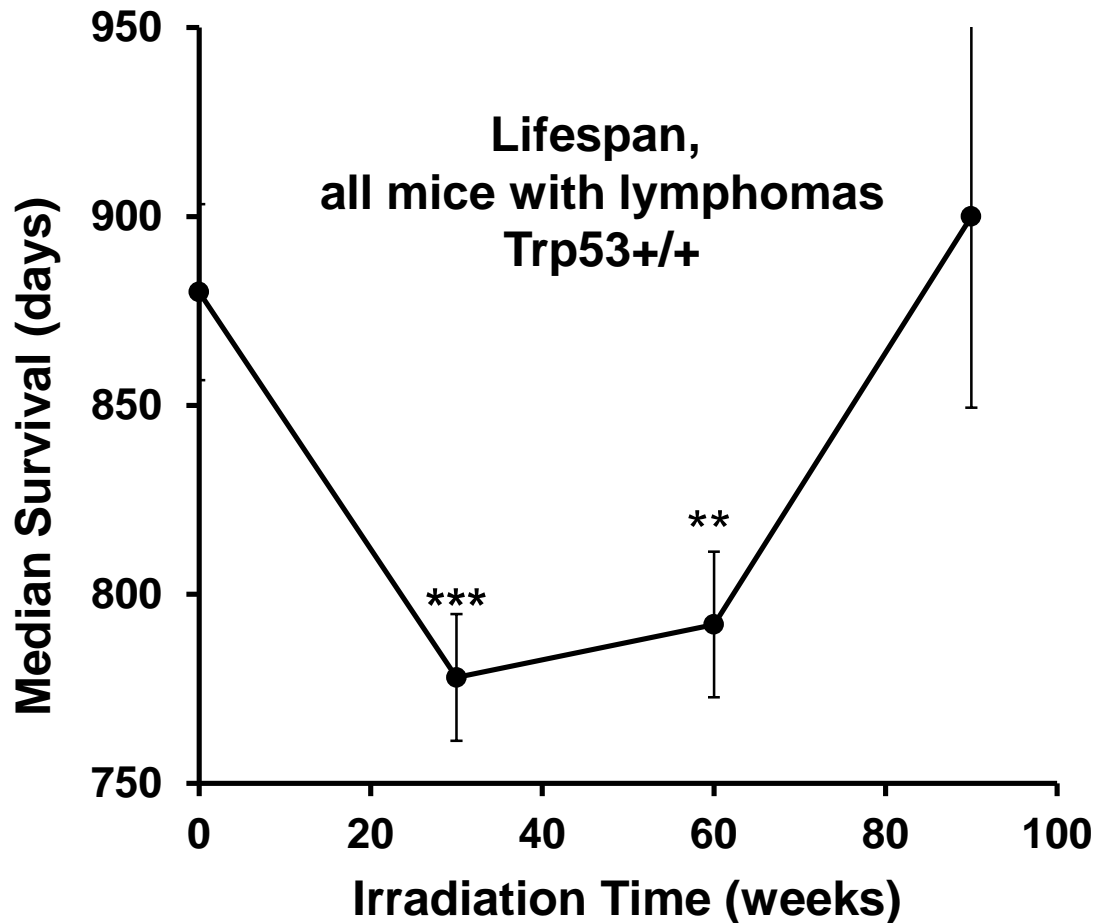
(and what influences them??)

LOWER DOSE LIMIT FOR PROTECTION IN CHRONICALLY EXPOSED MICE

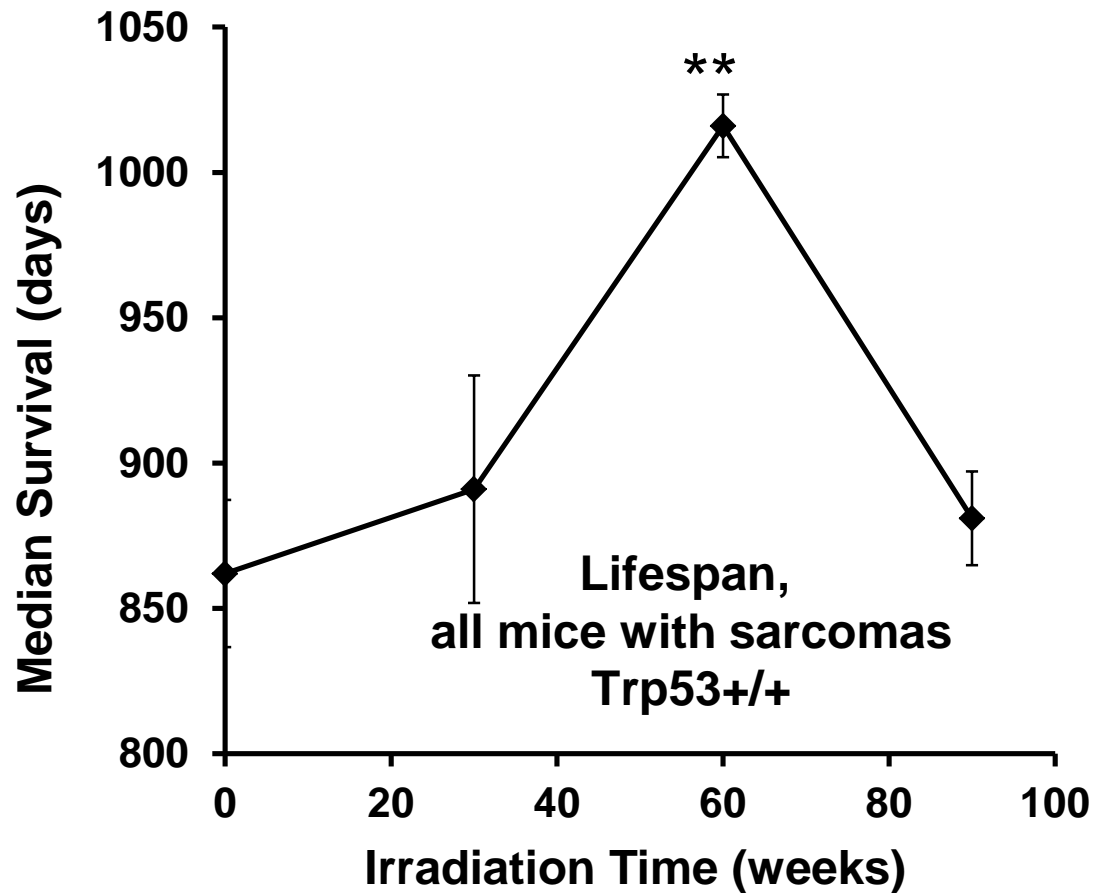


⁶⁰Co- γ
0.3 mGy/d, 0.7 mGy/h, 5d/wk,
for
30 Wks, 60 Wks, or 90 Wks

LOWER DOSE LIMIT FOR PROTECTION IN CHRONICALLY EXPOSED MICE



LOWER DOSE LIMIT FOR PROTECTION IN CHRONICALLY EXPOSED MICE



CONCLUSIONS

SCOPE OF PROTECTIVE EFFECTS VERY BROAD

- **Cancer**
- **Teratogenesis**
- **Non-cancer diseases**
- **Heritable mutations**

LIMITATIONS FOR NEW RADIATION PROTECTION REGULATIONS

- 1. Radiation adaption occurs in a window between upper and lower threshold levels of stress**
- 2. Radiation stress levels outside the window of adaption can increase risk**
- 3. Radiation is additive with other adapting stresses**
- 4. Adaption thresholds are disease and tissue specific**
- 5. Trp53 functional level controls adaption and risk in a tissue and disease specific manner**
- 6. Multiple mechanisms are likely involved**

