

***CANCER AND LOW DOSE RESPONSES  
IN VIVO:***

***IMPLICATIONS FOR RADIATION  
PROTECTION***

**Ron Mitchel**

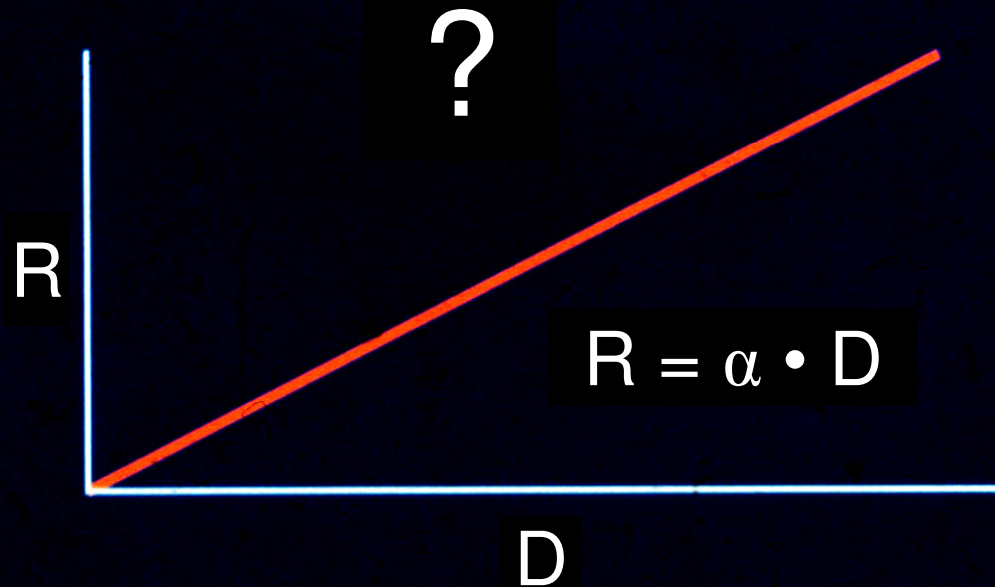
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# The Linear Dose-Risk Function (risk of cancer from irradiation)



$R$  = risk in exposed tissue  
 $D$  = absorbed dose

# **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**

# Radiation at Low Doses

- **Dose = energy/unit mass**
- **Radiation deposits energy in tracks**
- **The lowest dose a cell can receive is one track**
- **At doses  $< 1$  track/cell, not all cells are hit. Those that are hit still receive 1 track**

**Linear No Threshold  
Hypothesis is Accepted by  
Regulatory Agencies**

**ISSUE**

**Is the LNT hypothesis true for  
cancer risk at low doses??**

# Radiation Protection: LNT Hypothesis

- **Dose is a surrogate for risk**
- **Risk per unit dose is constant without a threshold, overall and for each tissue**
- **Dose (risk) is additive (normalized using Sv) and can only increase**
- **At low doses and dose rates risk is reduced 2 fold (DDREF=2)**

# Cancer

**Does the LNT approach adequately predict risk at all doses for:**

- Normal individuals**
- Cancer prone individuals**

**A radiation exposure  
is a change in the environment  
that creates a stress**

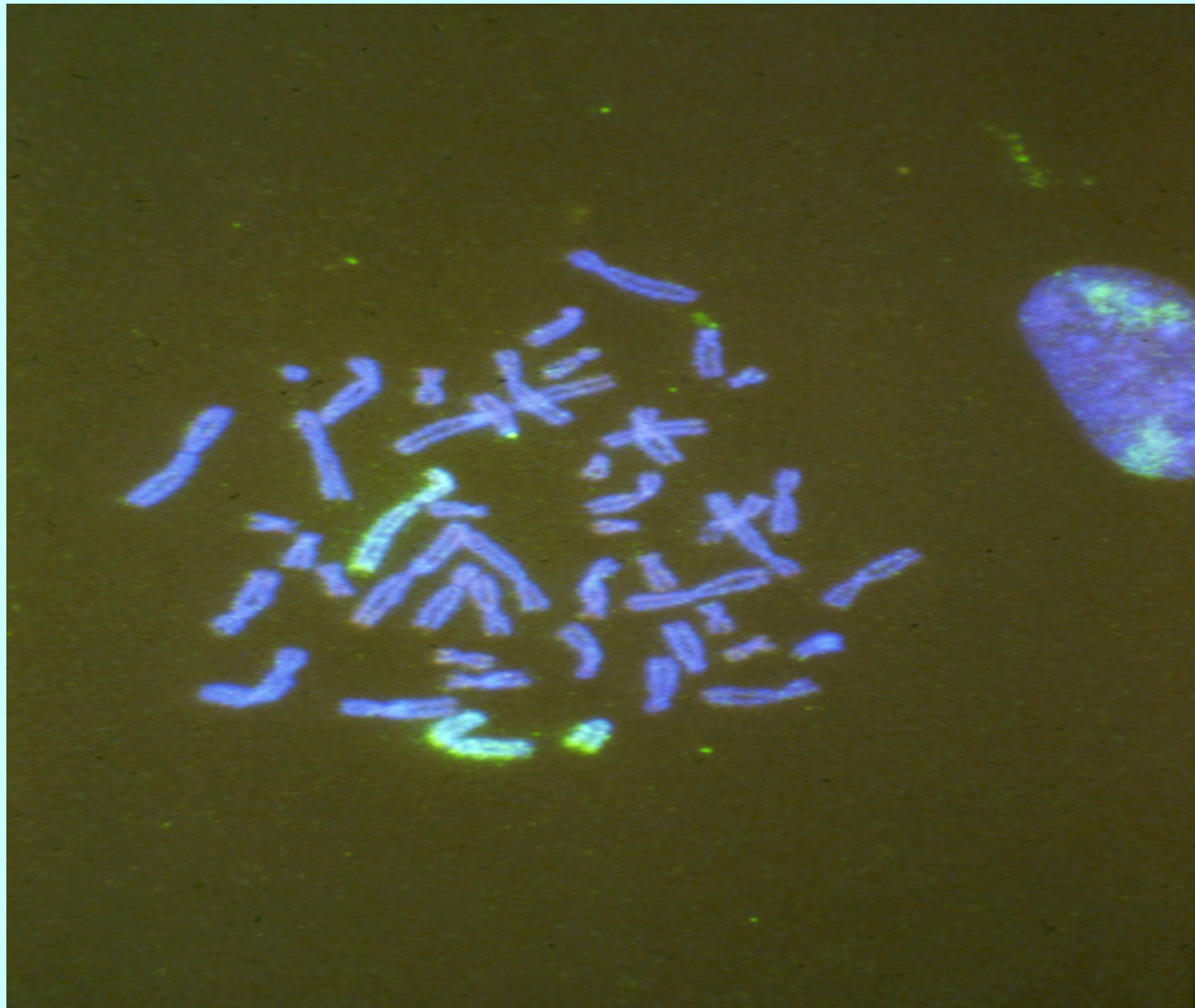
**The Basic Rule of Biology  
In a Changing Environment:**

***“Adapt or Die”***

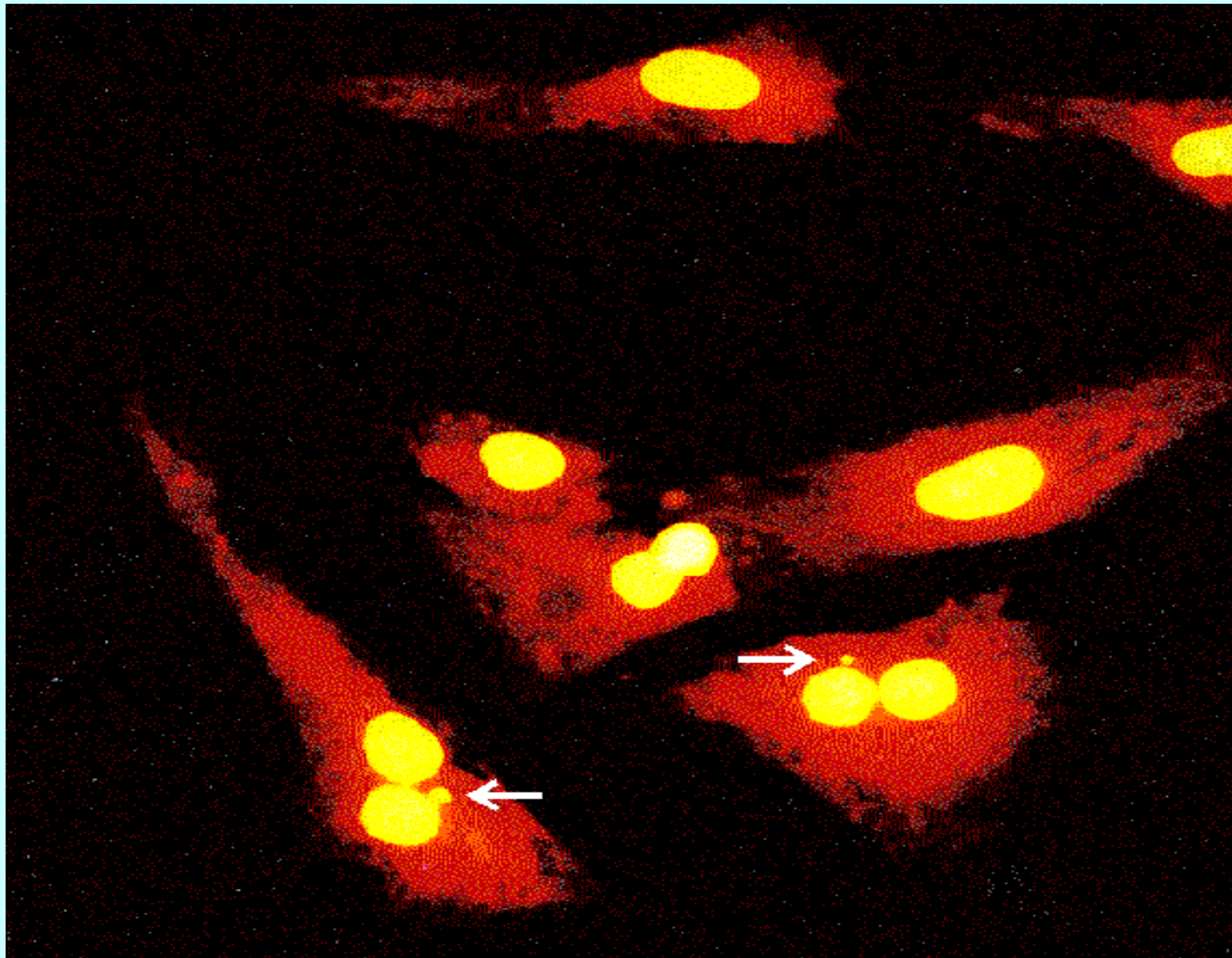
# **ADAPTIVE RESPONSE**

**Exposure  
of cells or animals to radiation  
at a low dose and dose rate  
induces mechanisms that protect  
against the detrimental effects  
of other events or agents,  
including radiation**

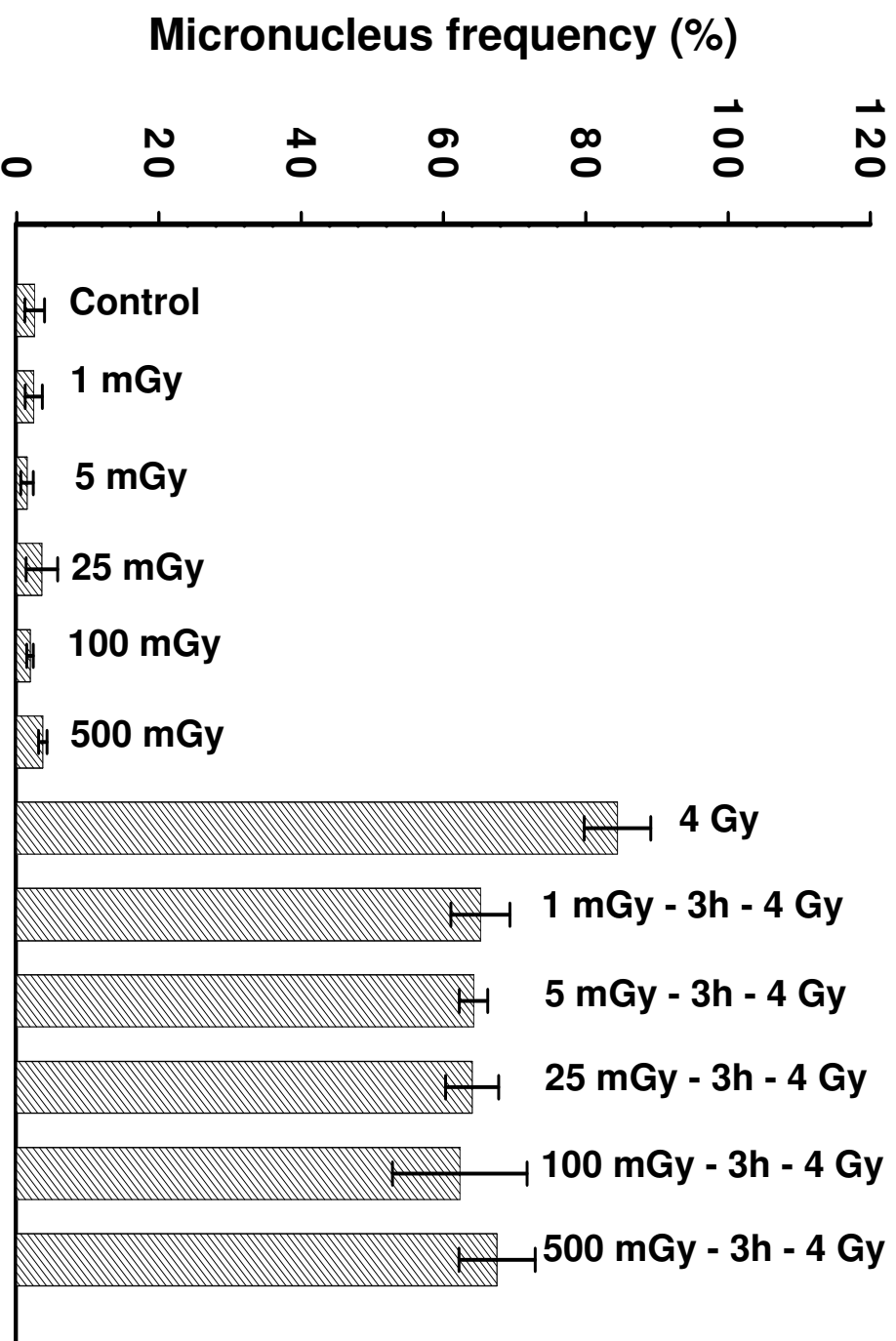
# Radiation-Induced Chromosome Breaks



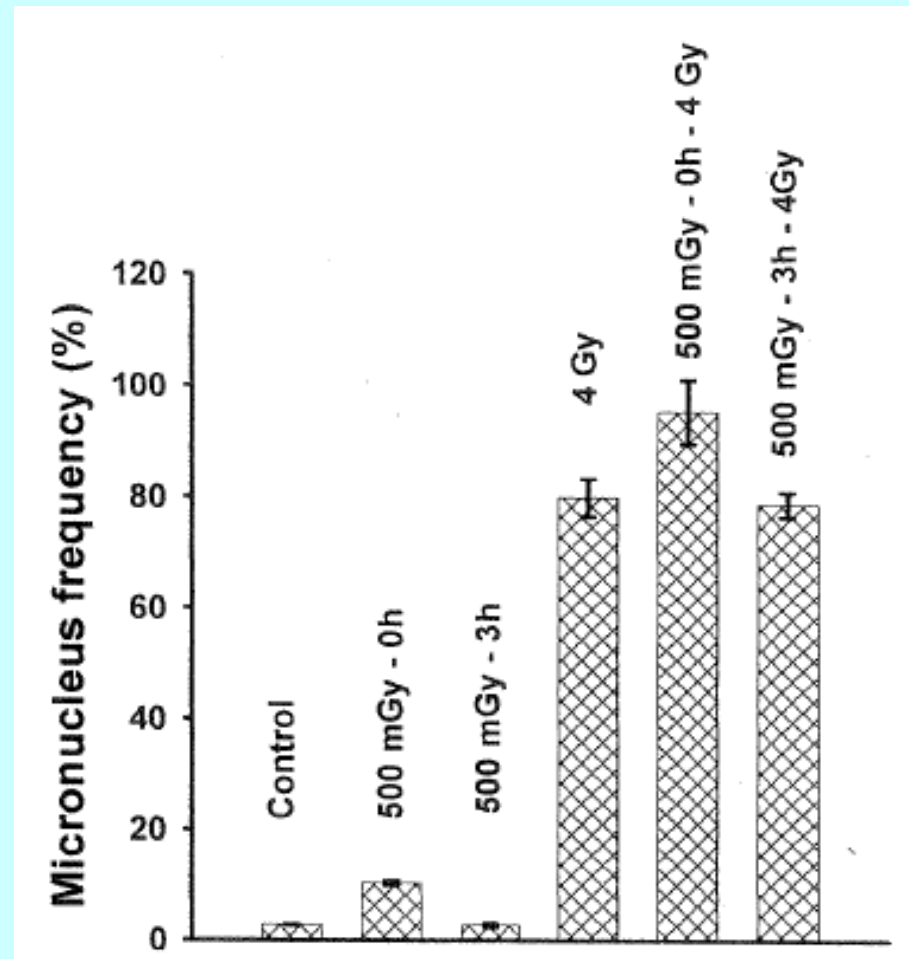
# Broken Chromosomes in Micronuclei



# Ability to Repair Broken Chromosomes in Cells Adapted by Exposure to Low Doses



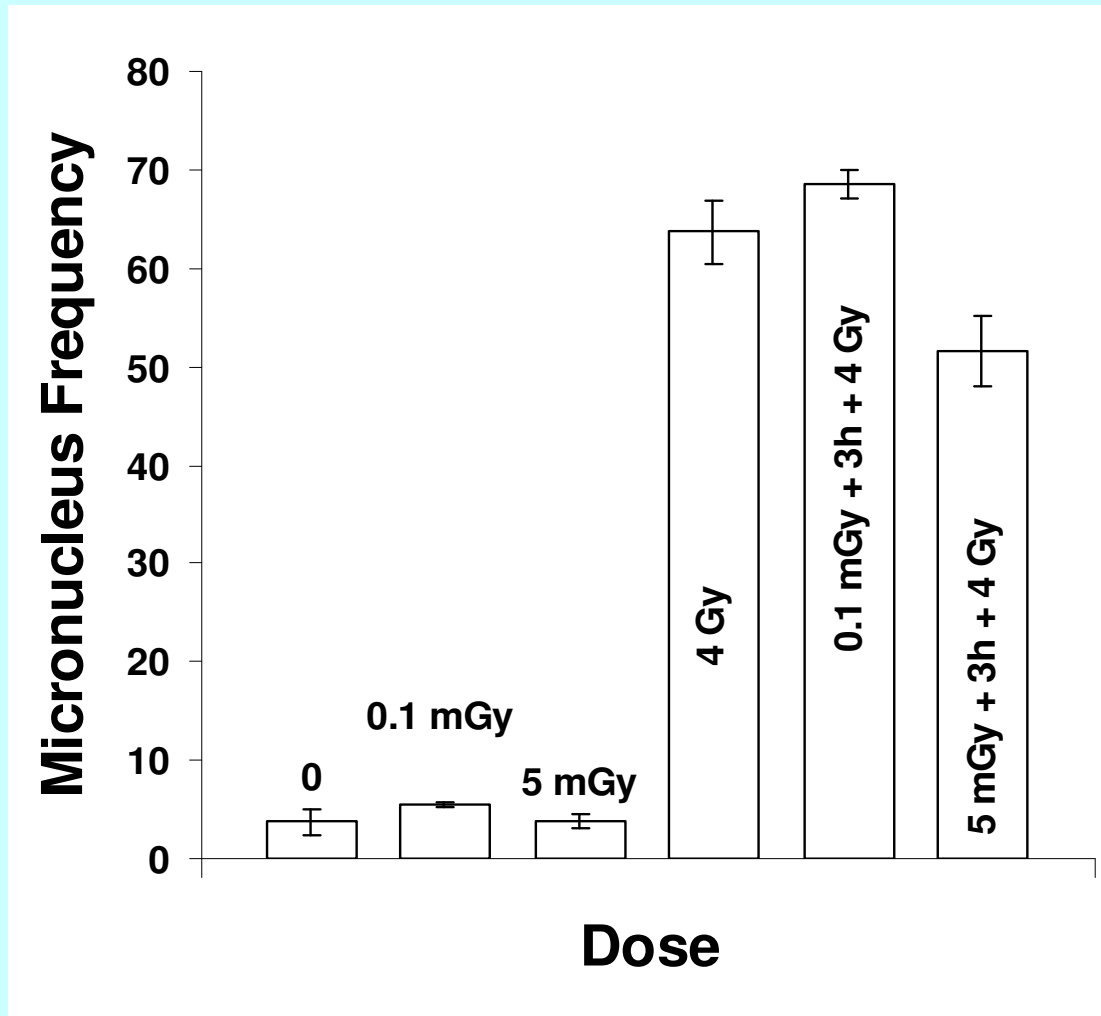
# No Adaptation in Human Cells at High Dose Rate



0.77 Gy/min  
 $^{60}\text{Co } \gamma$

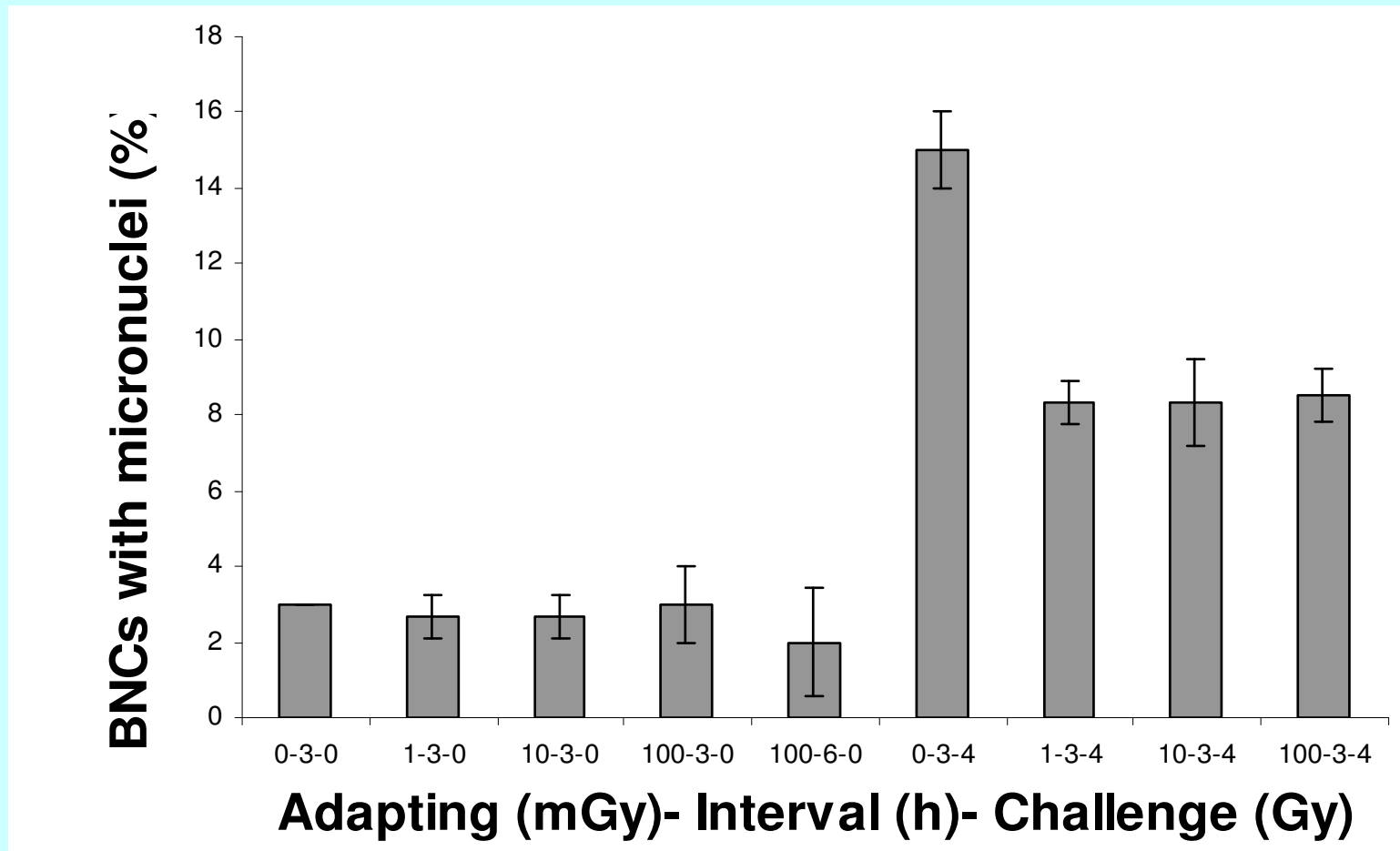
Broome, Brown and Mitchel. Radiat. Res. 158, 181-186 (2002)

# Sub-critical Dose for Adaptation in Human Cells



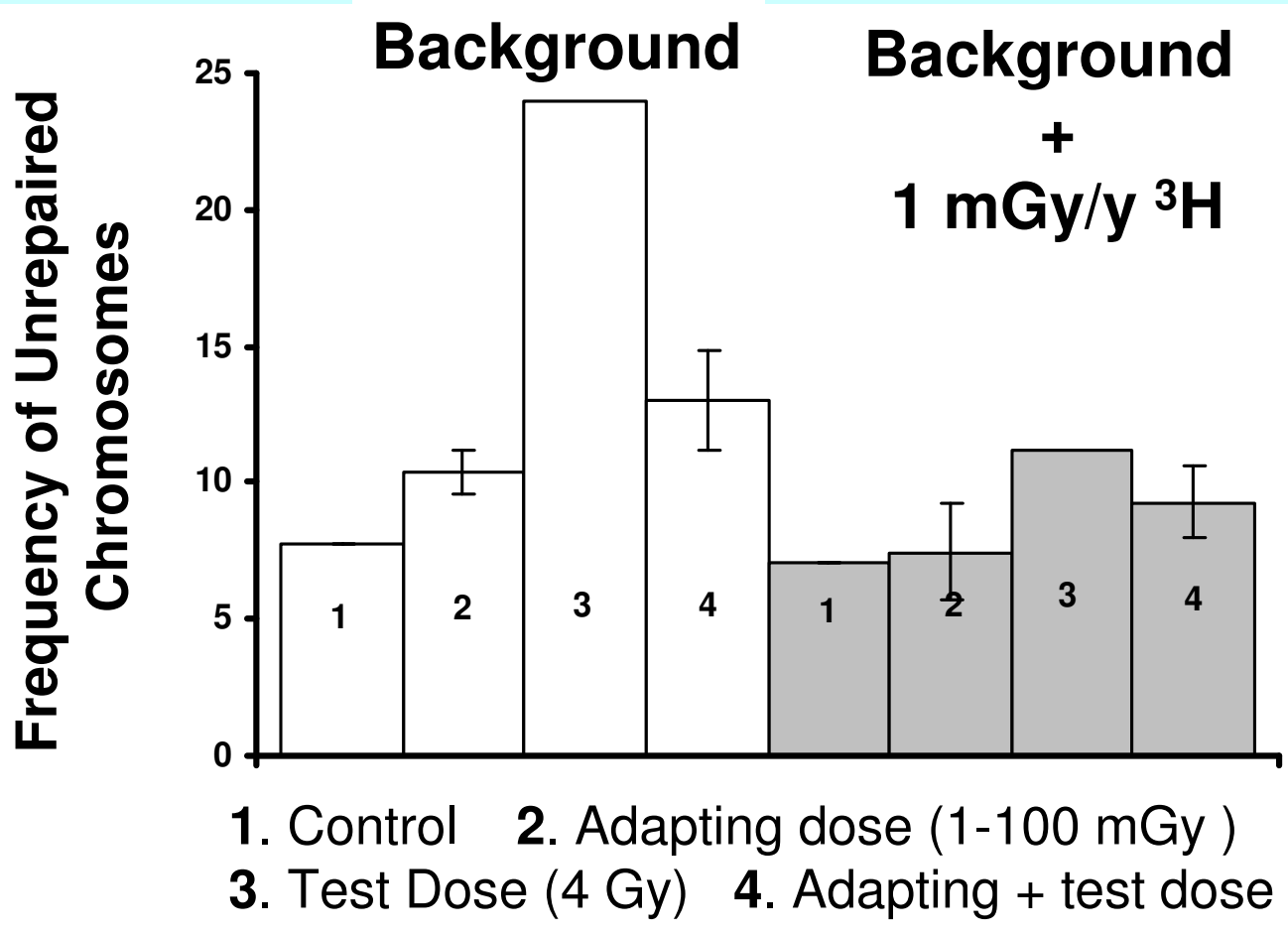
Broome, Brown and Mitchel. Radiat. Res. 158, 181-186 (2002)

# Adaptation in Whitetail Deer Cells



Ulsh, Miller, Mallory, Mitchel, Morrison, and Boreham  
*J Environ Radioact* 74, 73-81 (2004)

# Environmental Adaptation in Frogs *in vivo*



**M. Stuart, AECL, unpublished**

# Adaptation to radiation shown in:

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

*This is an Evolutionarily  
Conserved Response*

# Low Doses Protect Cells Against Malignant Transformation by High Doses

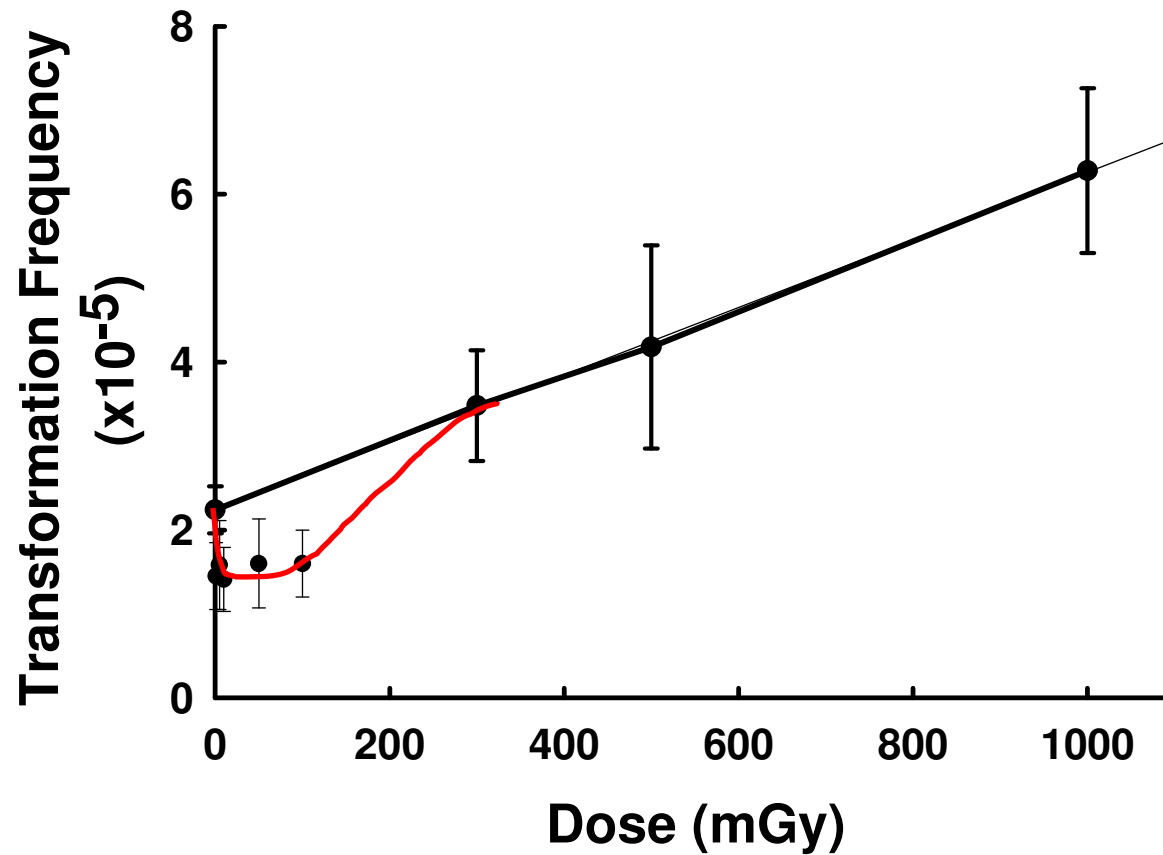
<u>Treatment</u>	<u>Transformation Frequency</u> (x 10 <sup>-4</sup> )
Control	3.7
4 Gy (high dose rate)	41
100 mGy (low dose rate) +24h + 4 Gy (high dose rate)	16

# The Influence of Low Doses On the Risk of Spontaneous Malignant Transformation

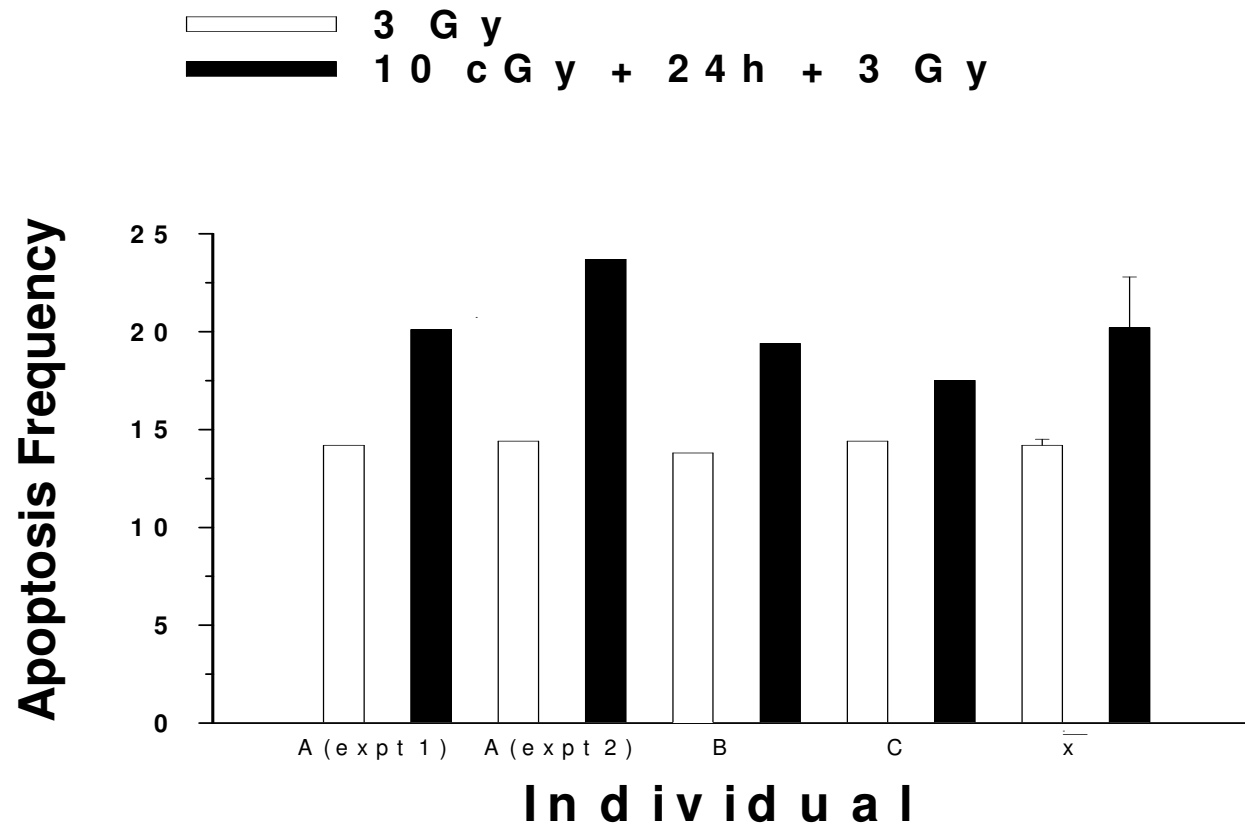
<u>Treatment</u>	<u>Transformation Frequency</u> (x 10 <sup>-3</sup> )
Control	1.8
1.0 mGy	0.53
10 mGy	0.42
100 mGy	0.53

# Transformation in Human Cells

J. L. Redpath and R.J. Antoniono,  
Radiat. Res. 149, 517-520 (1998)



# Low Doses Sensitize Non-Dividing Human Lymphocytes to Apoptosis



# Increased Sensitivity for Radiation-Induced Apoptosis in Human Lymphocytes Previously Exposed to a 10 cGy Adapting Dose

Number of Individuals

Sensitivity Increase

18

27.5 ± 5.7 %

8

7.0 ± 3.0 %

*Is This Genetic Variation?*

# BYSTANDER EFFECT

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

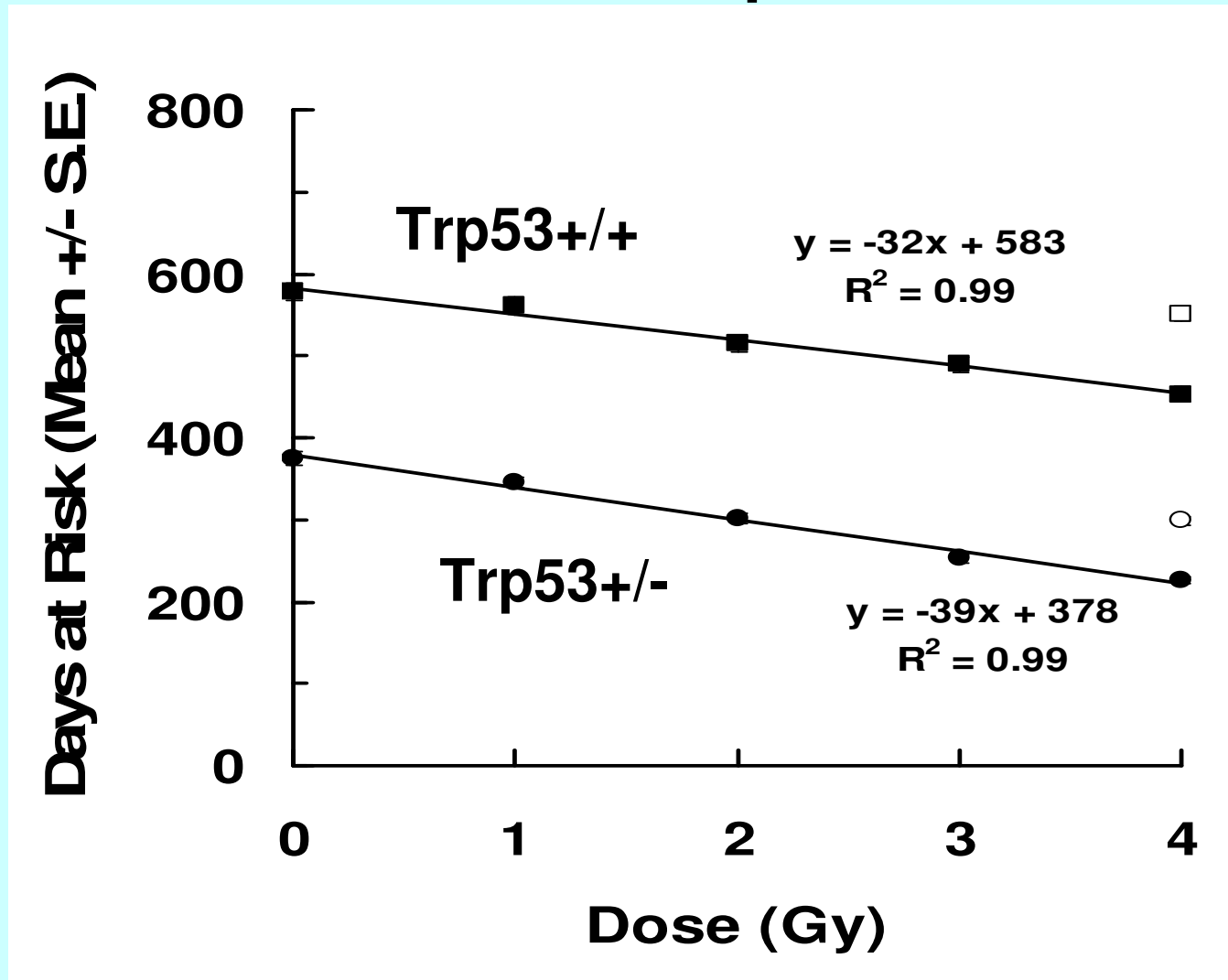
Control Cells	Irradiated Cells (10 mGy)	50% Control Cells + 50% Irradiated Cells
7.7 ± 4.1	17.8 ± 3.3 p<0.01	22.6 ± 4.8 p<0.01

Y. Xu, C.L. Greenstock, A. Trivedi and R.E.J. Mitchel

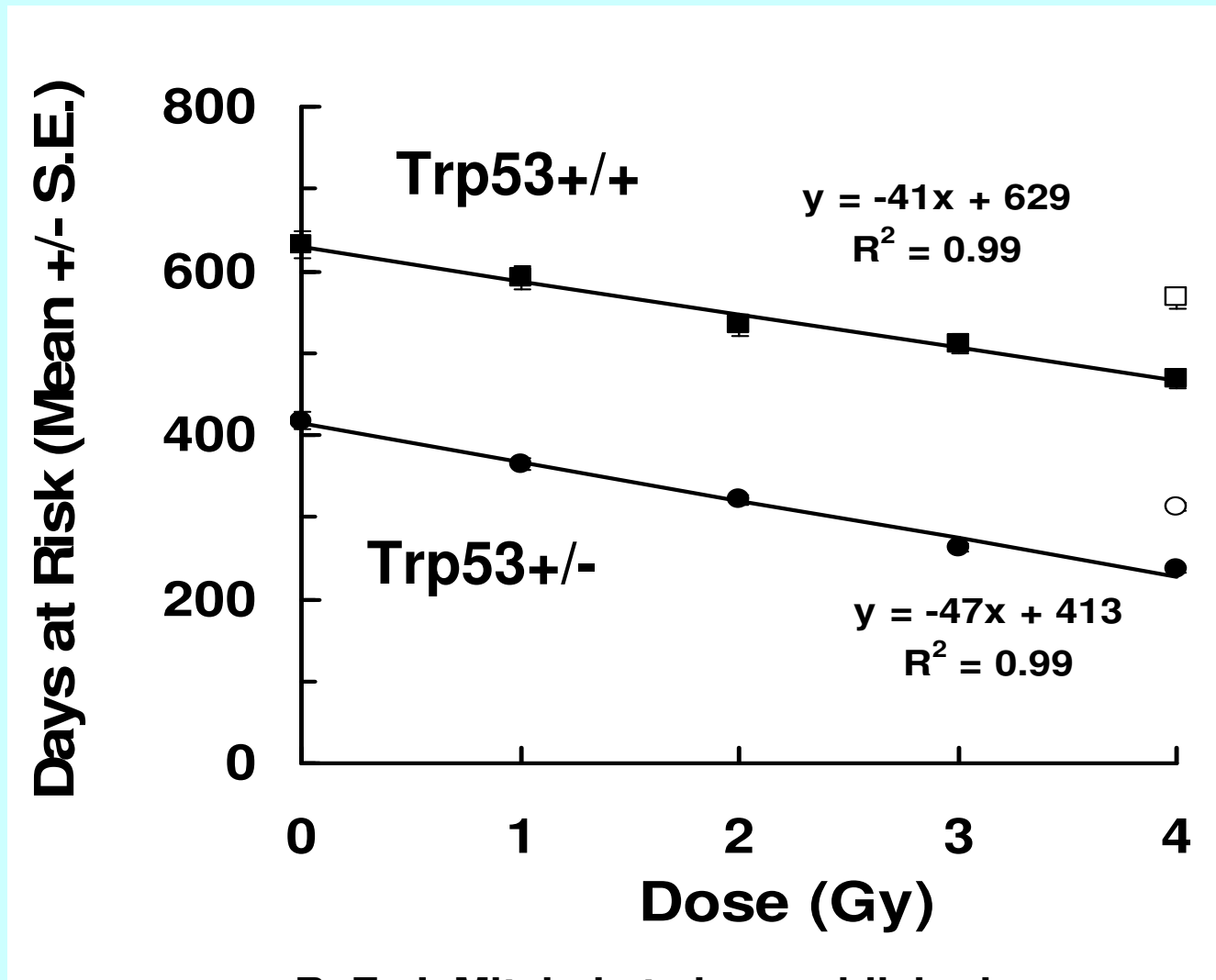
*Radiation and Environmental Biophysics* 35: 89-93 (1996)

**DO THESE  
RADIATION-INDUCIBLE  
ADAPTIVE PROCESSES  
PRODUCE  
PROTECTIVE EFFECTS  
*IN VIVO*??**

# LOSS OF LIFE FROM HIGH DOSE EXPOSURE IN NORMAL AND Trp53 +/- MICE

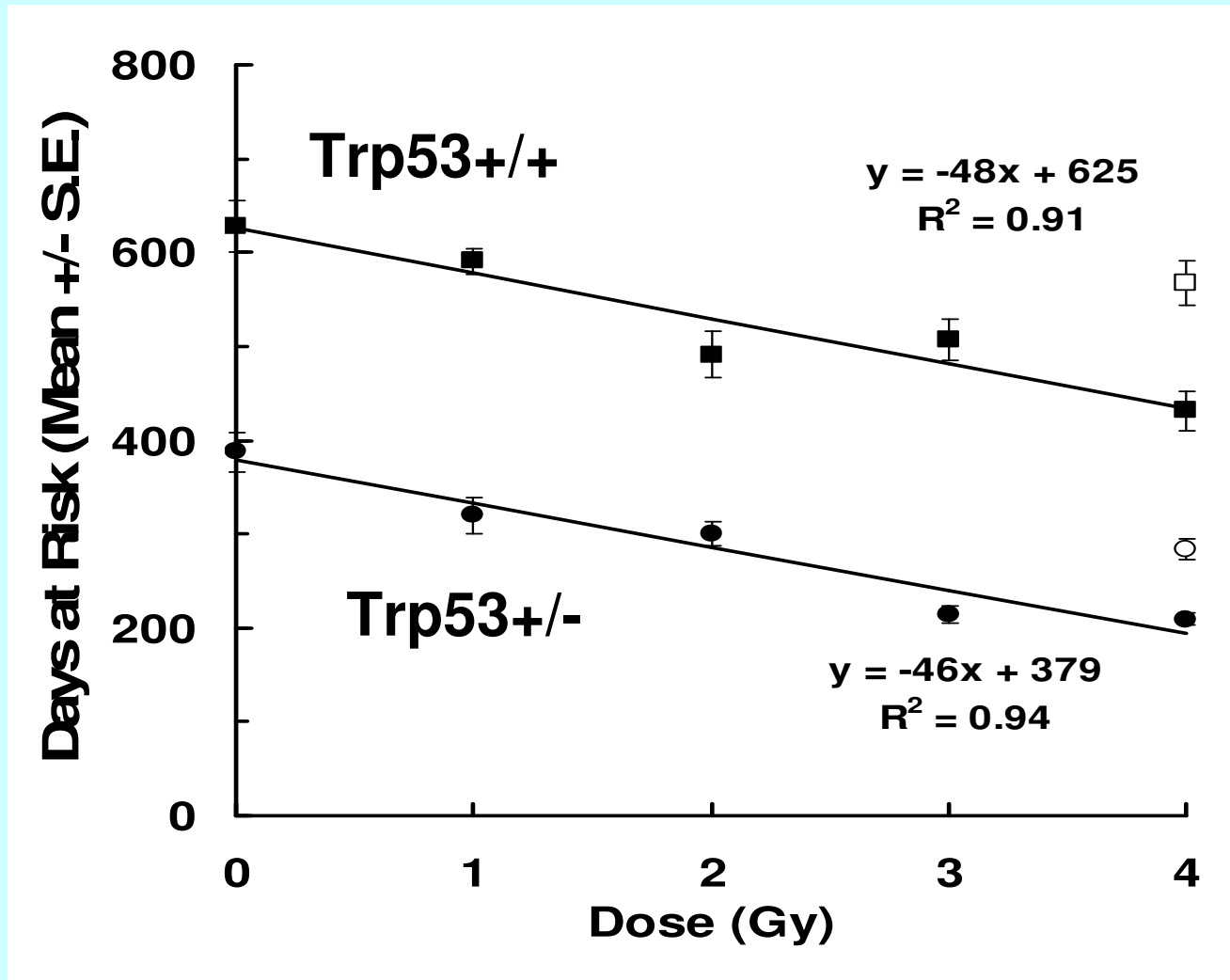


# LOSS OF LIFE FROM HIGH DOSE EXPOSURE IN NORMAL AND TRP53 +/- MICE WITH CANCER



R. E. J. Mitchel et al. unpublished

# LOSS OF LIFE IN NORMAL AND Trp53 +/- MICE WITH LYMPHOMAS



# **SKIN TUMORS IN MICE**

## **Protection by Radiation Against Chemical Tumor Initiation**

### **Initiation Treatment**

### **Tumors per Animal**

**MNNG**

**2.04**

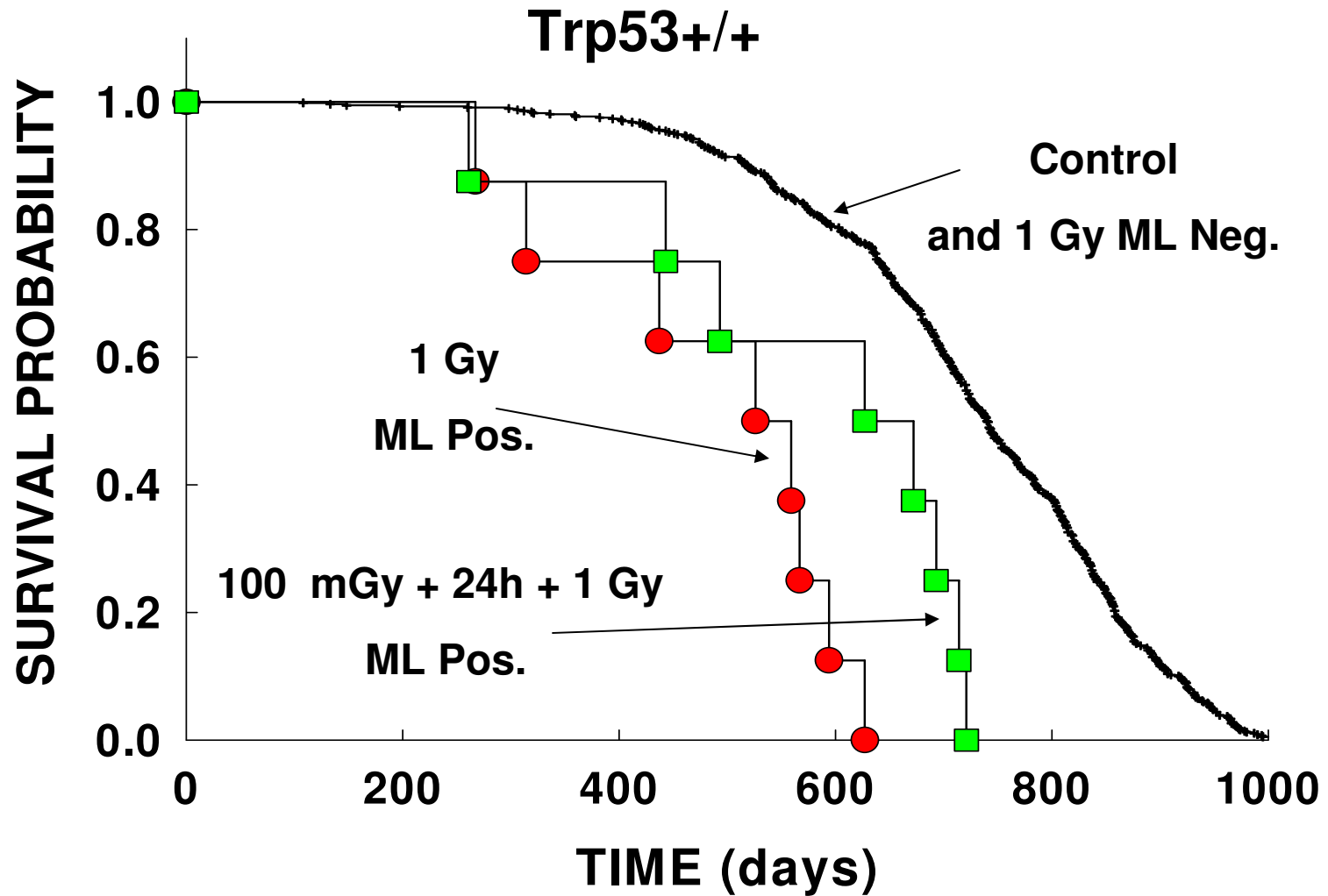
**Beta Radiation (0.5 Gy)**

**0**

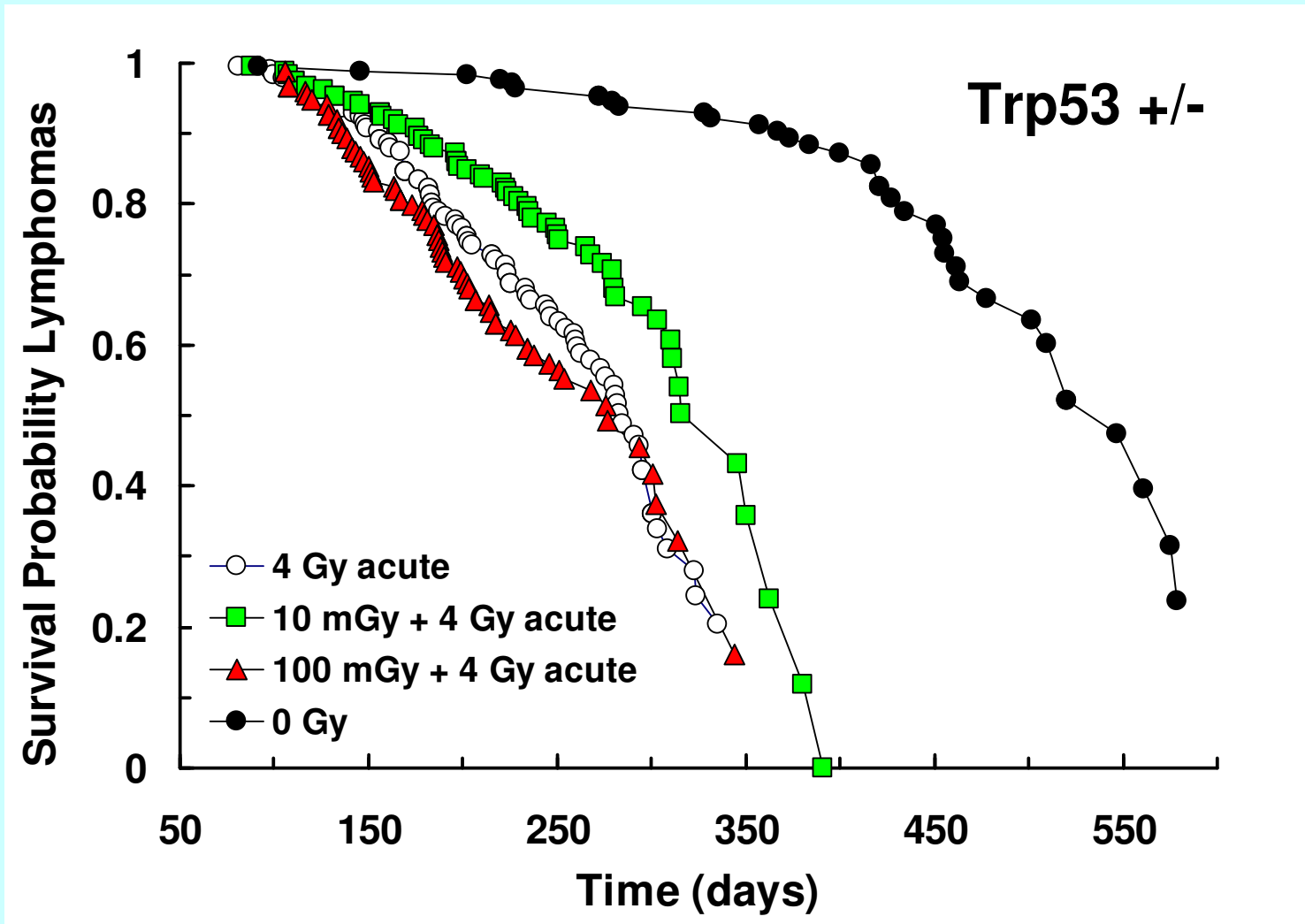
**Beta + MNNG**

**0.39**

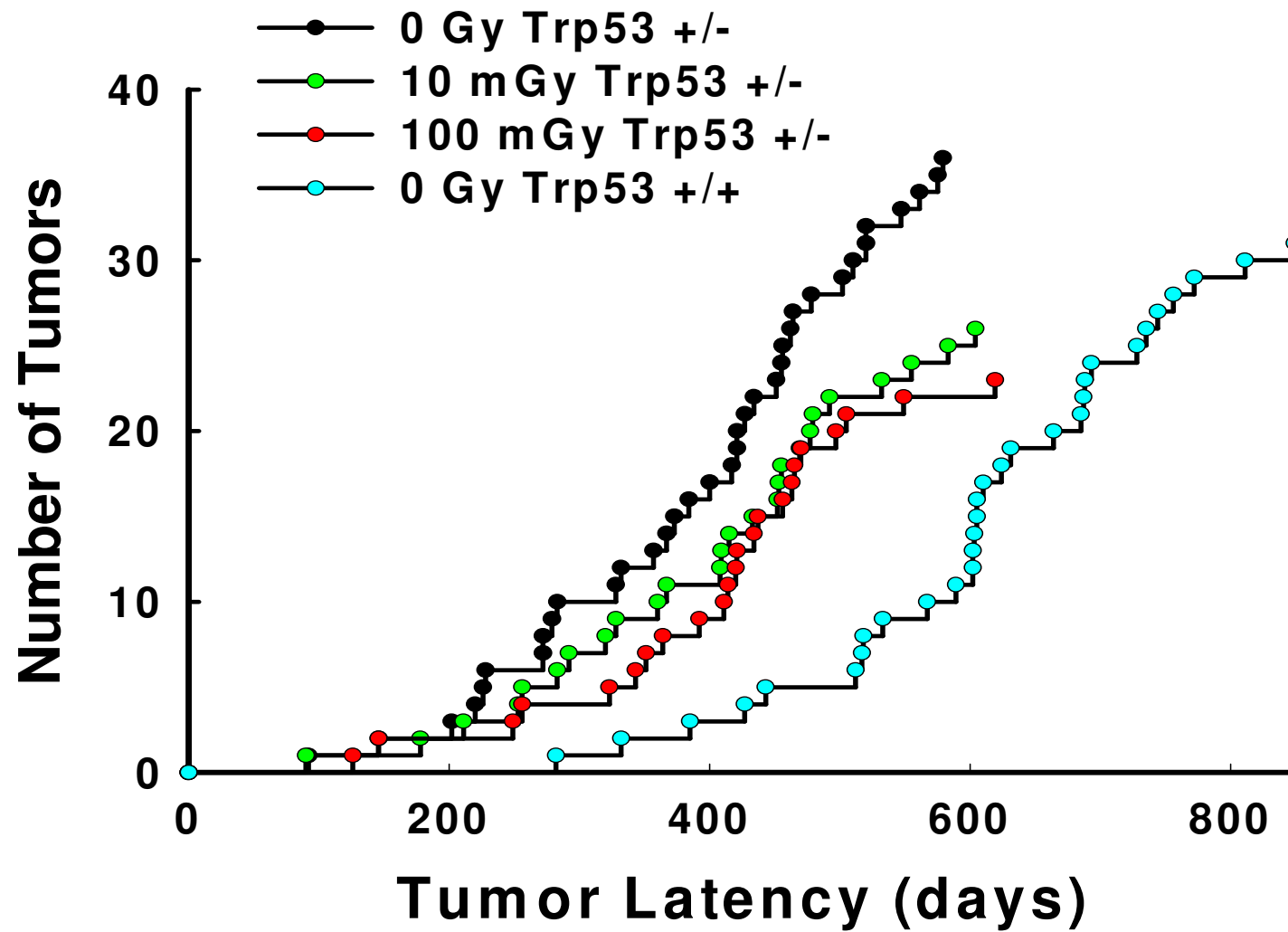
# Myeloid Leukemia in Genetically Normal Mice



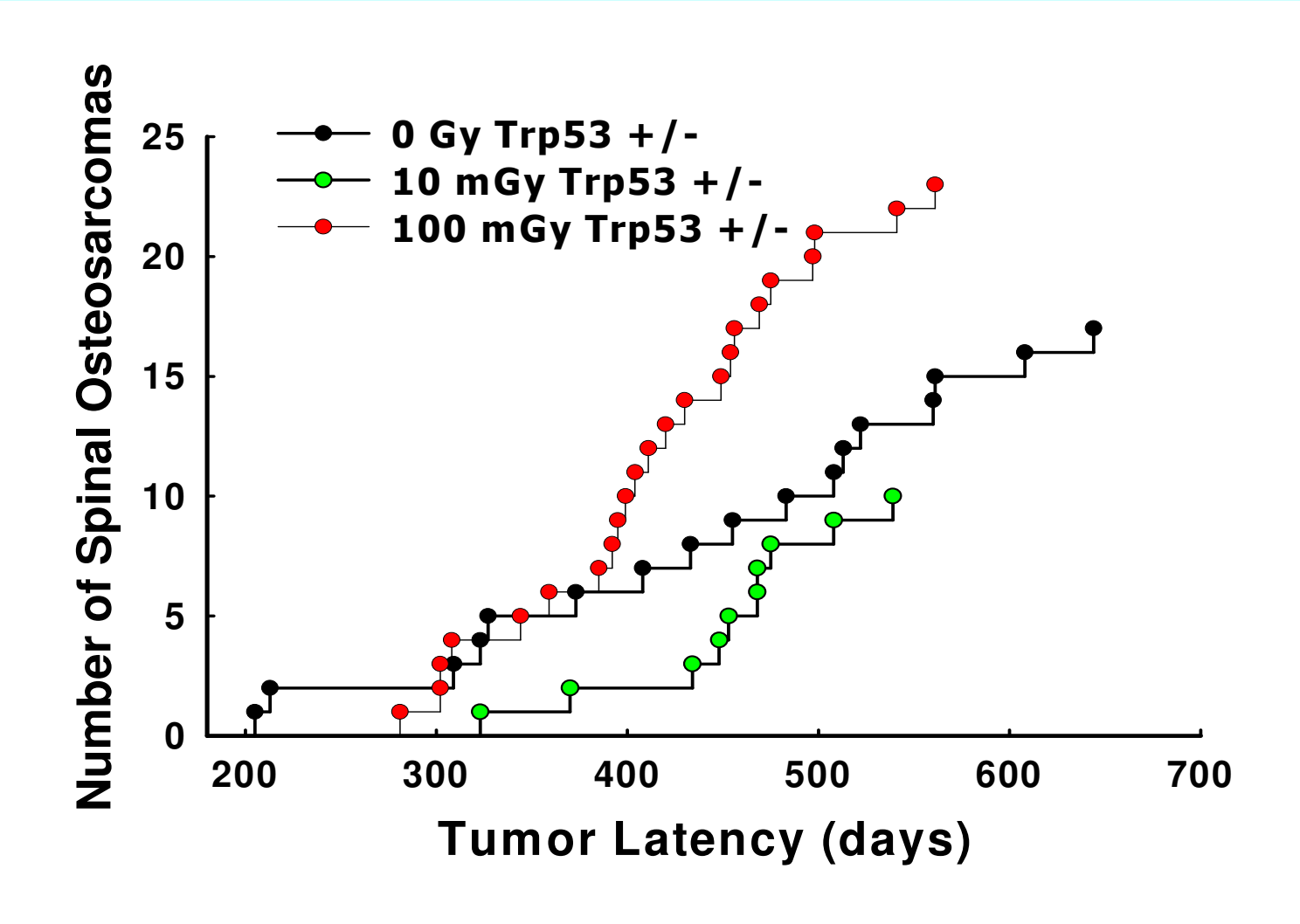
# Lymphomas in Cancer-Prone Mice



# Lymphoma Latency



# Spinal Osteosarcomas in Trp53+/- Mice



# Bottom Line

**Low doses of low LET  
radiation, at low dose rate,  
reduce, not increase, risk  
*in vivo***

# **IMPLICATIONS for LNT**

- **High dose responses cannot be extrapolated to low doses**
- **At low doses *in vivo*, cancer risk is not proportional to dose**
- **Dose thresholds for increased risk exist in both normal and cancer prone individuals**
- **Cancer susceptibility modifies threshold (zero risk) dose**

# **IMPLICATIONS** **FOR DOSE ADDITIVITY**

- **Radiation protection assumes dose (i.e risk) additivity (Sv)**
  - **If some doses protect, doses are not additive**
- **Further complicated if some doses protect some but not all organs**

# IMPLICATIONS FOR DDREF

- Assumed DDREF = 2  
for increased risk
- If risk from low dose/dose rate  
 $\leq 0$  then DDREF may =  $\infty$

# **IMPLICATIONS FOR $W_t$**

- **Tissue Weighting Factors ( $W_t$ ) are not constant with dose**
- **$W_t$  changes from positive values through zero to negative values as dose decreases**
  - **Cancer proneness and/or a second dose modify  $W_t$**

# IMPLICATIONS FOR $W_R$

- Radiation weighting factors ( $W_R$ ) for high LET are based on the RBE ratio with low LET
- BUT: Low doses of low LET are protective *in vivo* (negative risk)
- THEREFORE: At low doses  $W_R$  and dose in Sv have no meaning

# **IMPLICATIONS** **FOR “ALARA”**

**Preventing an exposure that would  
induce an adaptive response  
will *INCREASE* risk!**

# **THE BIG QUESTION**

**Regulations are based on  
human epidemiological data:**

**So**

**Why is the accepted  
human epidemiological data  
inconsistent with data  
from all other organisms???**

**Statistically significant increases in cancer risk in humans can be only detected down to about 100mGy**

- ***100 mGy is very close to the transition point between protection and harm in rodent and human cells and in mice.***

# **RADIATION PROTECTION** **CONCLUSIONS**

- **The assumptions of the LNT hypothesis and radiation protection practices are not compatible with the observations *in vitro* or *in vivo***
- **Environmental assessments must consider real effects**
- **A new approach to radiation protection at low doses is needed**

# **POTENTIAL REGULATORY** **SOLUTION**

**Adopt**  
**“Linear With Threshold”**  
**hypothesis**