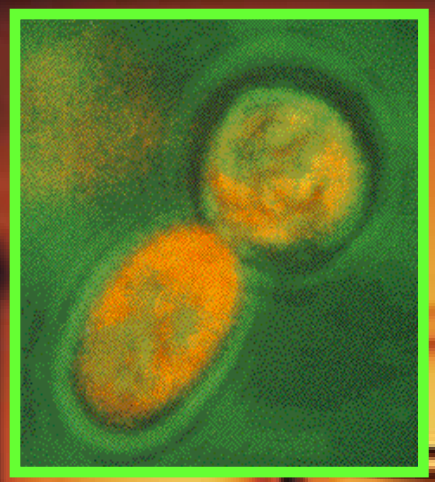
Adaptive Responses and Risk – Yeast to the Clinic



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Dose-Response 2009

McMaster University
Radiation Biology Laboratory

The Adaptive Response

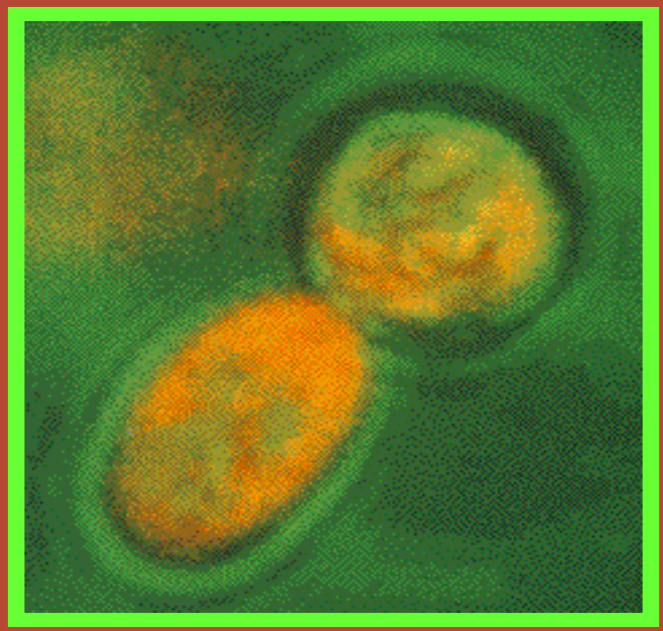
Cellular response to an environmental stress that induces a mechanisms that confers resistance to subsequent stress.

Signal ⟶ Time ⟶ Resistance

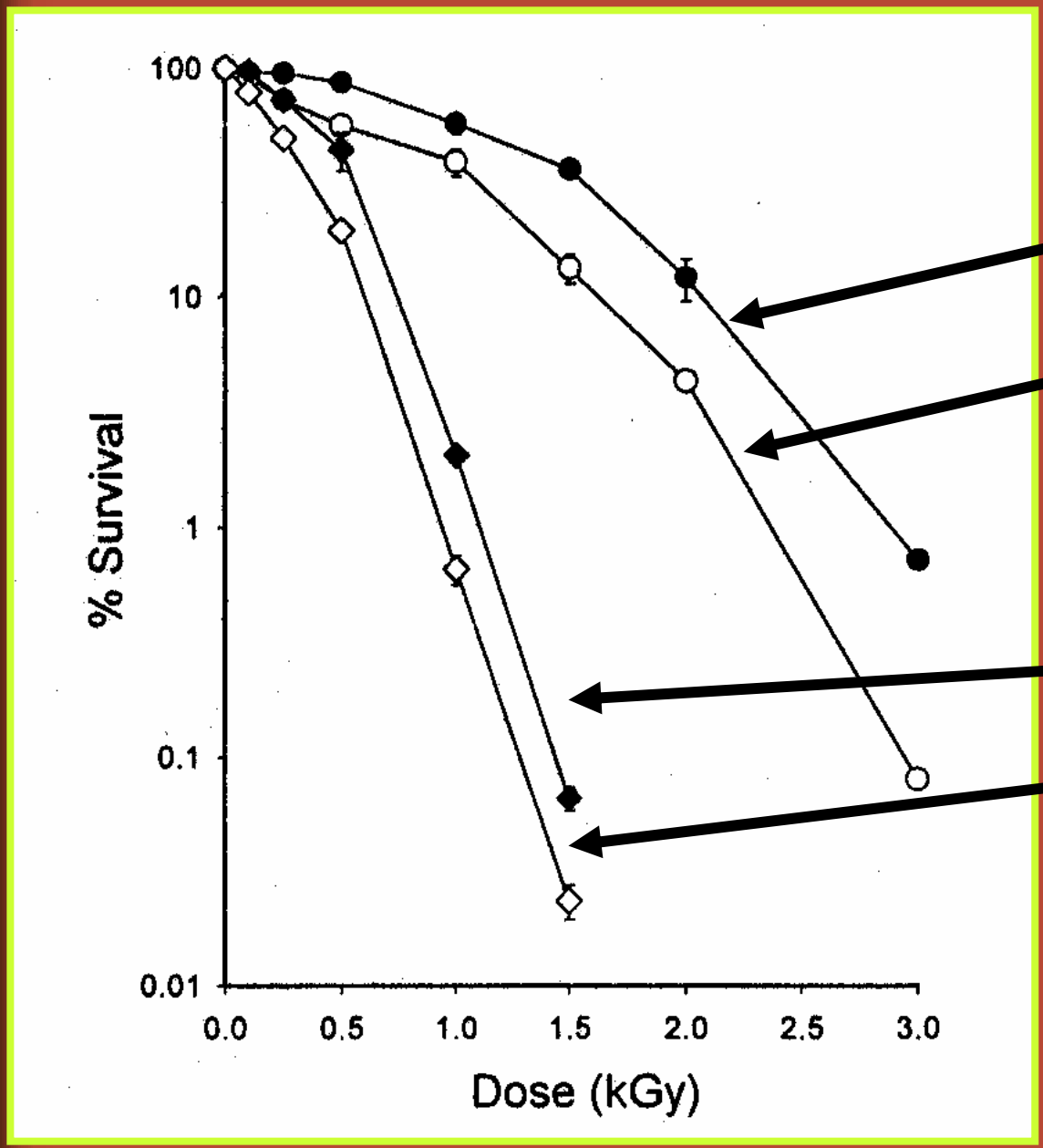
YEAST
MAMMALS
HUMANS

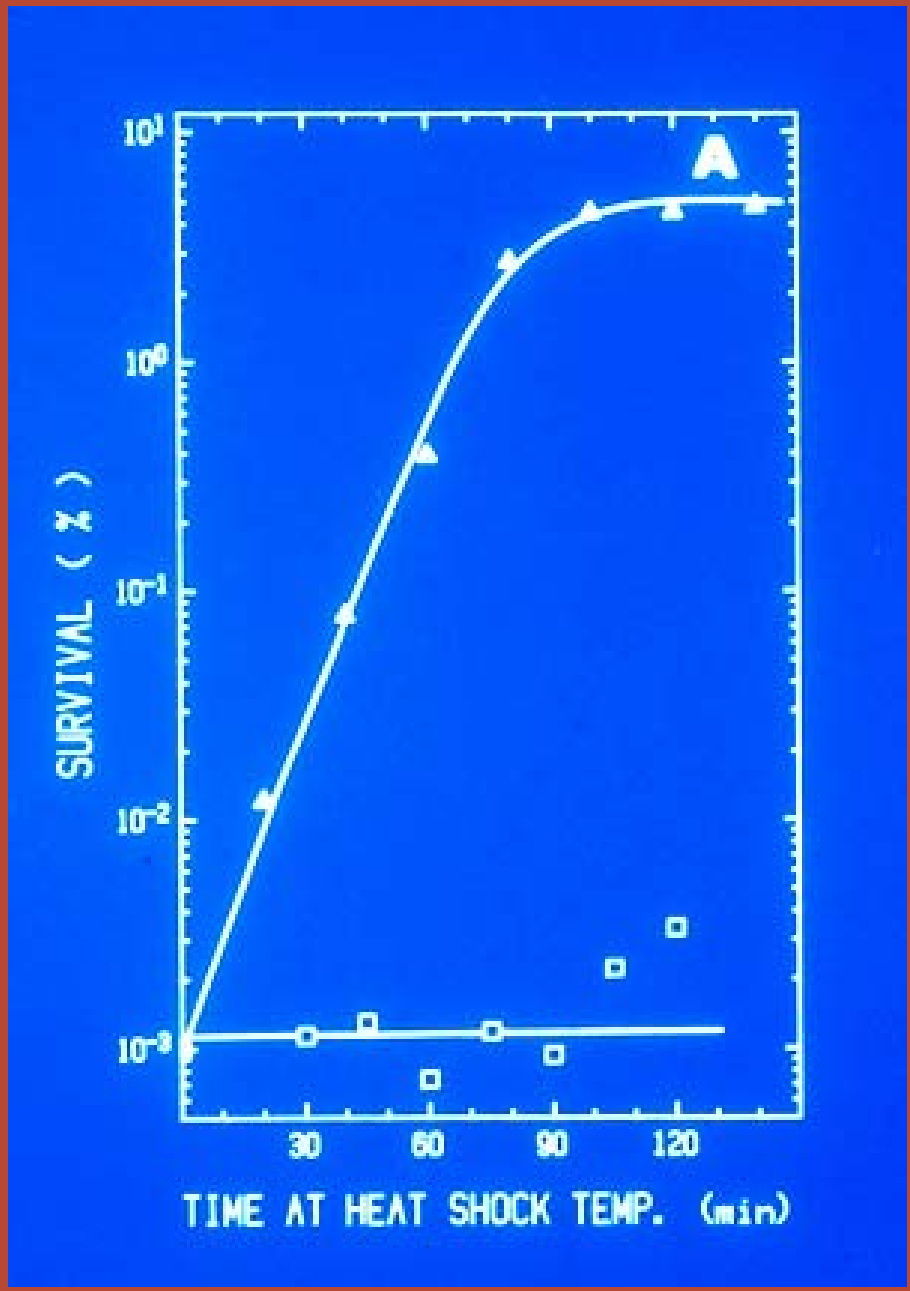
Saccharomyces cerevisiae
(Brewer' Yeast, Baker's Yeast, Budding Yeast)

Cellular Responses to Environment
-Adaptive Response
-Stress Response



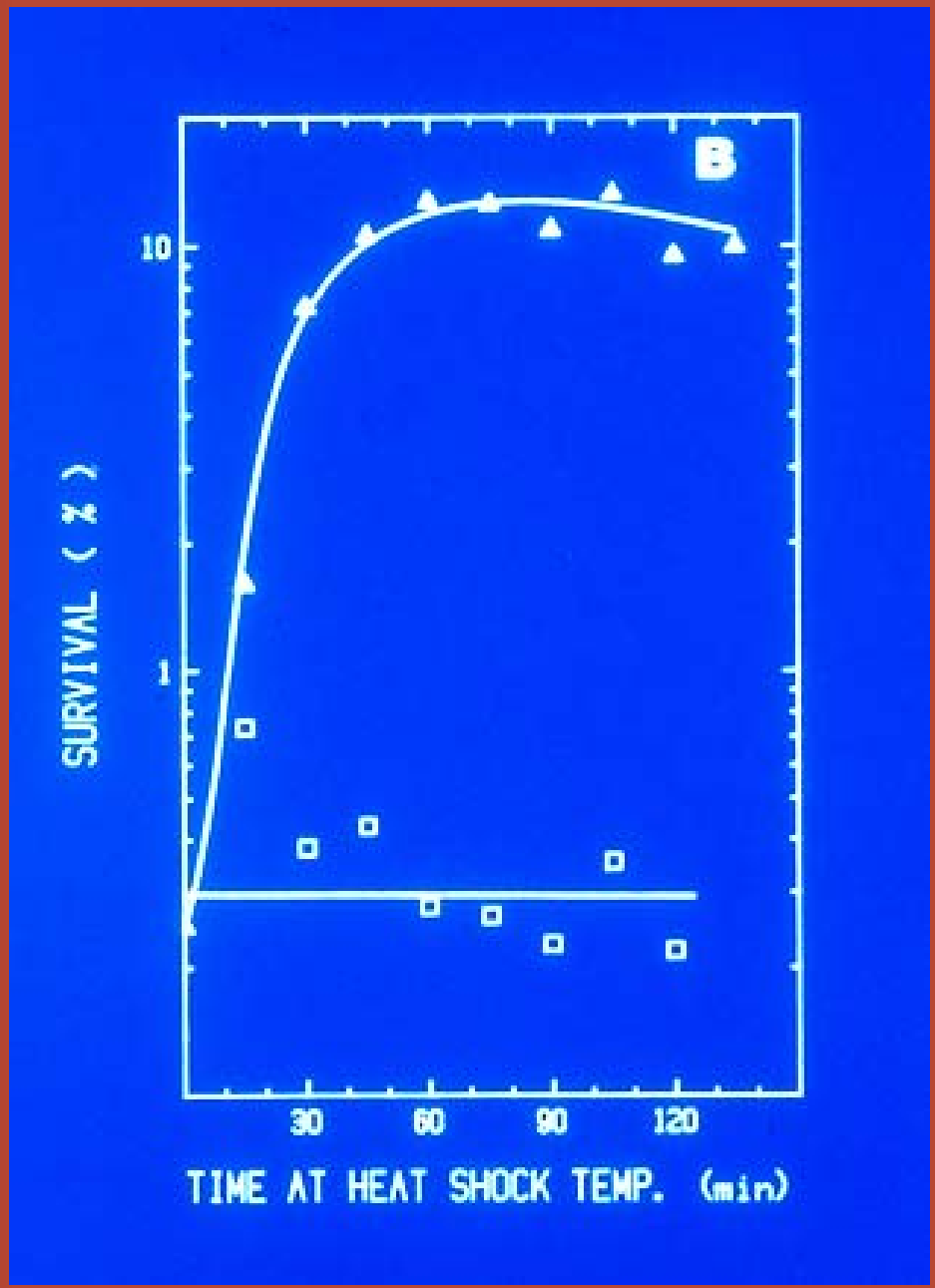
Radiation Survival in Yeast - OER





Heat Resistance
(4 min. @ 52°C)

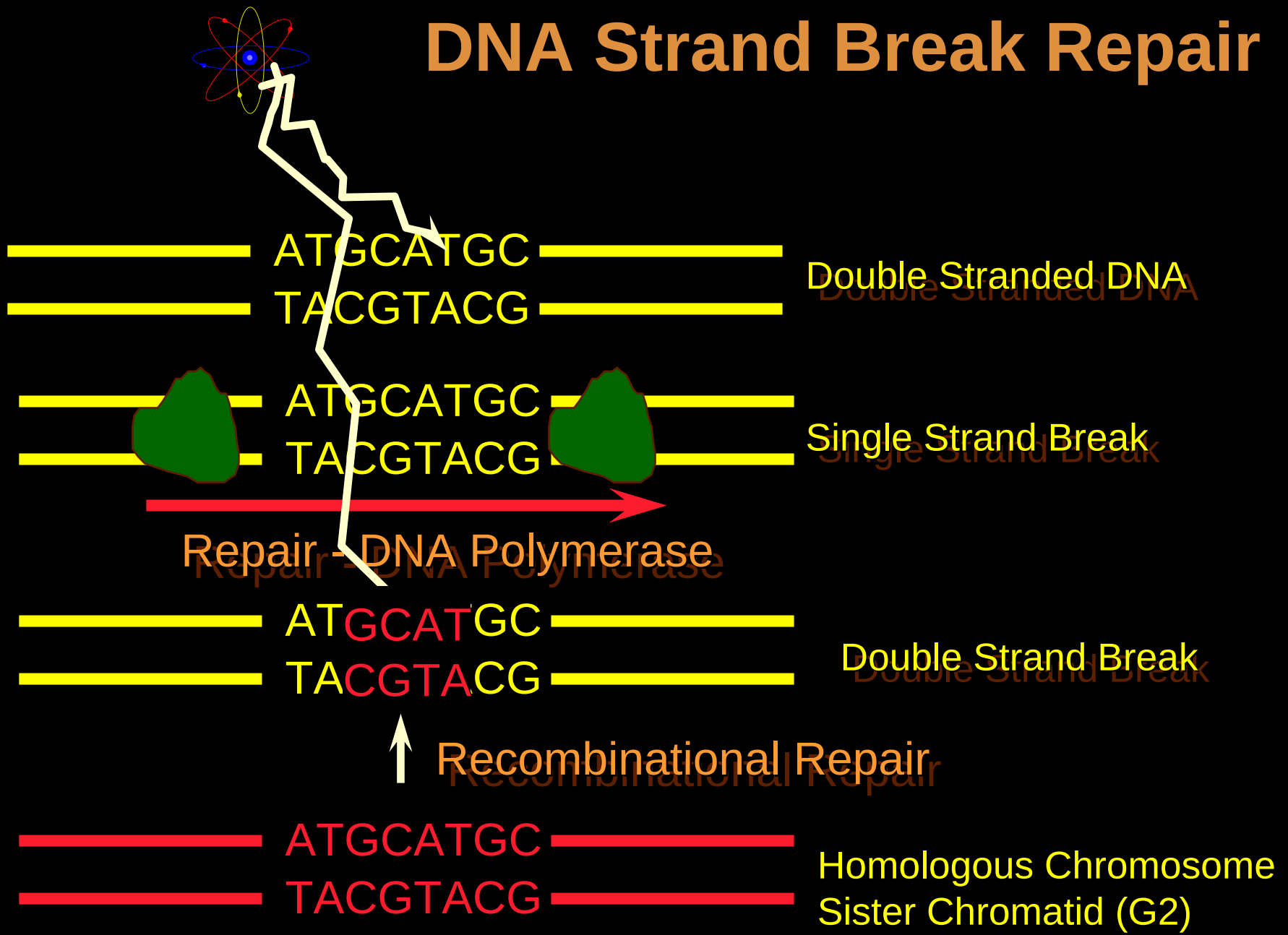
Heat Shock
23°C to 37°C



Radiation Resistance
(150kGy in Oxygen)

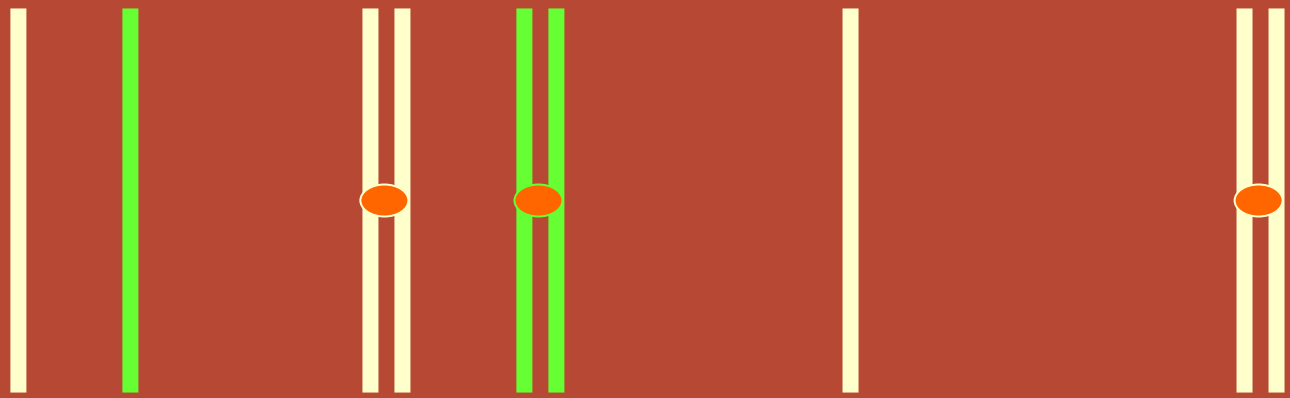
Heat Shock
23oC to 37oC

DNA Strand Break Repair



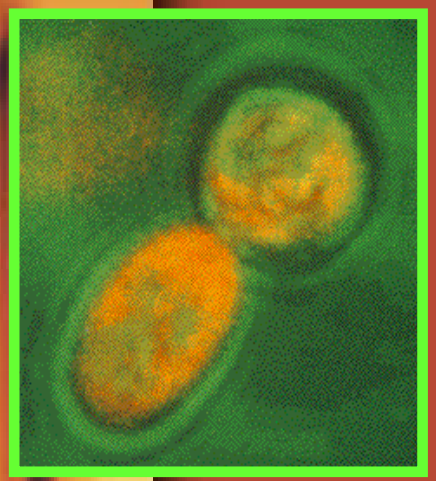
Recombinational Repair and ploidy and cell cycle

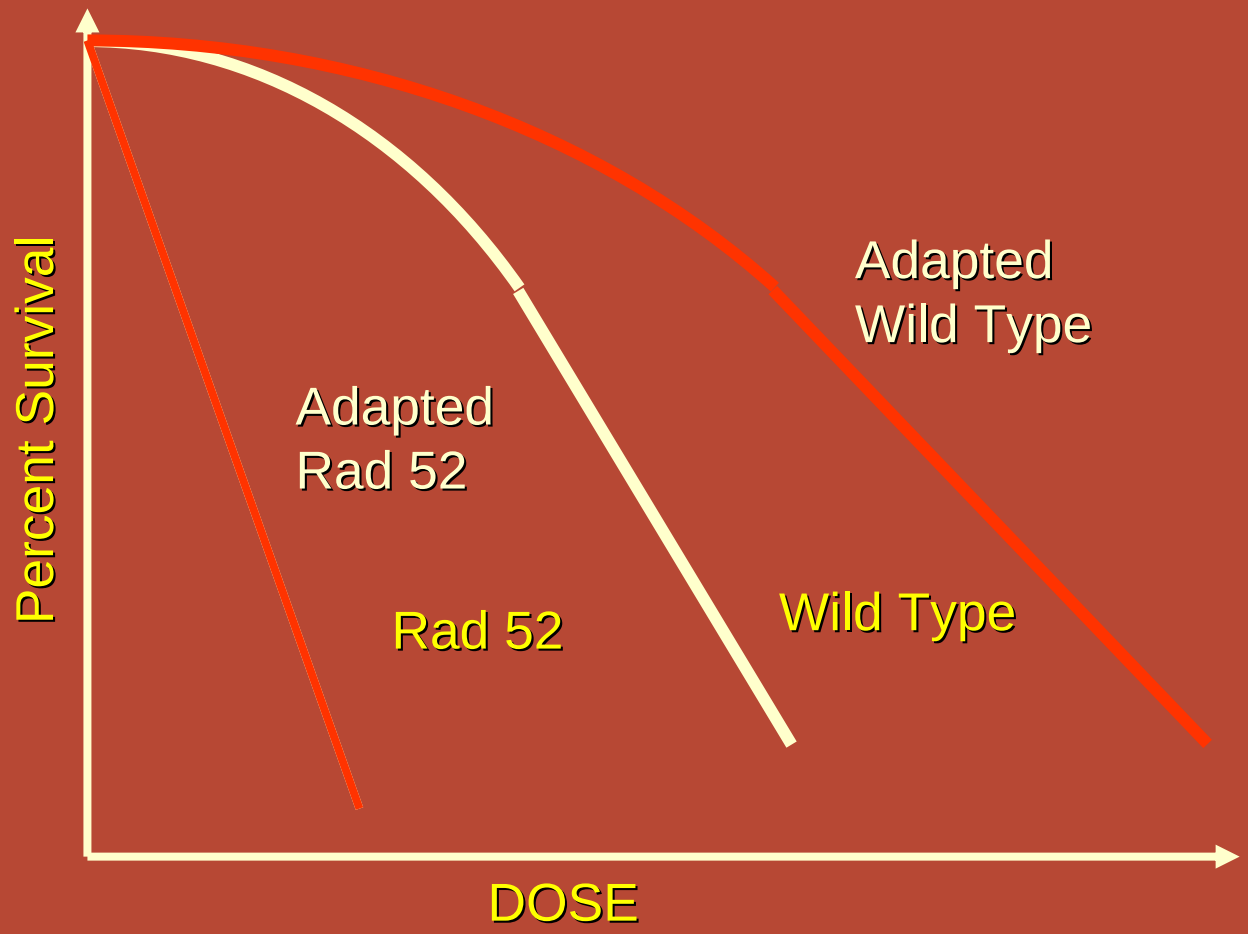
Diploid G1 | Diploid G2 | Haploid G1 | Haploid G2



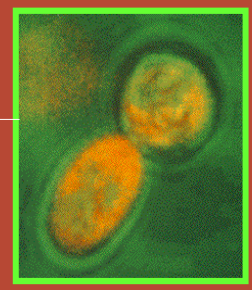
(Rec -)

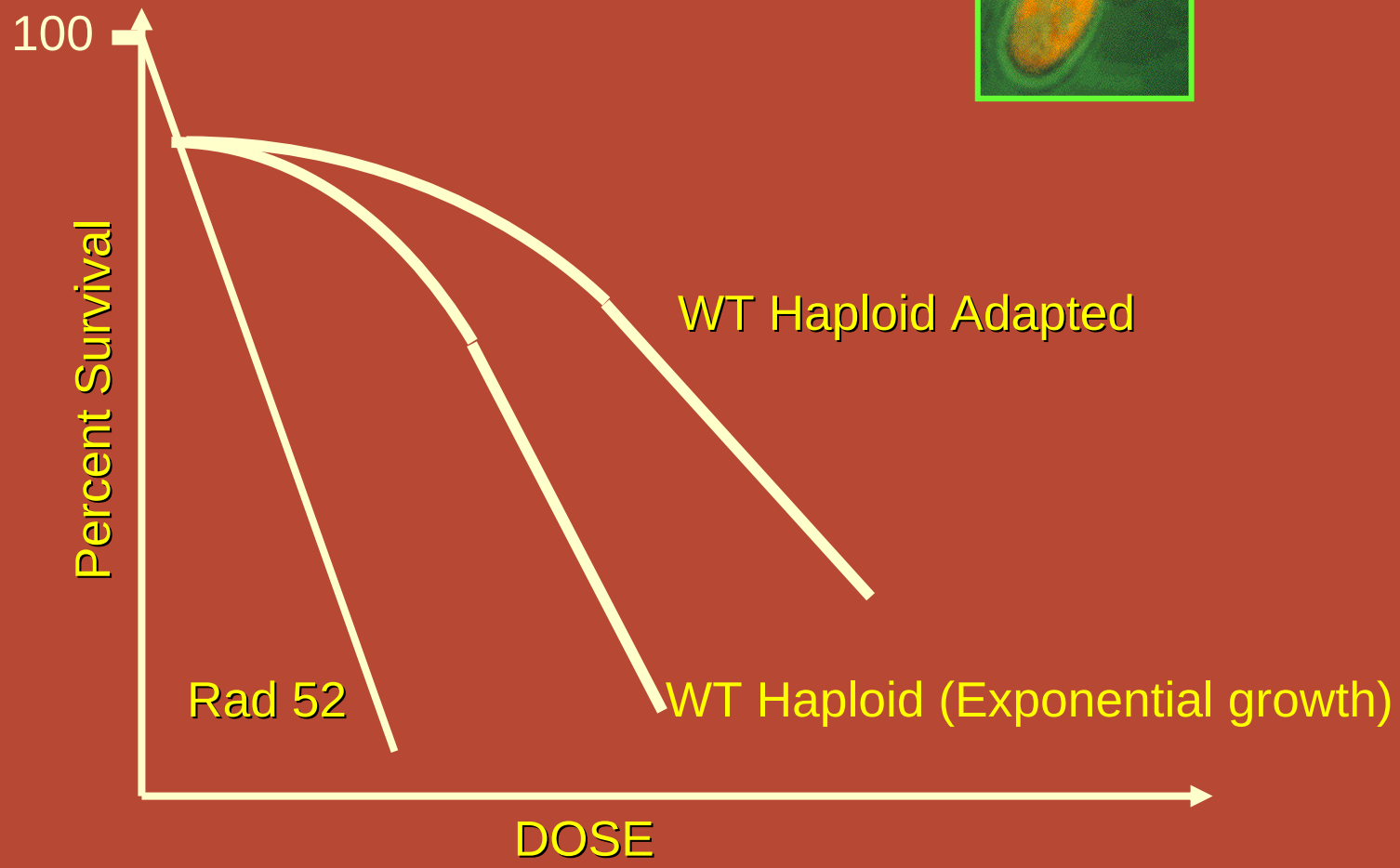
Survival of yeast cells after exposure to gamma radiation





Survival of yeast cells after exposure to gamma radiation



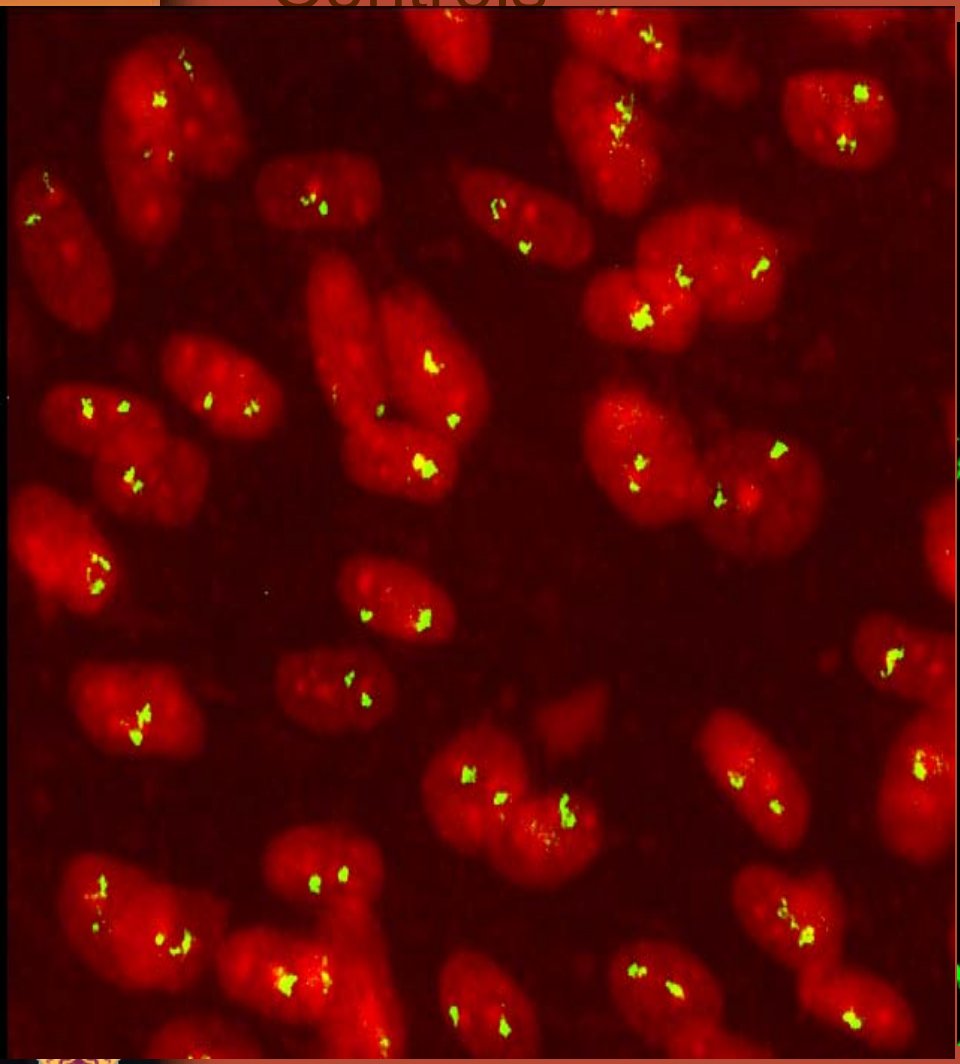


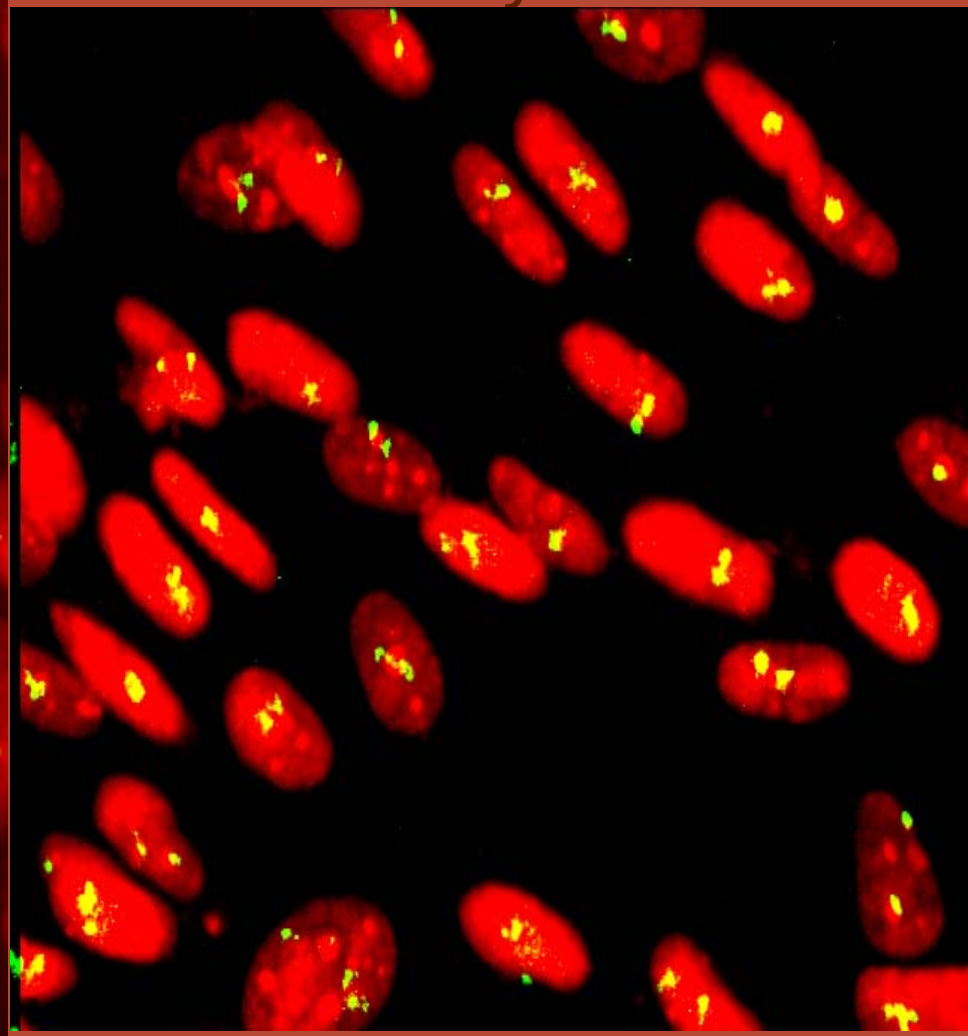
Chromosome Domains (21)

Int. J. Radiat. Biol. 1997 303-311

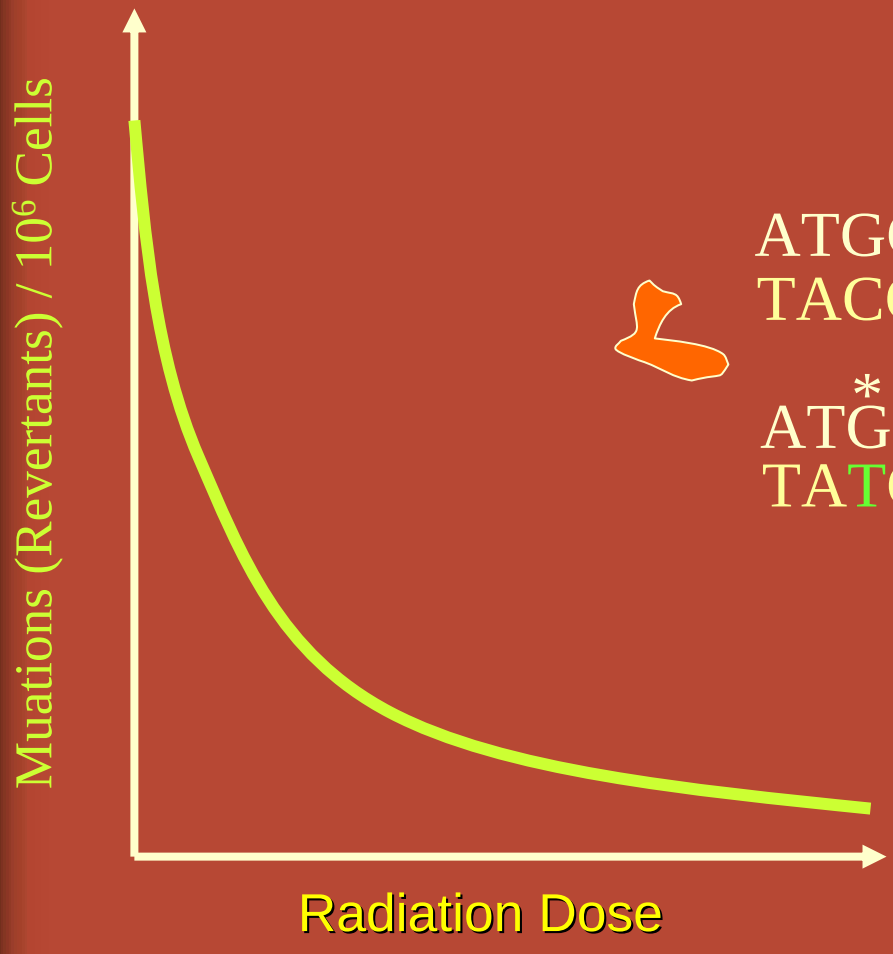
Controls

200 mGy + 2 hours



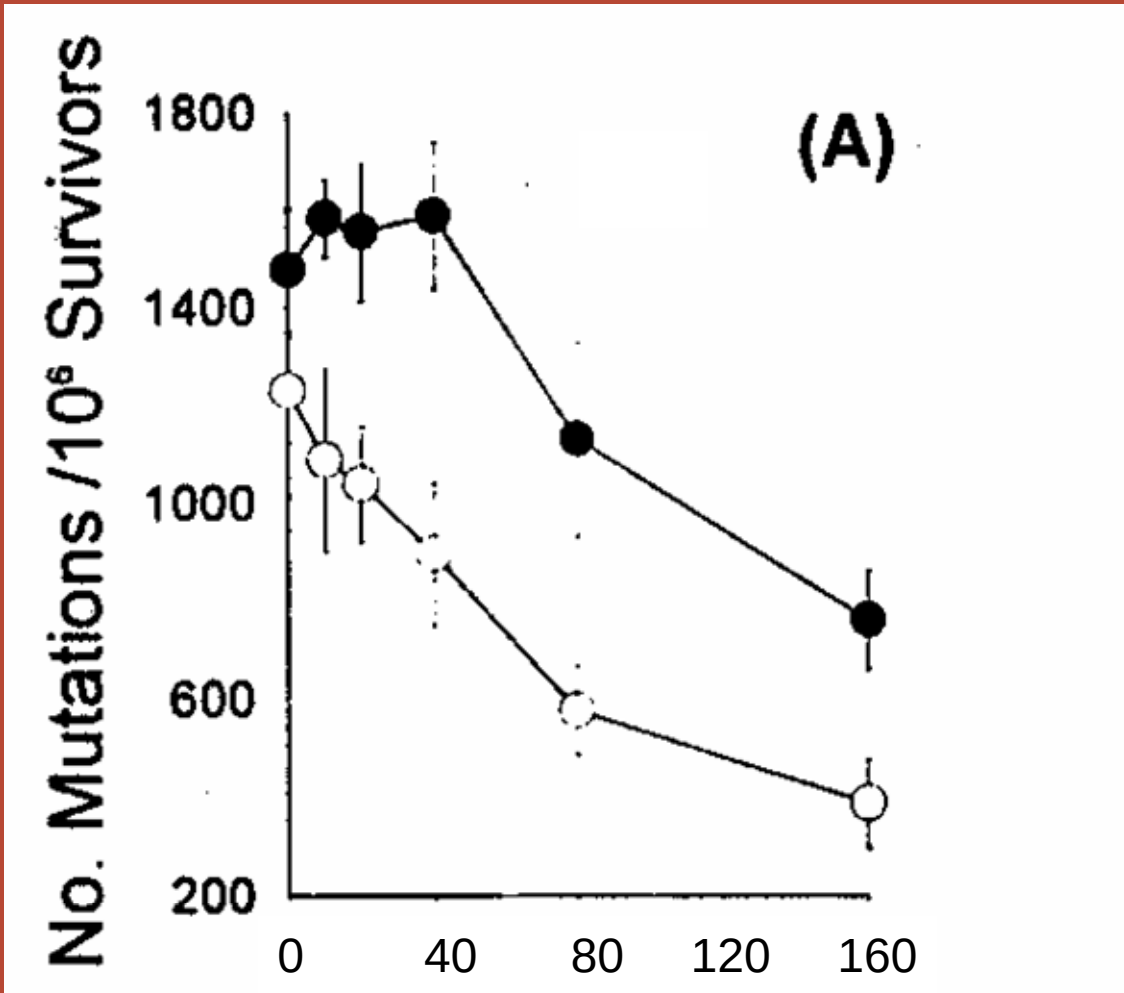


Mutation (reversion to histidine independence) of yeast cells after exposure to MNNG (*N*-methyl-*N'*-nitro-*N*-nitrosoguanidine)



20 ug MNNG for 30 min.
Causes:
O-6 methylation of guanine
GC to AT transition

Suppression of MNNG Mutation in Yeast



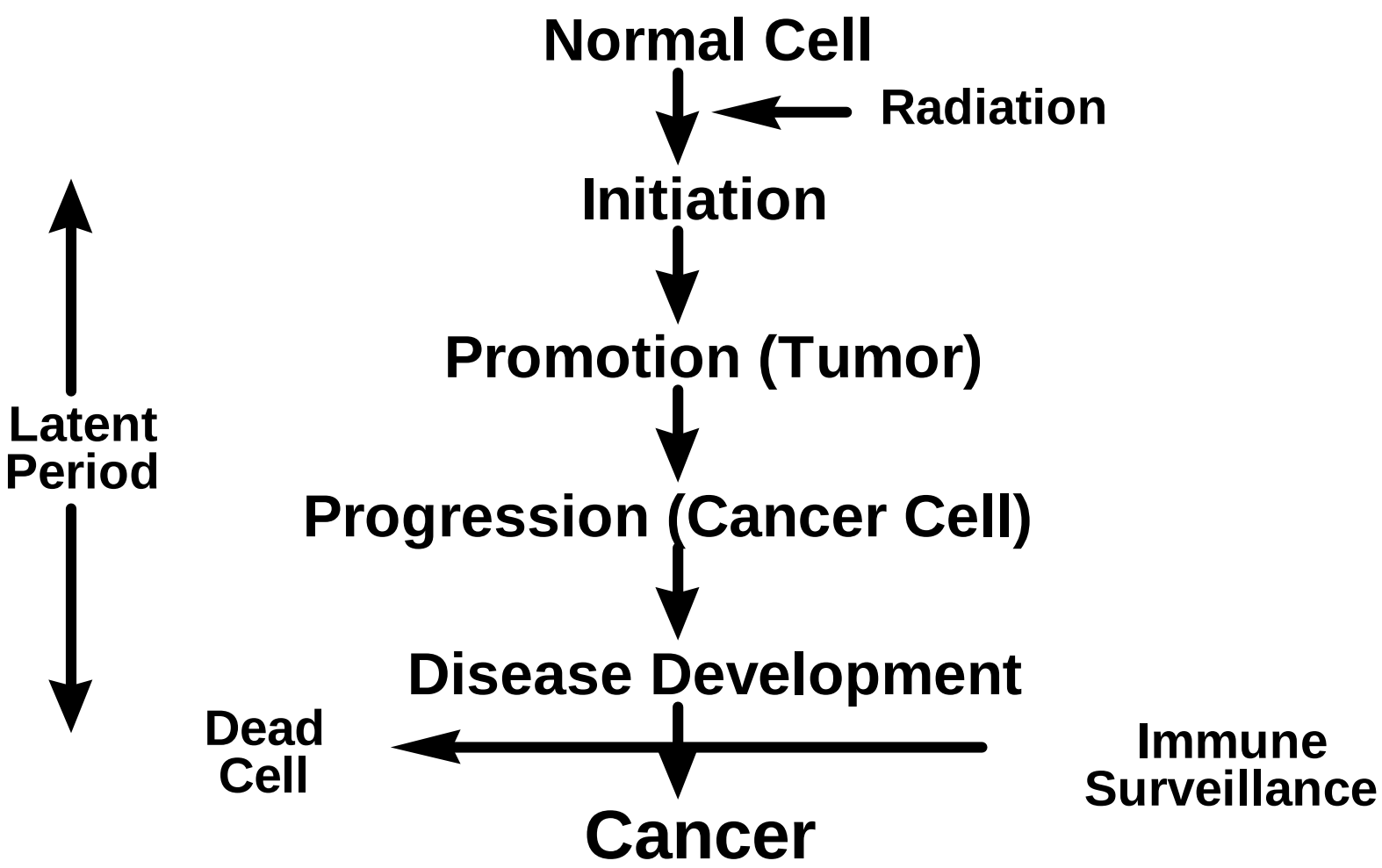
MNNG (20 ug/ml)

Dose (Gy)

Mutation Res 433 (1999) 127-36

Adaptive Response in Yeast

- Shows an oxygen effect
- Dependent on recombinational repair (homologues)
- Signaled by OH ▪
- Low LET radiation better
- Modified by topoisomerases
- Requires protein synthesis
- Induced by different stresses
- AR for chemicals

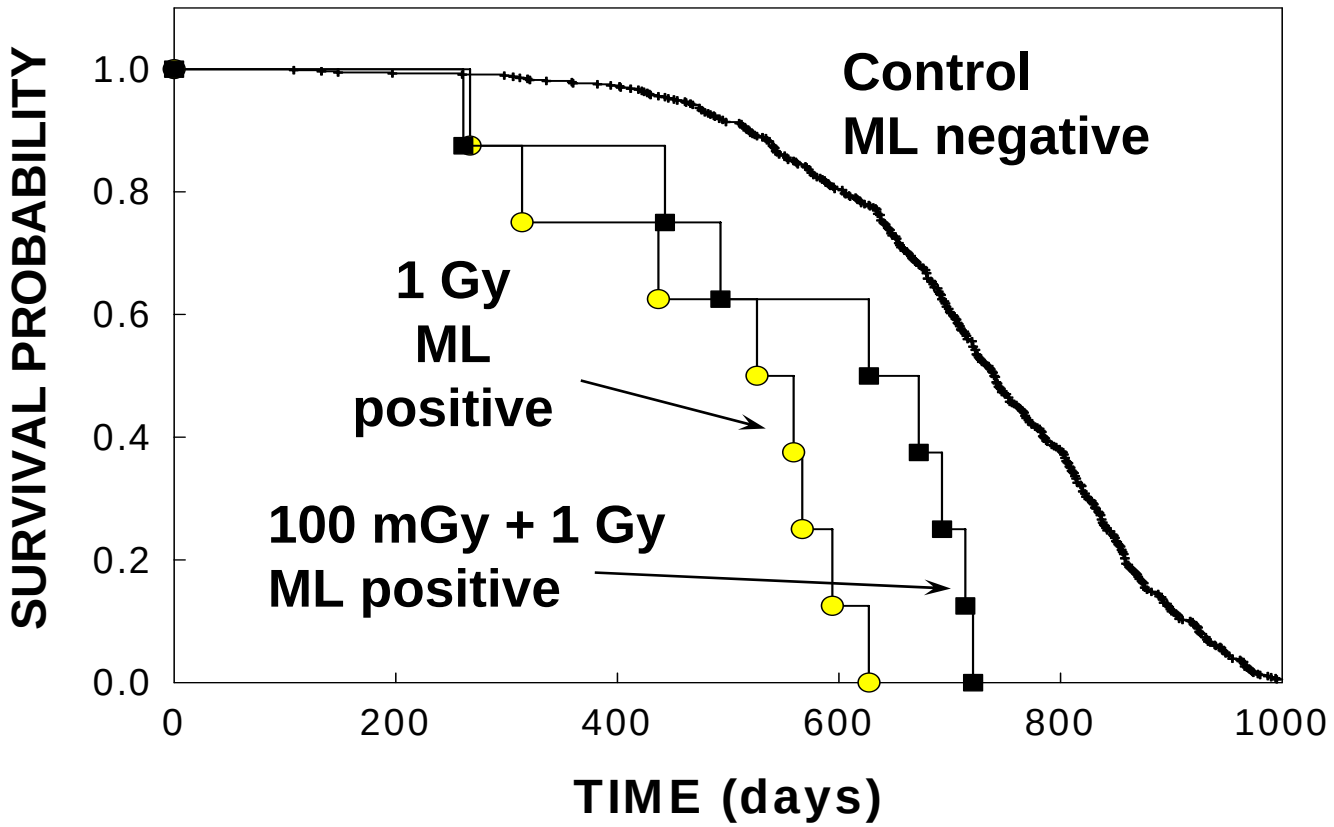

Normal Cell
Radiation
Initiation
Promotion (Tumor)
Progression (Cancer Cell)
Disease Development
Latent Period
Dead Cell
Immune Surveillance
Cancer

Skin Tumorgenesis

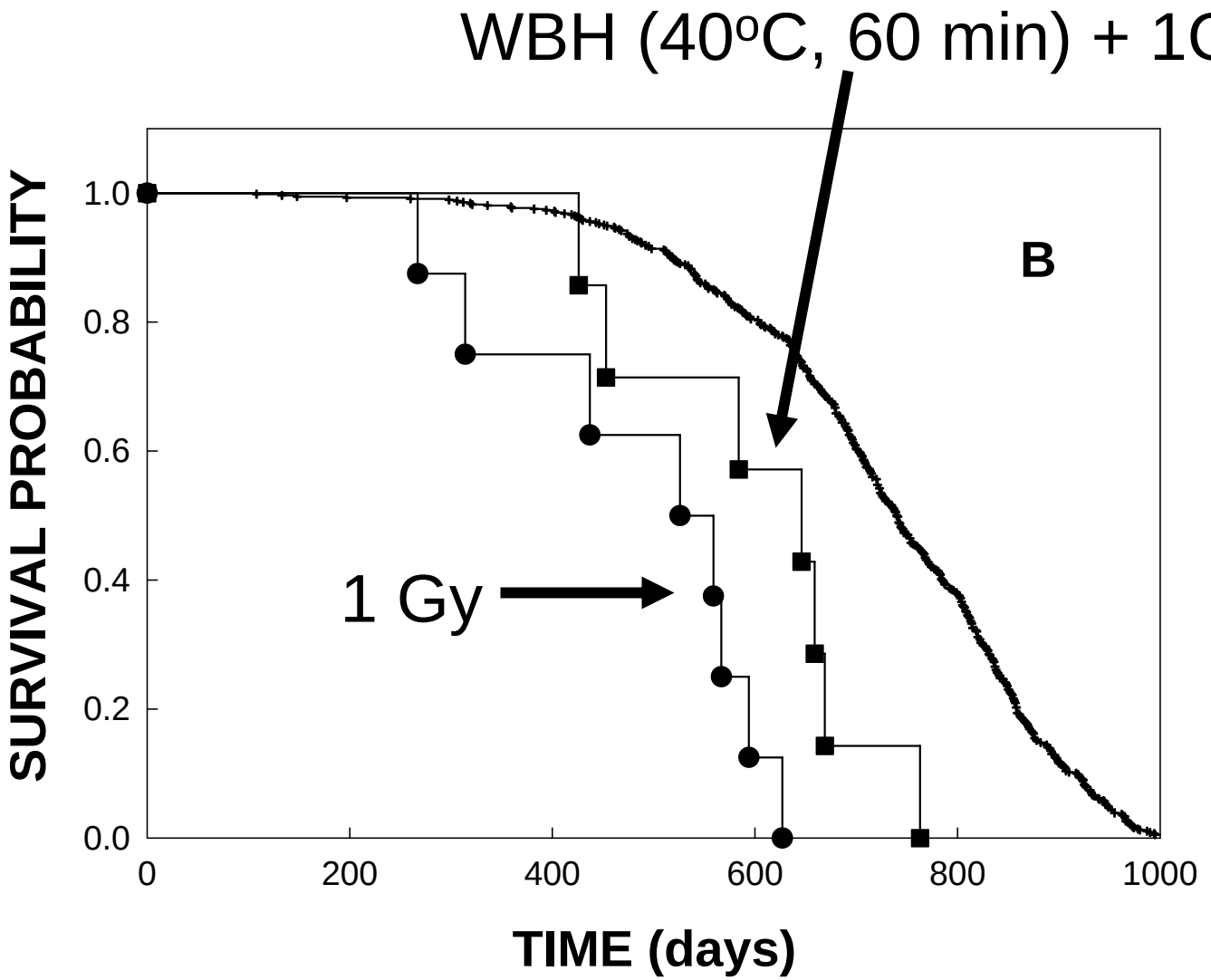
Low Doses Protect Mice Against Skin Tumors Initiated by a Chemical Mutagen

Initiation Treatment	Tumors per Animal
methyl-nitro-nitroso guanidine	2.04
β-radiation (100 mGy)	0
β-radiation + 24h + methyl-nitro-nitroso guanidine	0.39

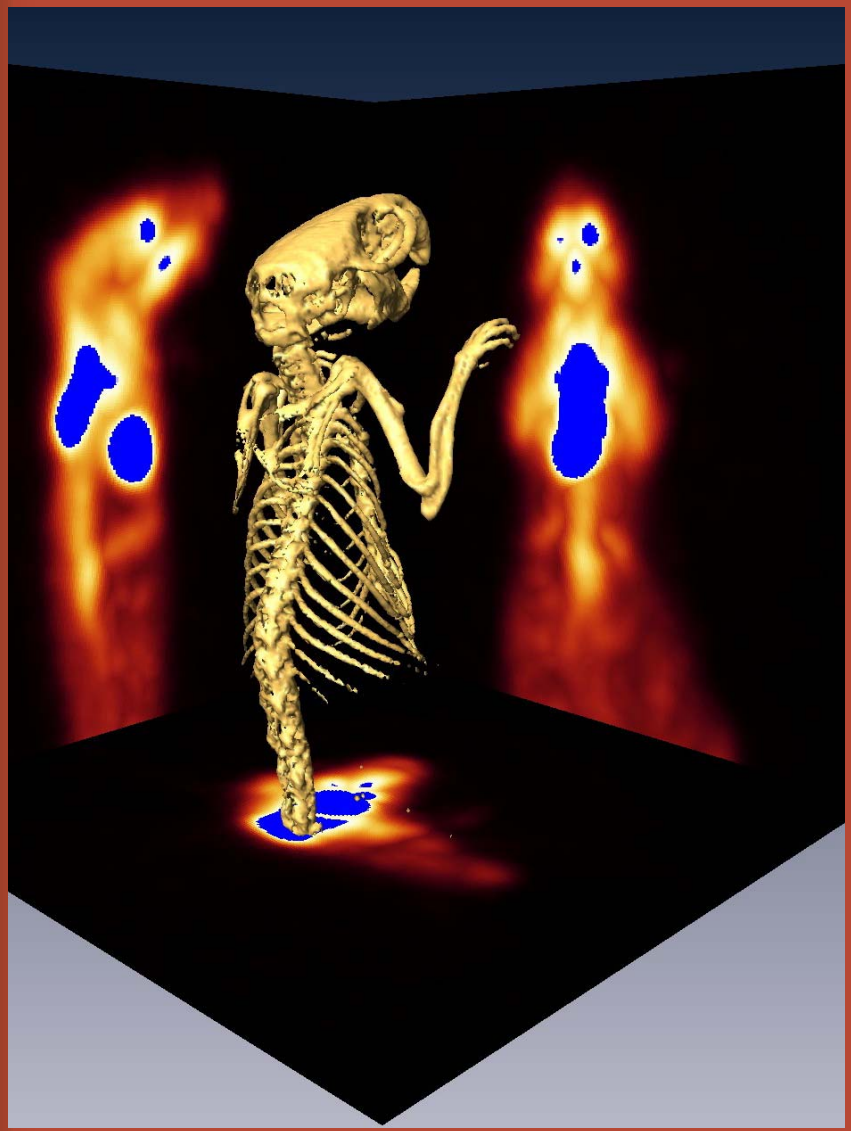
Low Doses Increase Latency for Myeloid Leukemia

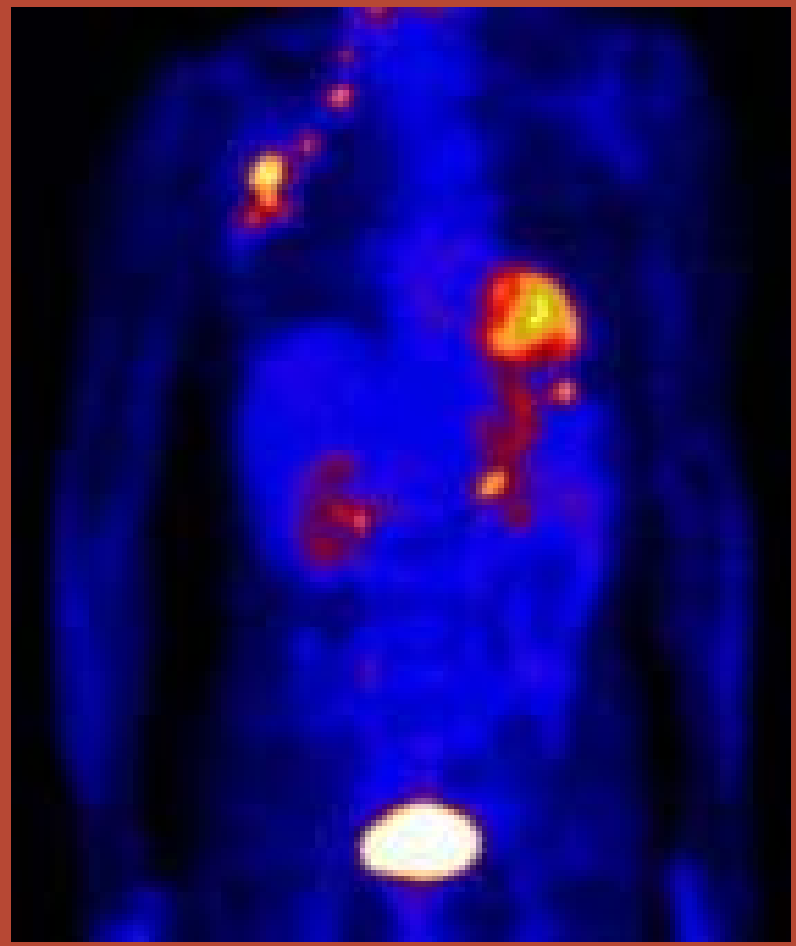


Radiation Research, **152,** 273-279.


WBH (40ºC, 60 min) + 1Gy
B
1 Gy
SURVIVAL PROBABILITY
1.0
0.8
0.6
0.4
0.2
0.0
0
200
400
600
800
1000
TIME (days)

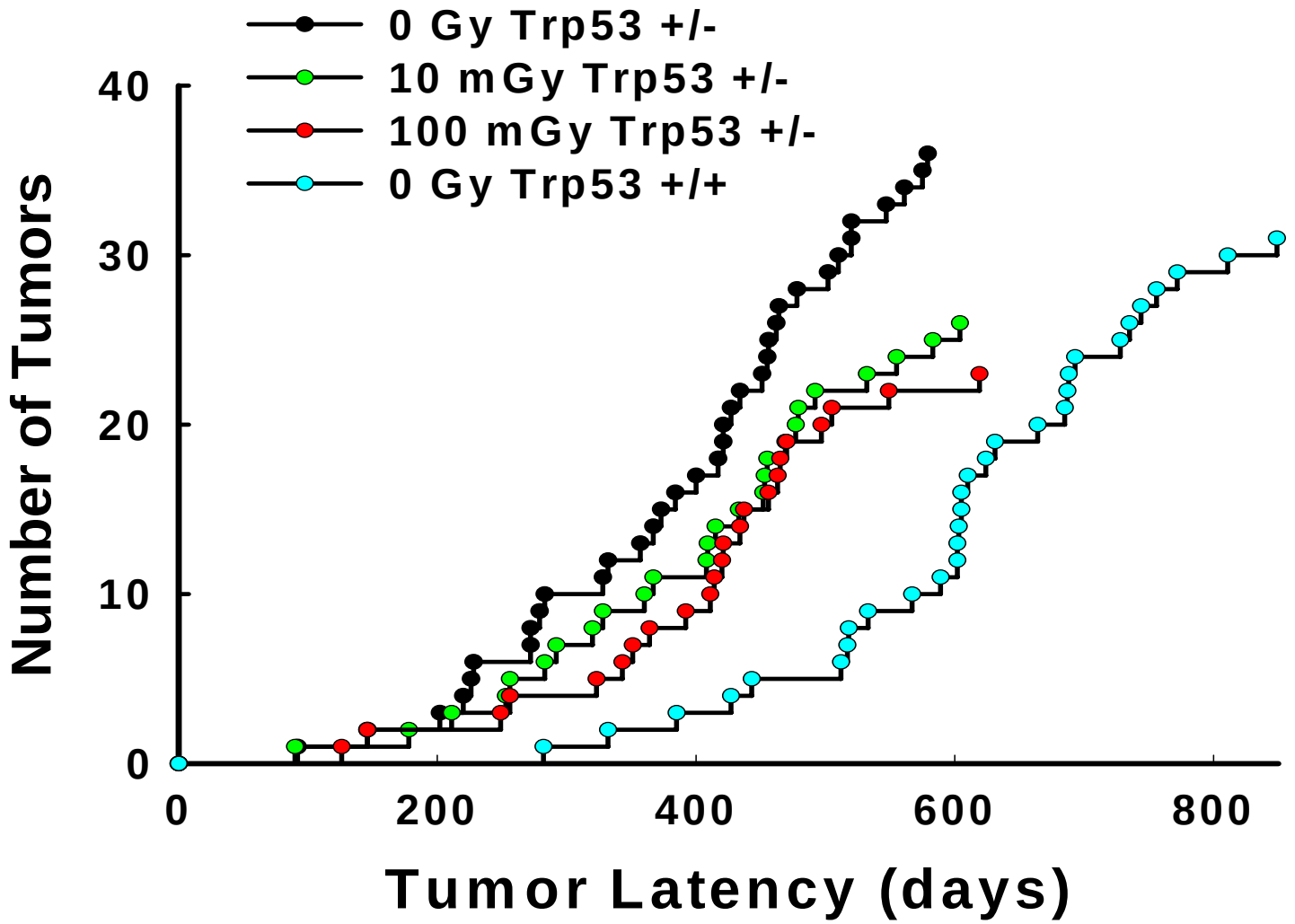
CT and PET Imaging Risk



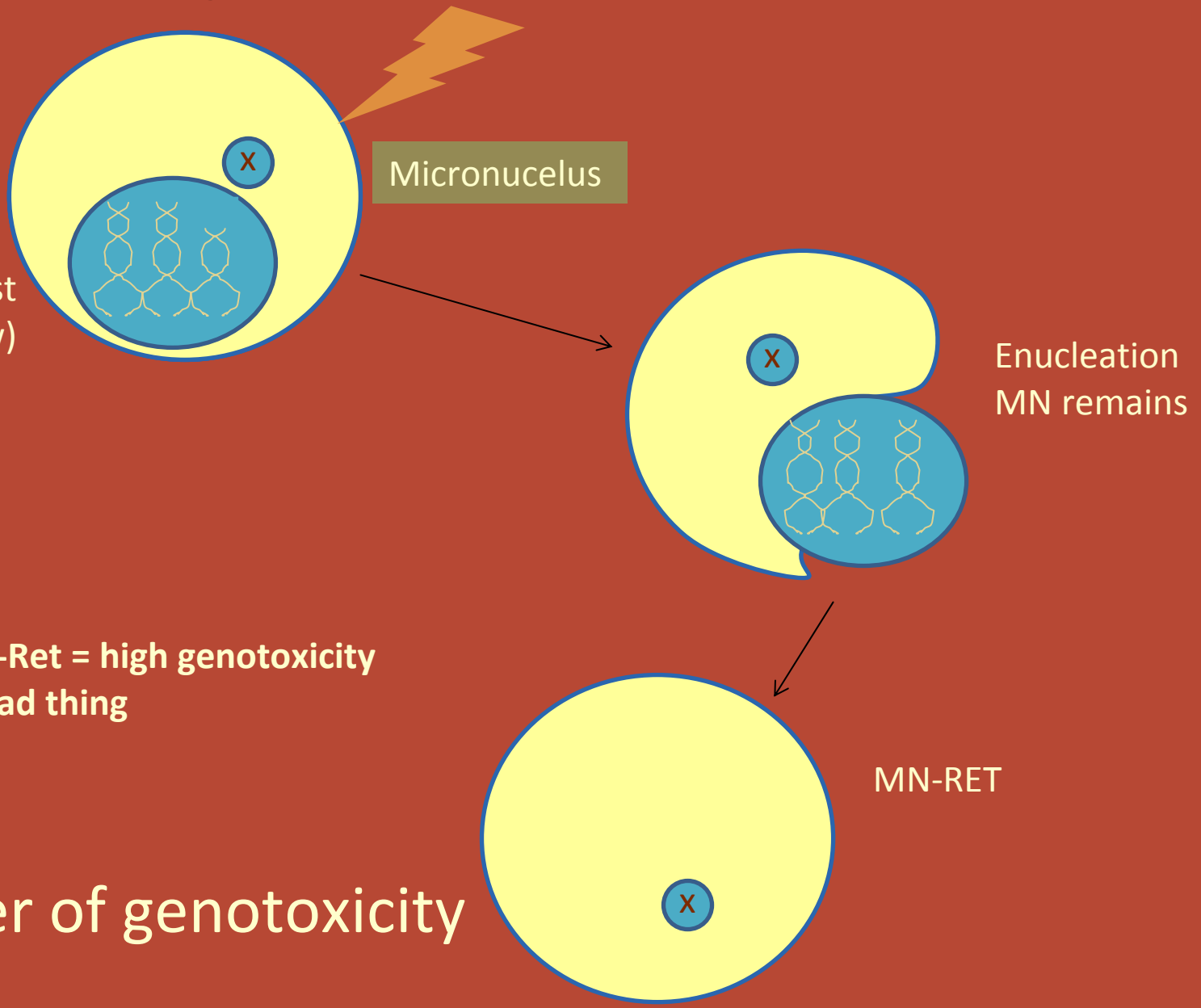


10-60 mGy

Lymphoma Latency

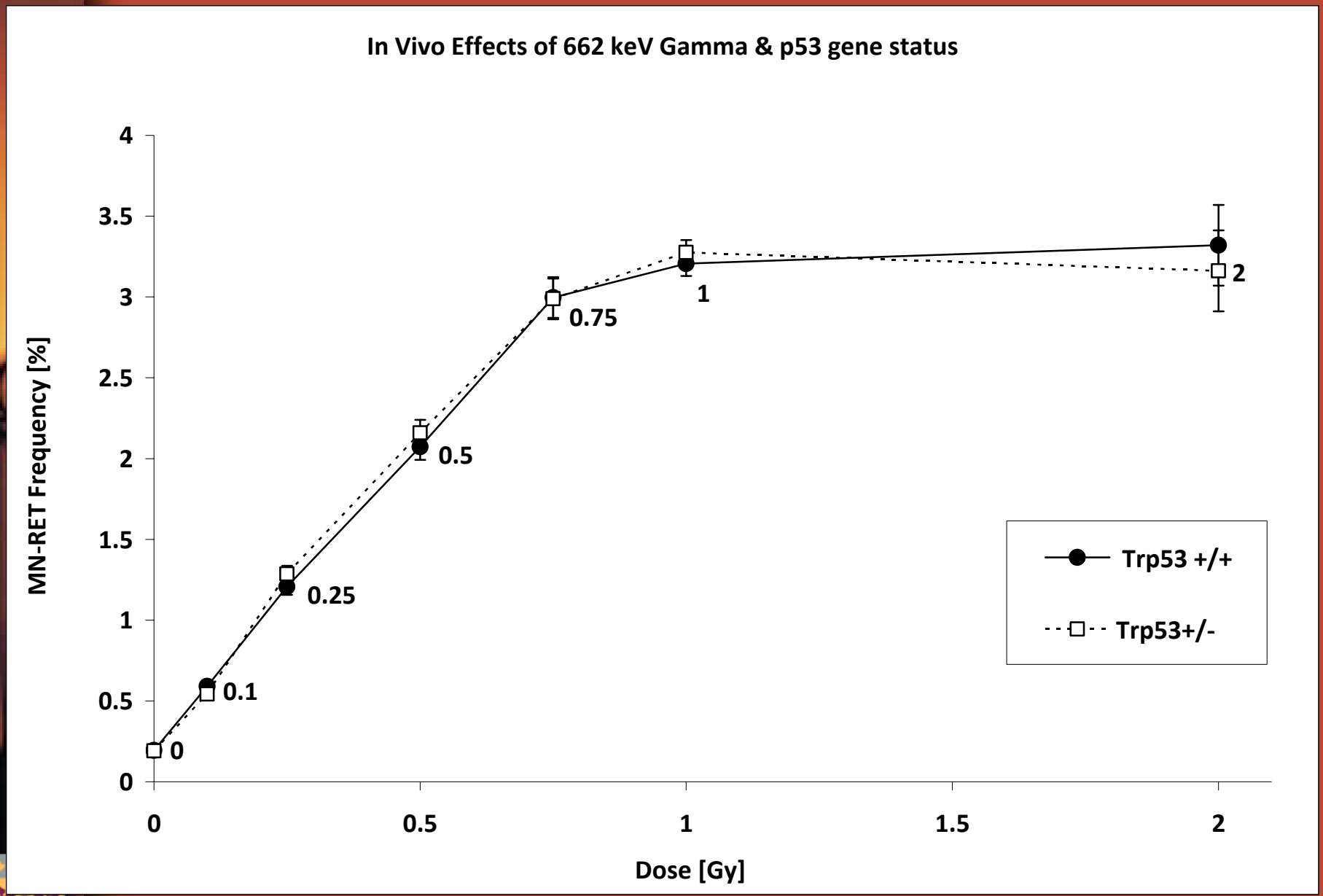


MN-Reticulocyte Formation

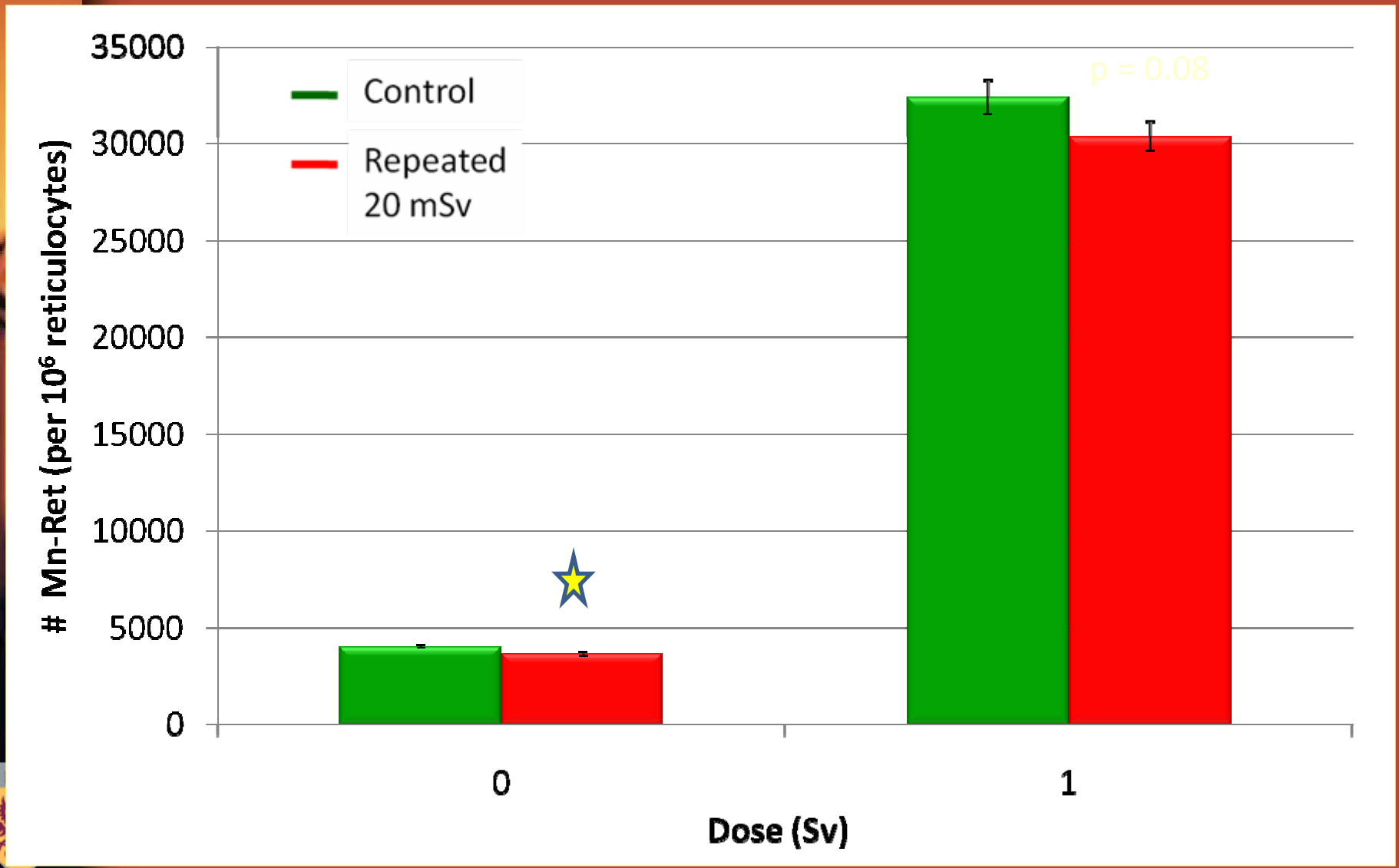


High MN-Ret = high genotoxicity
→ bad thing

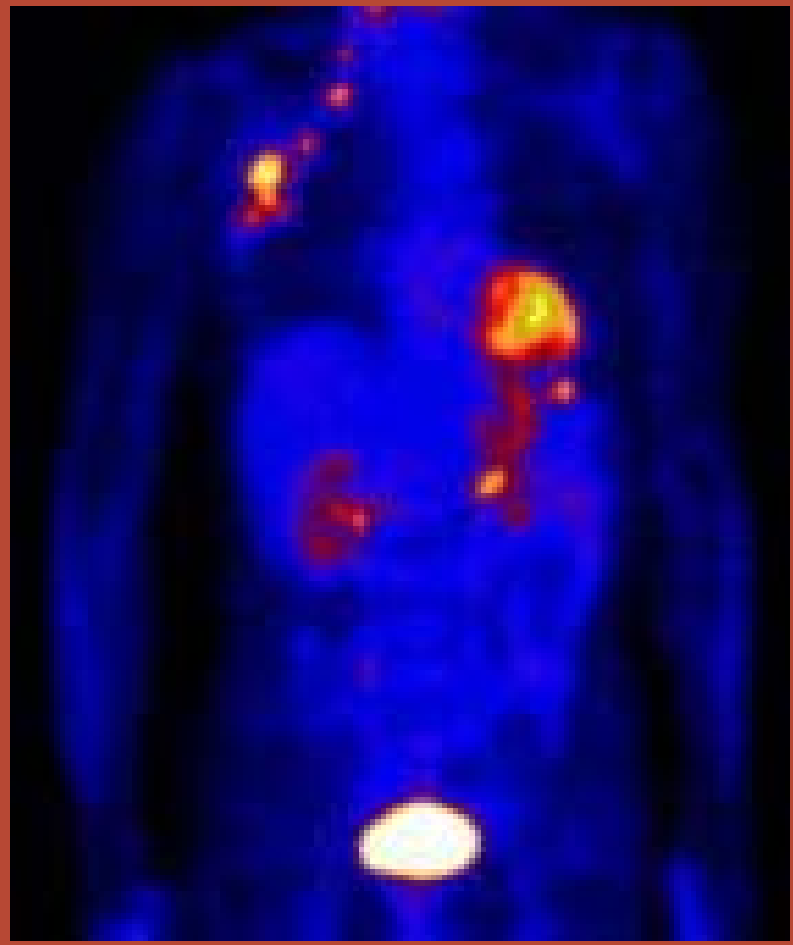
Marker of genotoxicity


In Vivo Effects of 662 keV Gamma & p53 gene status
MN-RET Frequency [%]
Dose [Gy]
0
0.5
1
1.5
2
2.5
3
3.5
4
0
0.1
0.25
0.5
0.75
1
2
Trp53 +/+
Trp53+/-

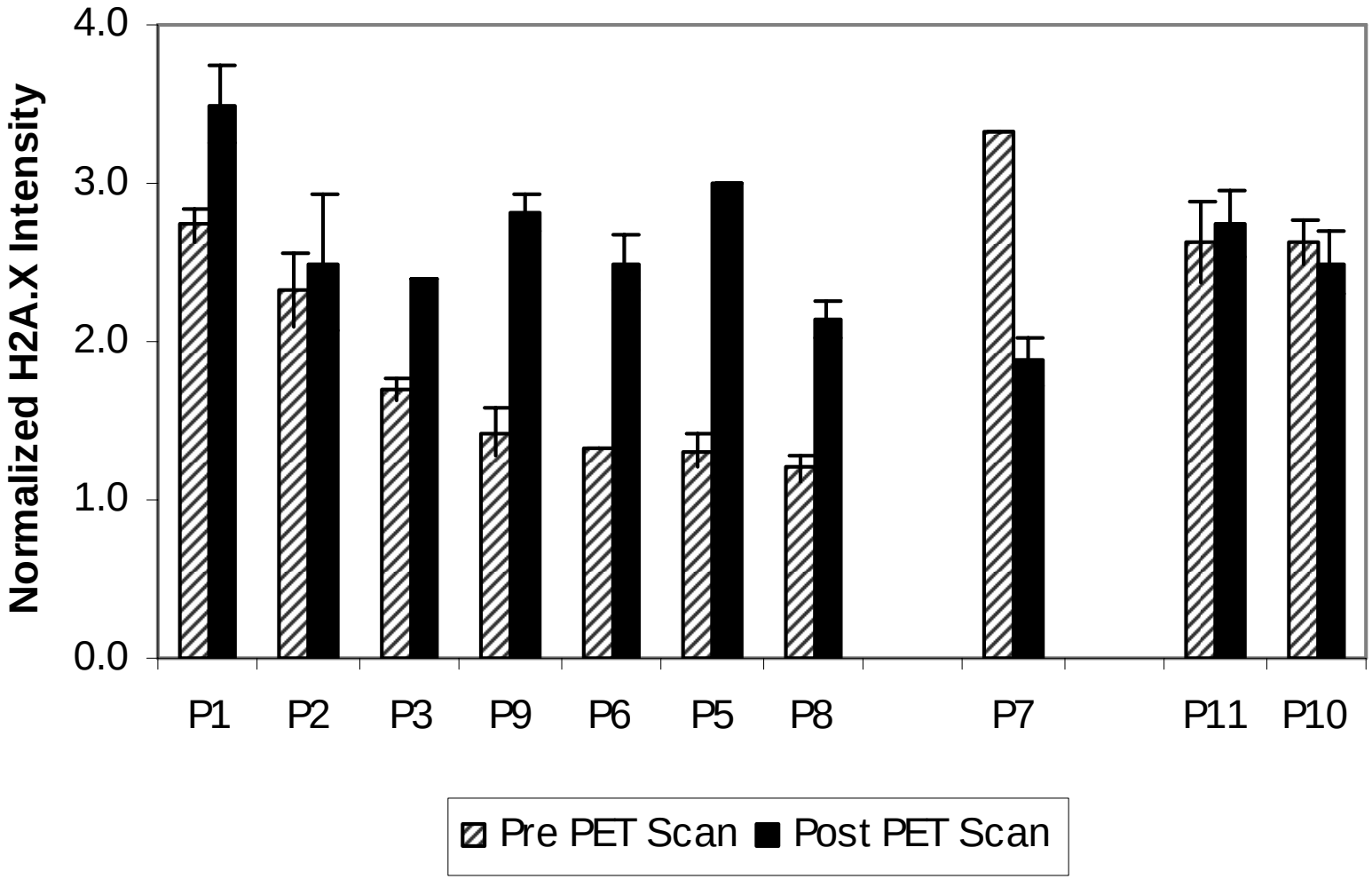
Genetic Damage to Stem Cells

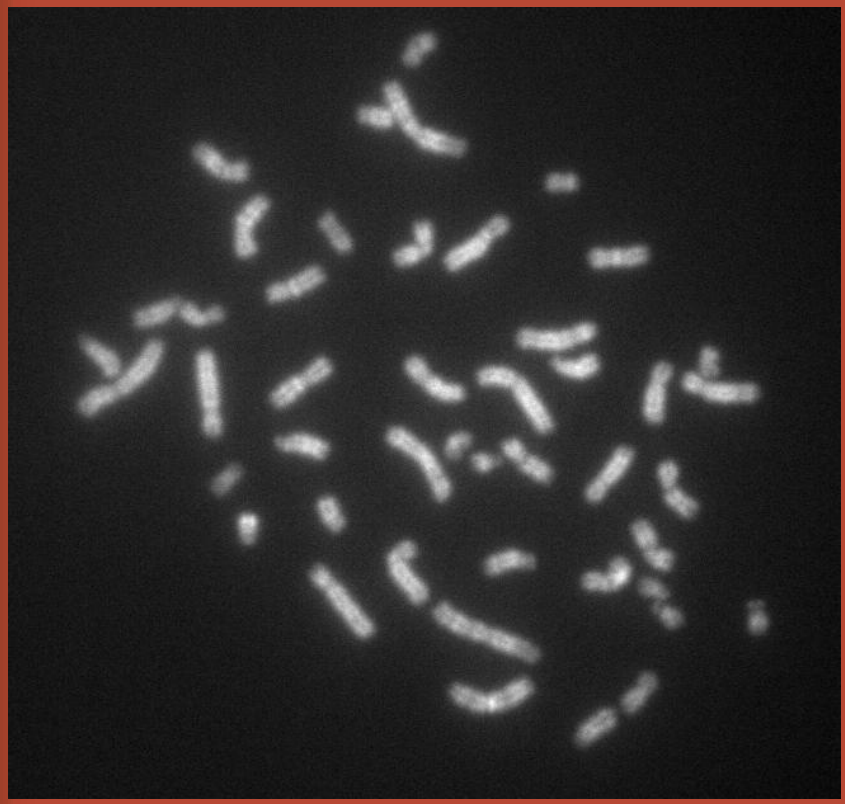


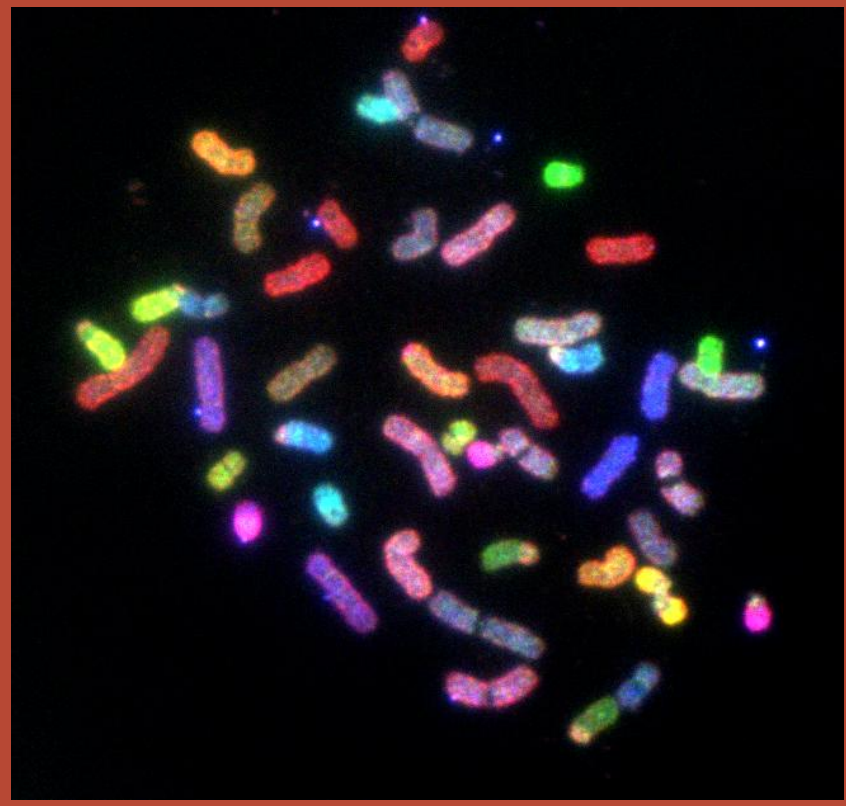
PET and Human Responses



10-60 mGy

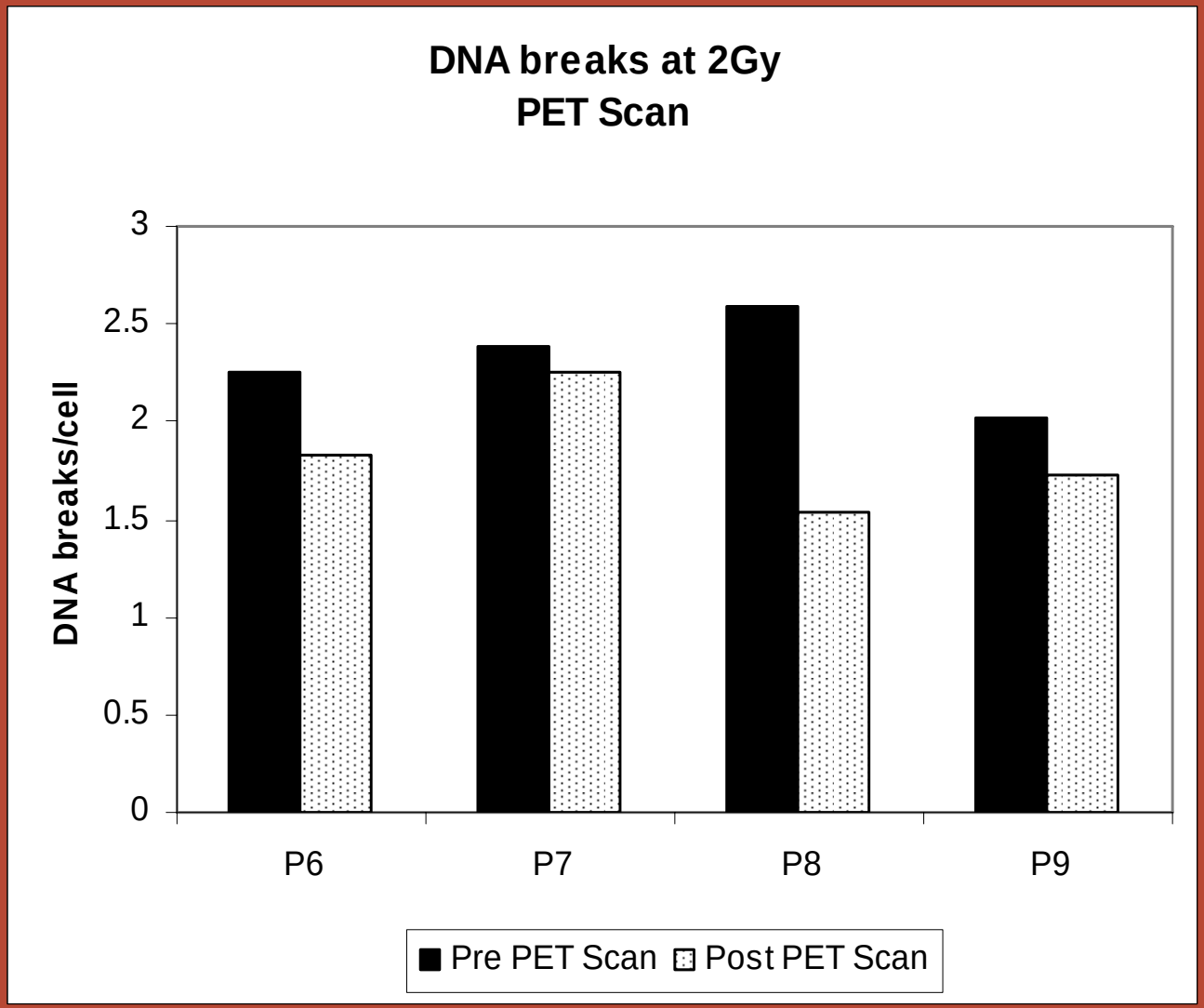

H2A.X Intensity Before and After PET Scan
Normalized H2A.X Intensity
4.0
3.0
2.0
1.0
0.0
P1
P2
P3
P9
P6
P5
P8
P7
P11
P10
Pre PET Scan
Post PET Scan

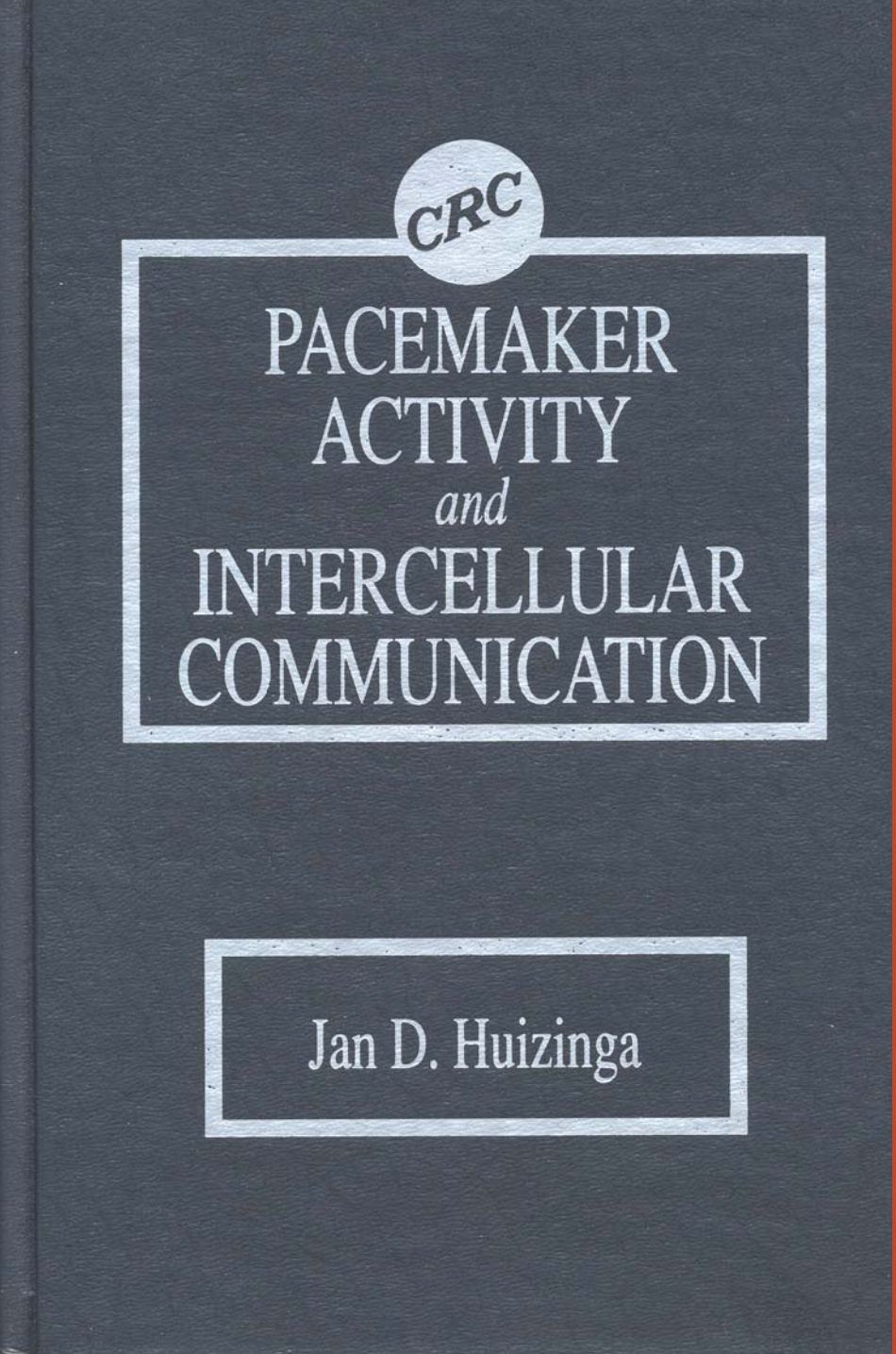





1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
X
Y

Radiation Resistance after PET

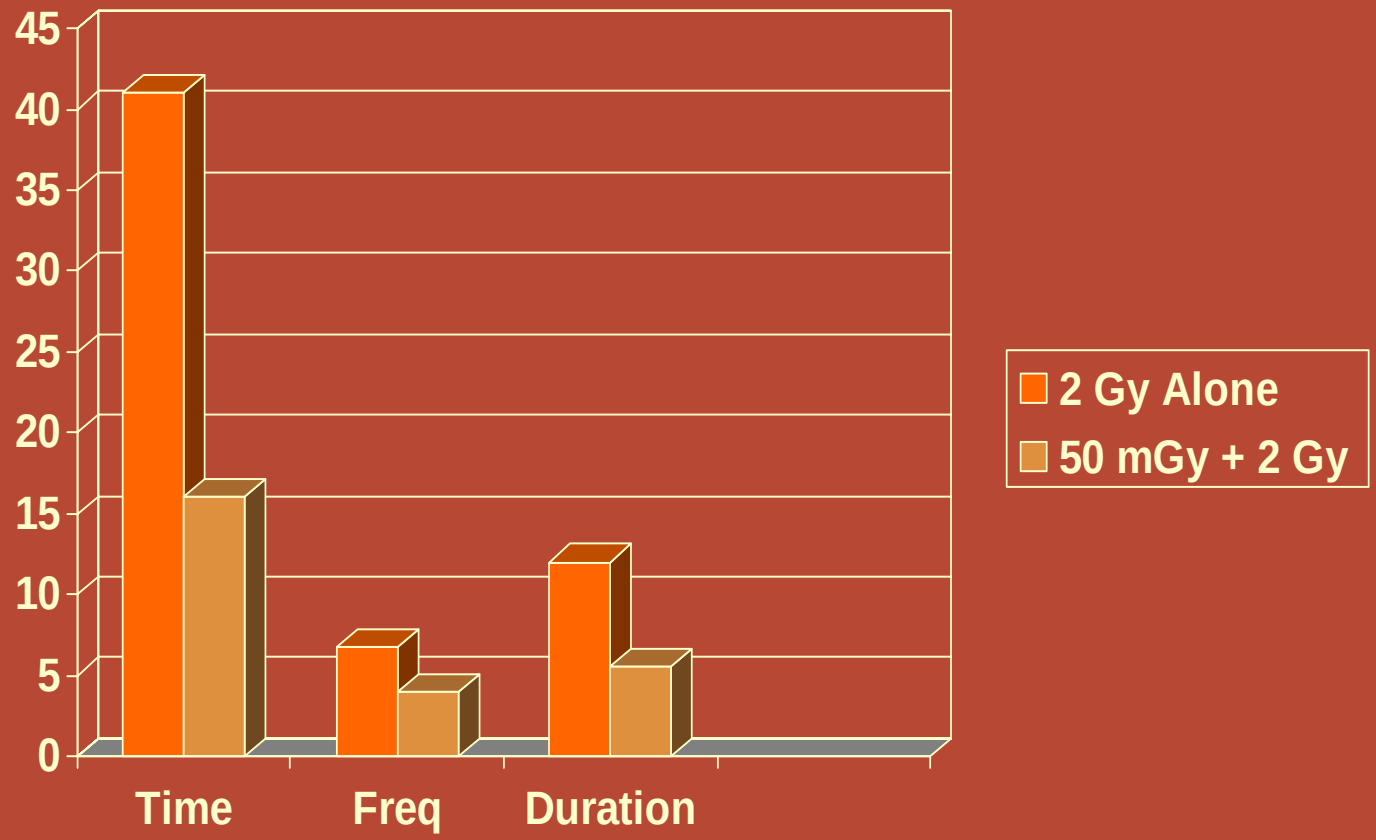




Low Dose Radiation to improve:

- ***gastric emptying***
- ***gut motility***
- ***radiation sickness (Emesis)***

Low Dose Modulation of Emesis in Ferrets



Bone Density Baseline Measurements

Low Dose Exposures

0.0001 mGy

DEXA

0.0004 mGy

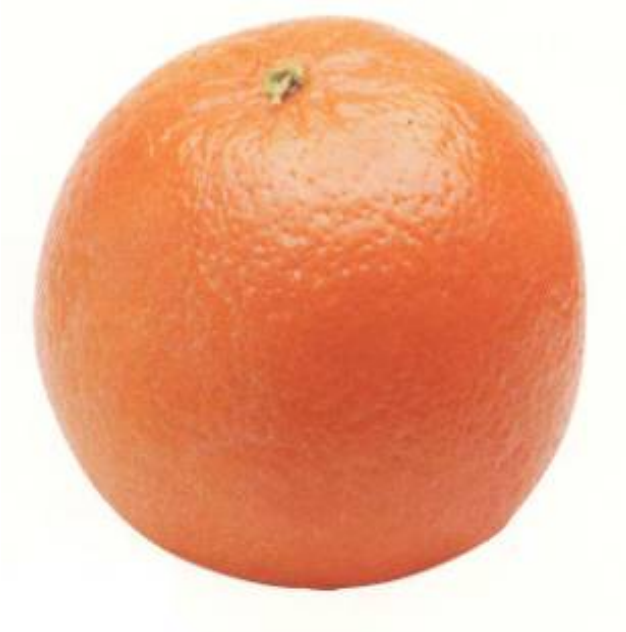
American Journal of Physicians and Surgeons. March 2008

B. Scott, R. Mitchel, Sanders and D. Boreham

*"Based on actual biological scientific evidence, and not calculated extrapolation, an opposite conclusion about CT cancer risk is equally plausible. That is, cancer risk in North America may be **reduced** by 2 % over the coming decades because of low-dose medical CT exposures"*

Take Home Message:

Biological **Defense** Mechanisms Against the Effects of ***High Doses***



Biological Response Mechanisms to the Effects of ***Low Doses***

Thank-you