History and Accomplishments: DOE Low Dose Radiation Research Program

HEALTH PHYSICS/AMERICAN NUCLEAR SOCIETY FEBRUARY 3-5, 2015

NORFOLK, VIRGINIA

The DOE Low Dose Research Program

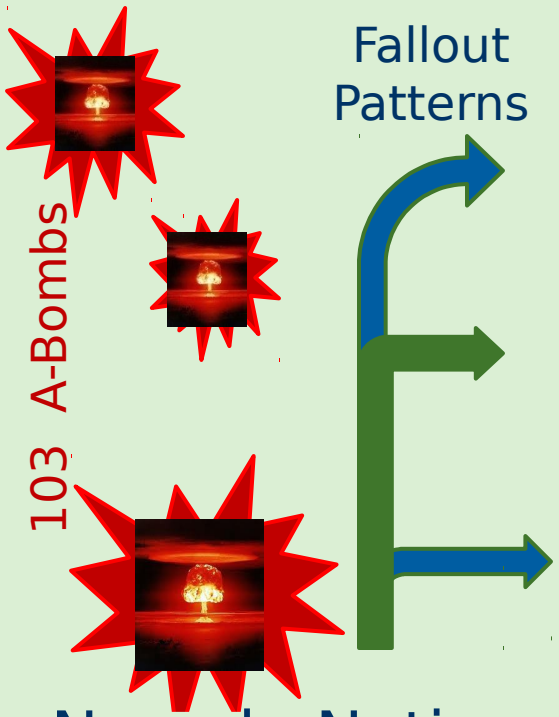
- My Background
- Goals and Brief History of the Program
- Early Observations and impact on Paradigms in the field of Radiation Biology
- Response of Scientific Community
- Mechanisms of Action
- Future Needs and communication of results.

Nuclear weapons were part of my early life

St. George, Utah
1955

Fallout from over 100 A-bombs tested above ground at the Nevada National Security Site

MS University of Utah



Goals and Expectations: Low dose Program

Senator Pete Domenici of New Mexico

"In this year's Energy and Water Appropriation Act (1998), we initiated a ten year program (13 million/year) to understand how radiation affects genomes and cells so that we can really understand how radiation affects living organisms. For the first time, we will develop radiation protection standards that are based on actual risk."

Nuclear Waste Cleanup

- Is expensive 
- Senator Peter Domenici
- Washington State University

Are our low dose regulations based on real science ?

New Technologies

- The Human Genome was sequenced
- New technologies, such as microbeams, were now available to test health risks in the low dose region, where it couldn't be measured before.

Can health risks in the low dose region now be understood?

Goals and Expectations

BERAC subcommittee (Dr. Robert Ullrich Chairman) was charged with developing a set of recommendations for the DOE

- Key Questions
- Description
- Decision Making Value
- Recommendations and Costs

❖ Key Questions

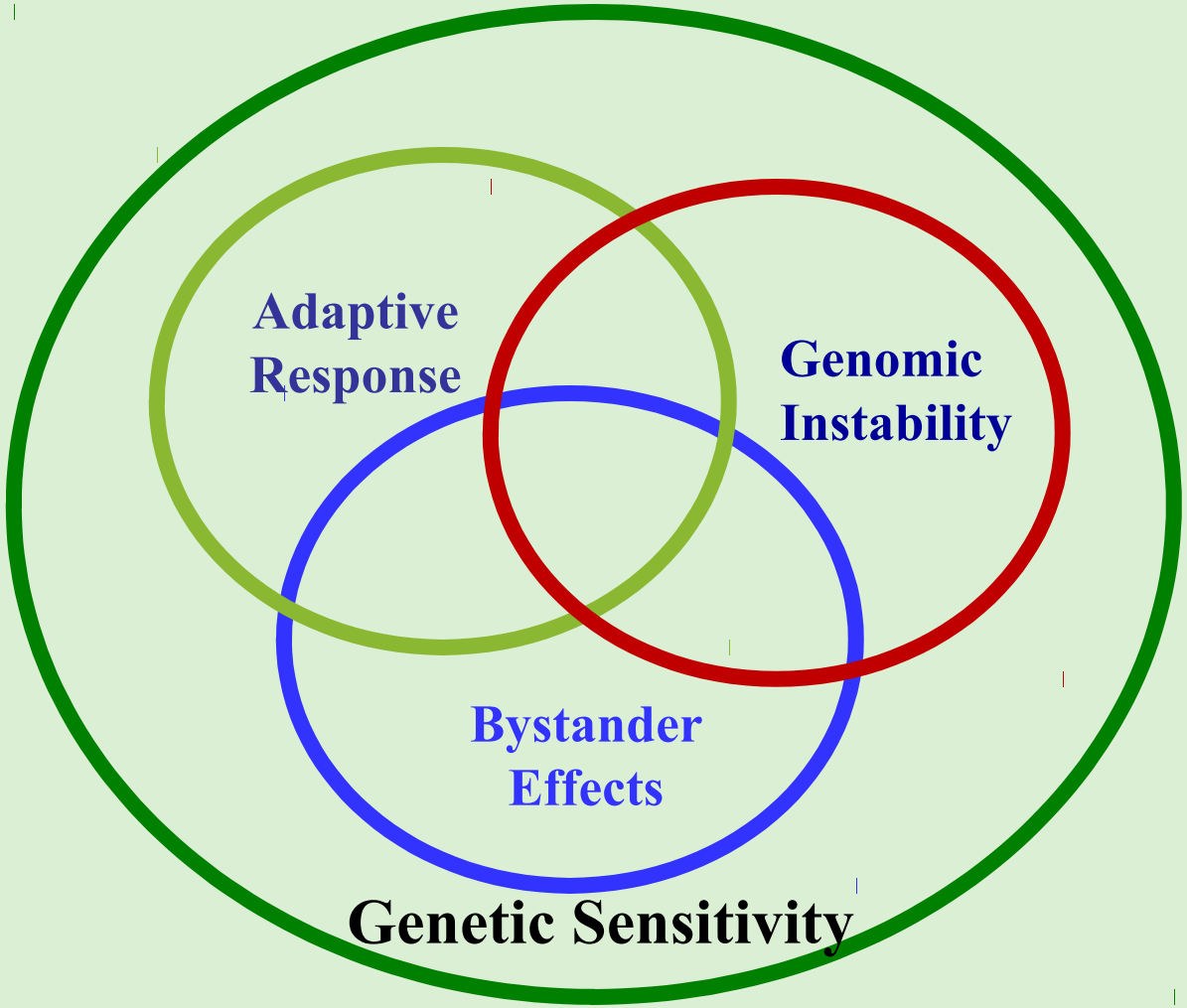
- **Are there adverse health effects induced by low dose and dose-rate exposure to ionizing radiation as predicted by the Linear-No-Threshold hypothesis?**
- **Is the damage induced by ionizing radiation and the repair of that damage different from the endogenous oxidative damage and repair present during normal life processes?**
- **Can endogenous repair capability prevent cancer induction following low levels of radiation exposure?**
- **Can molecular and tissue responses to radiation-induced damage prevent or reduce development of cancer? (Thresholds)**
- **Do genetic differences exist that result in the inability of some individuals to repair radiation-induced damage?”**

Chief Scientist for DOE Low Dose Radiation Research Program 1998-2006

- Review and evaluate science being conduced
- Make recommendations on scientific direction
- Communication of results to scientists, regulators and public
- Operate a Web-Site

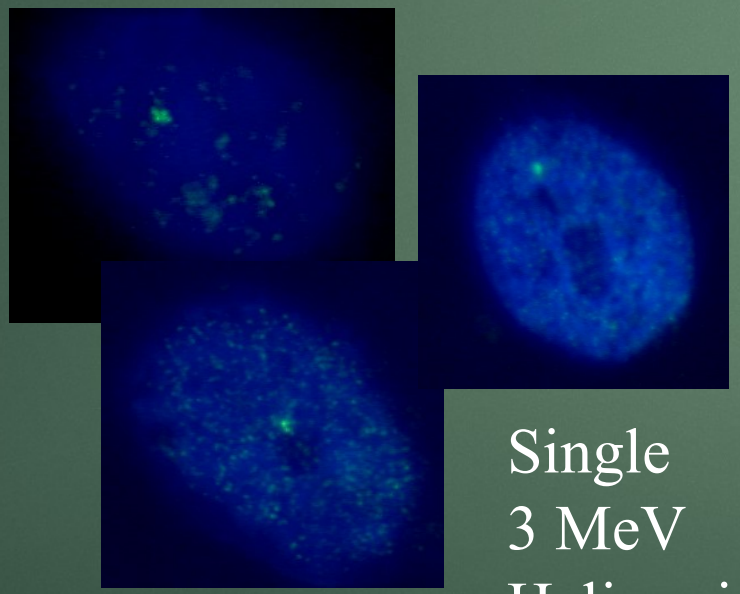
http://lowdose.energy.gov

Biological Responses Induced by Low Doses of Radiation



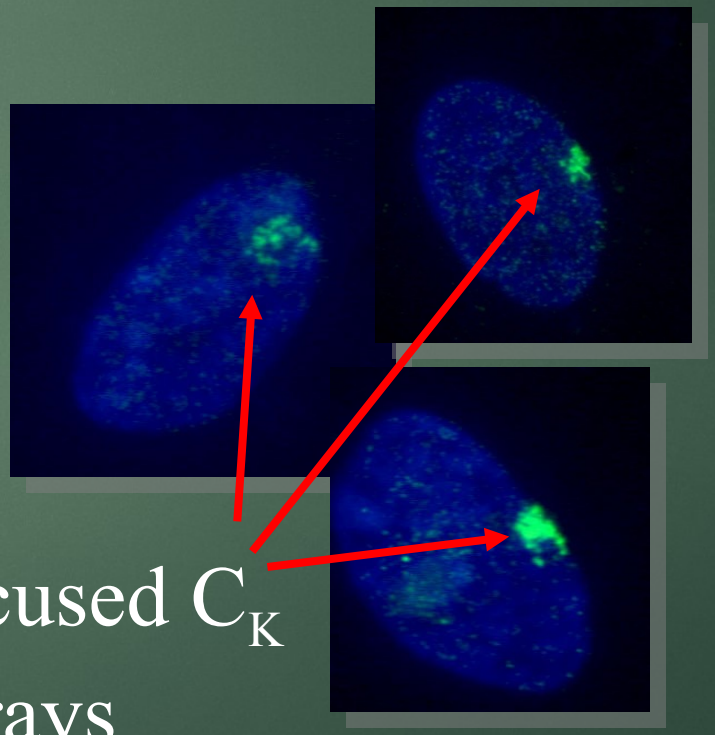
Microbeams: know where you shoot and where you hit

Localized DNA damage observed after both focussed soft X-ray production and charged particle induction using γH2AX



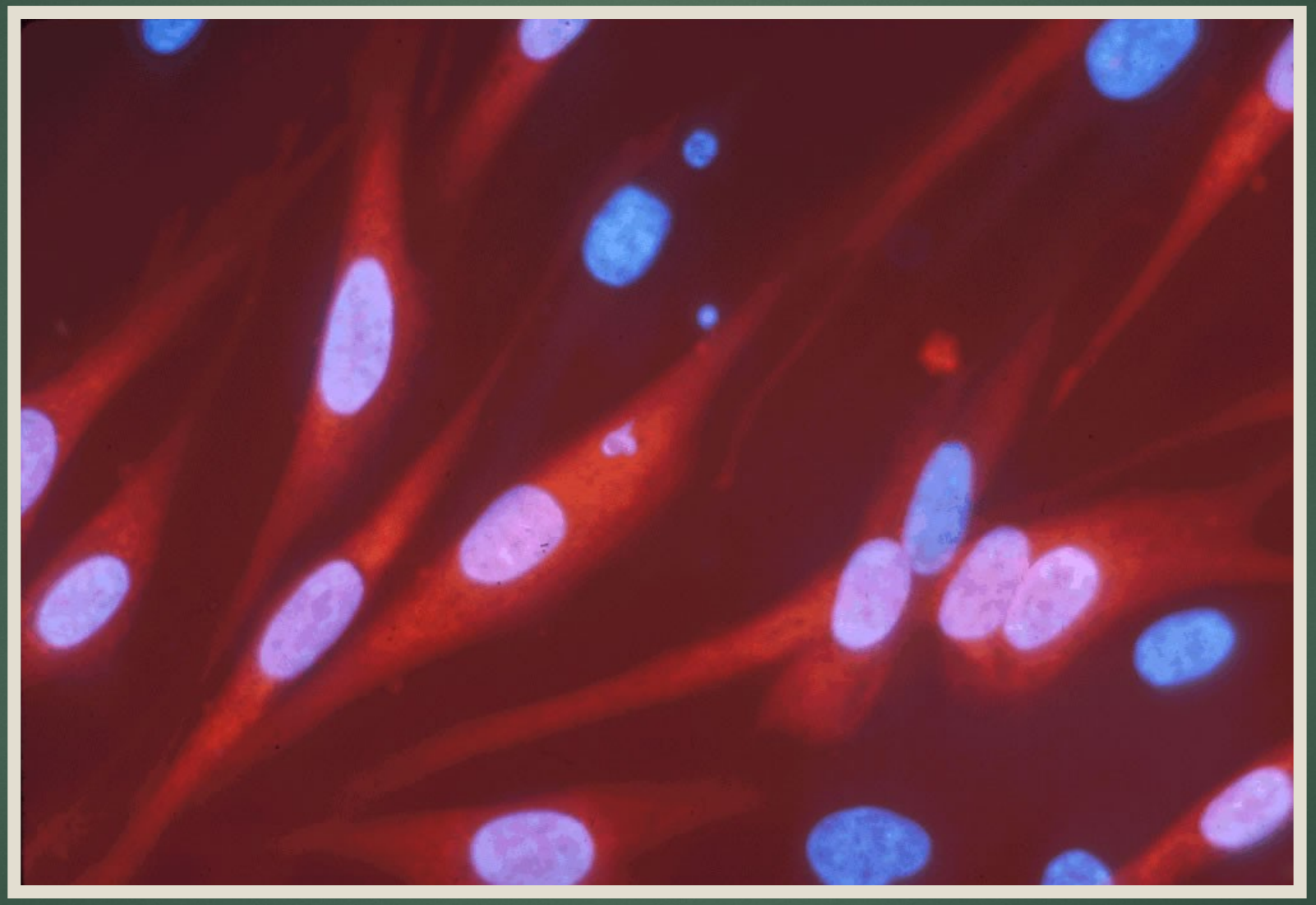
5 mm

Single
3 MeV
Helium ion



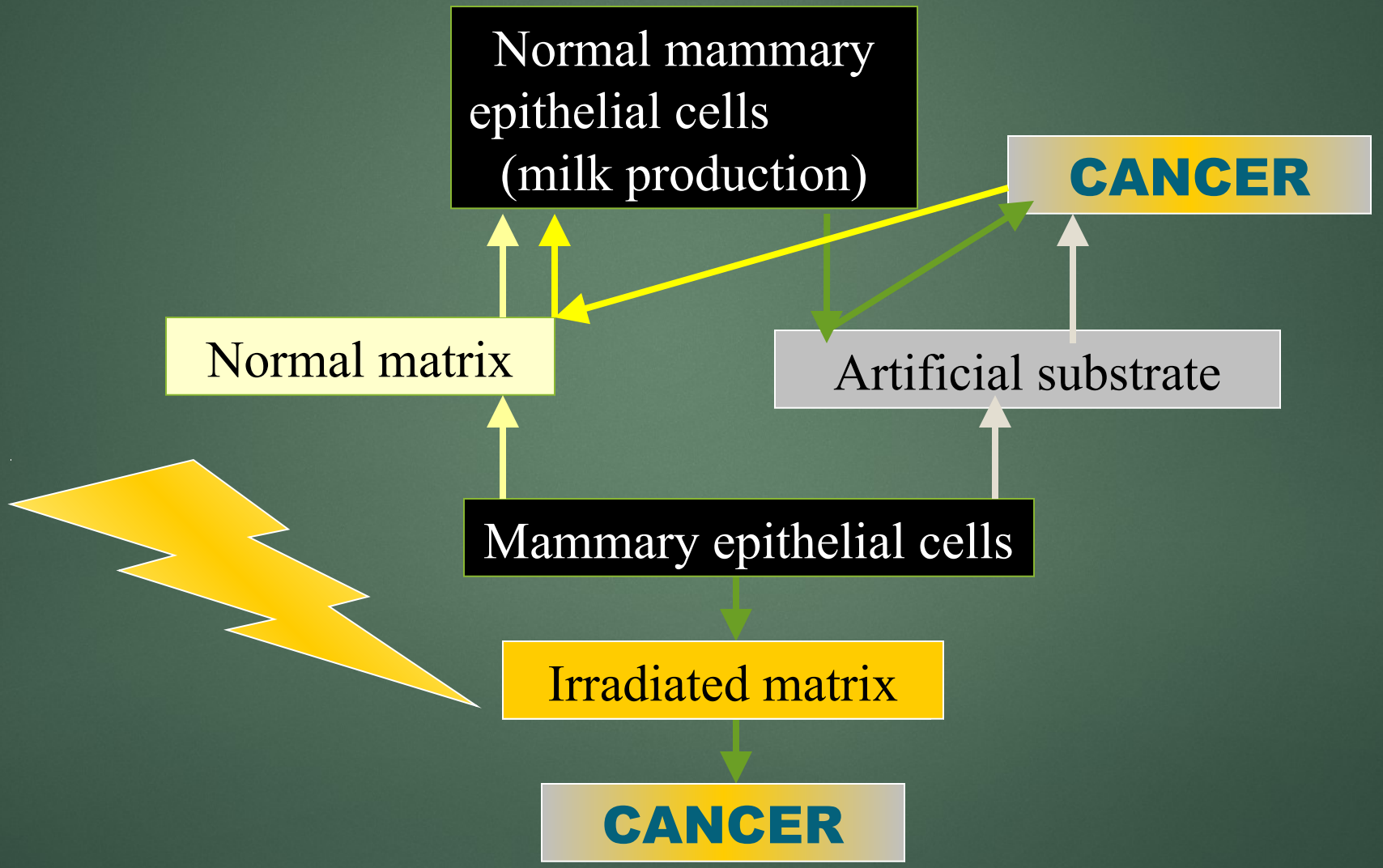
Focused C_K
X-rays

Micronuclei in Non-Exposed Cells



Geard

It takes a tissue to make a tumor…

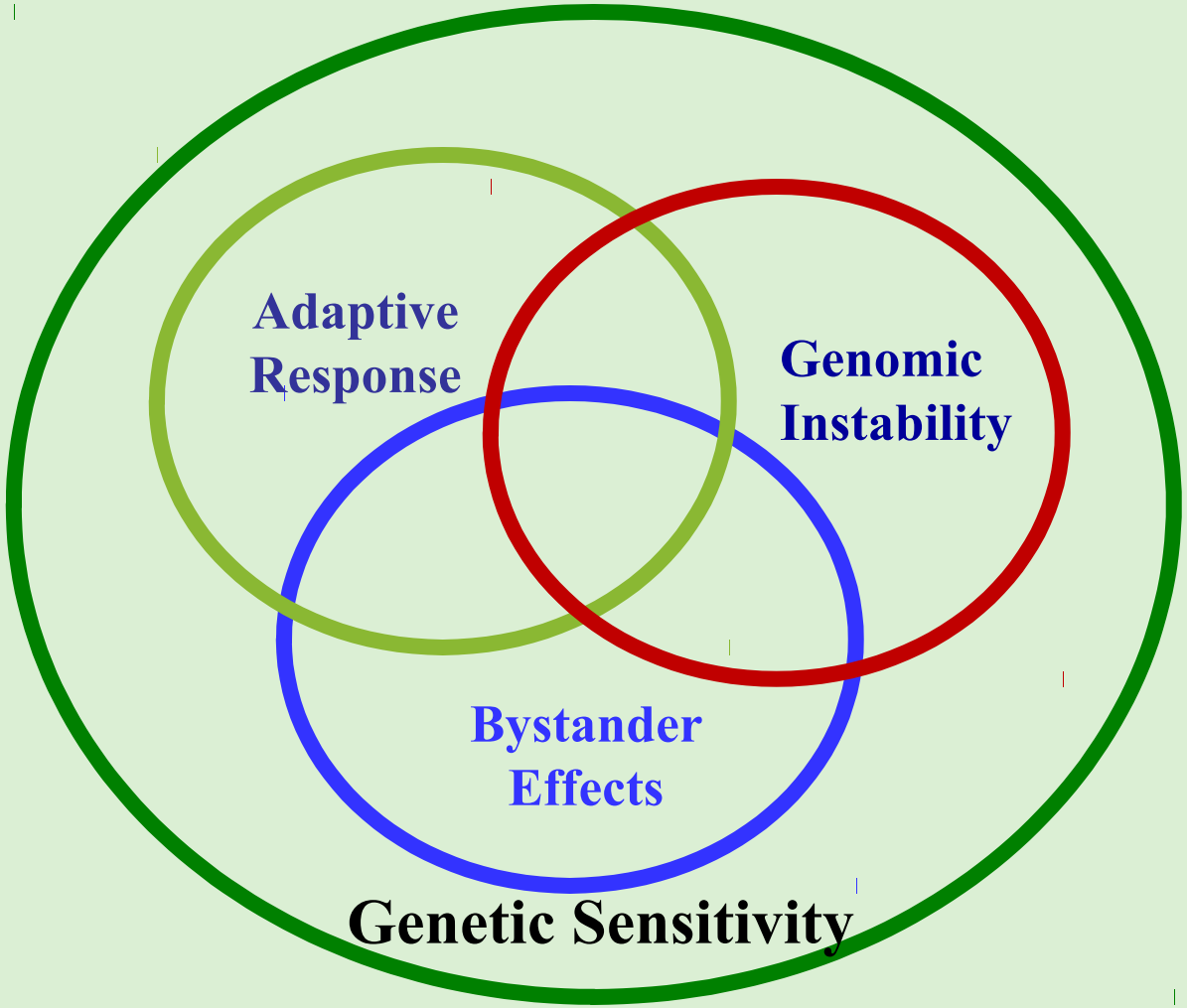


Barcellos-Hoff et al. 2000

Decision Making Value *(Bystander Effects)*

- Bystander effects demonstrates the importance of cell/cell and cell/matrix communication which occurs in tissues.
- Bystander effects suggest that whole tissues respond to radiation insult through this communication (DNA not the only target)
- Bystander effects suggest a mechanism for either increased risk or protection of the tissue in the low dose region.
- Bystander effects suggest that dose should be calculated to whole tissues not to small subsets of cells (Radon?).
- Bystander effects support the observations that non-uniform dose distribution in a tissue has minor impact on risk.

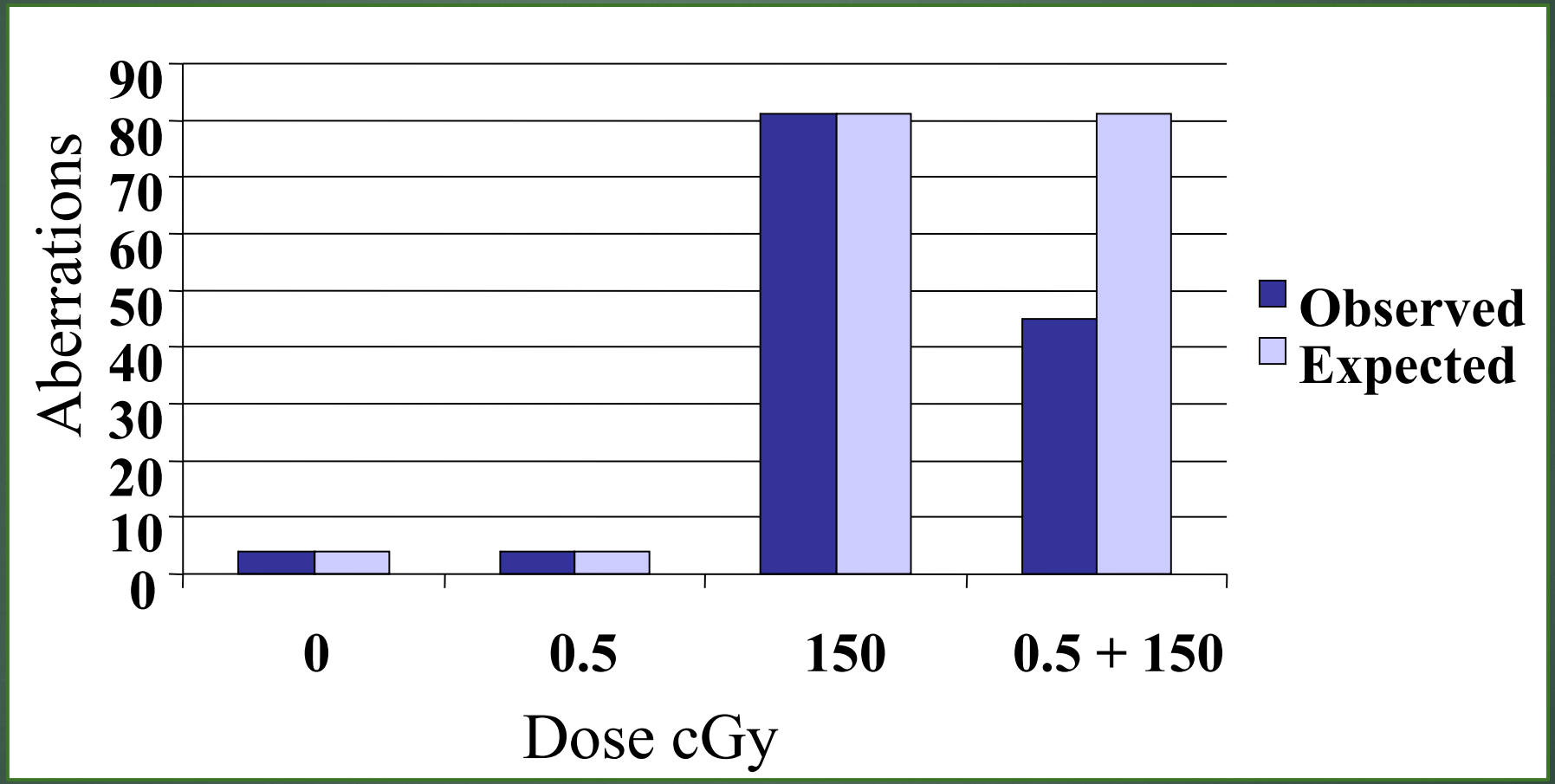
Biological Responses Induced by Low Doses of Radiation



Two Types of Adaptive Responses

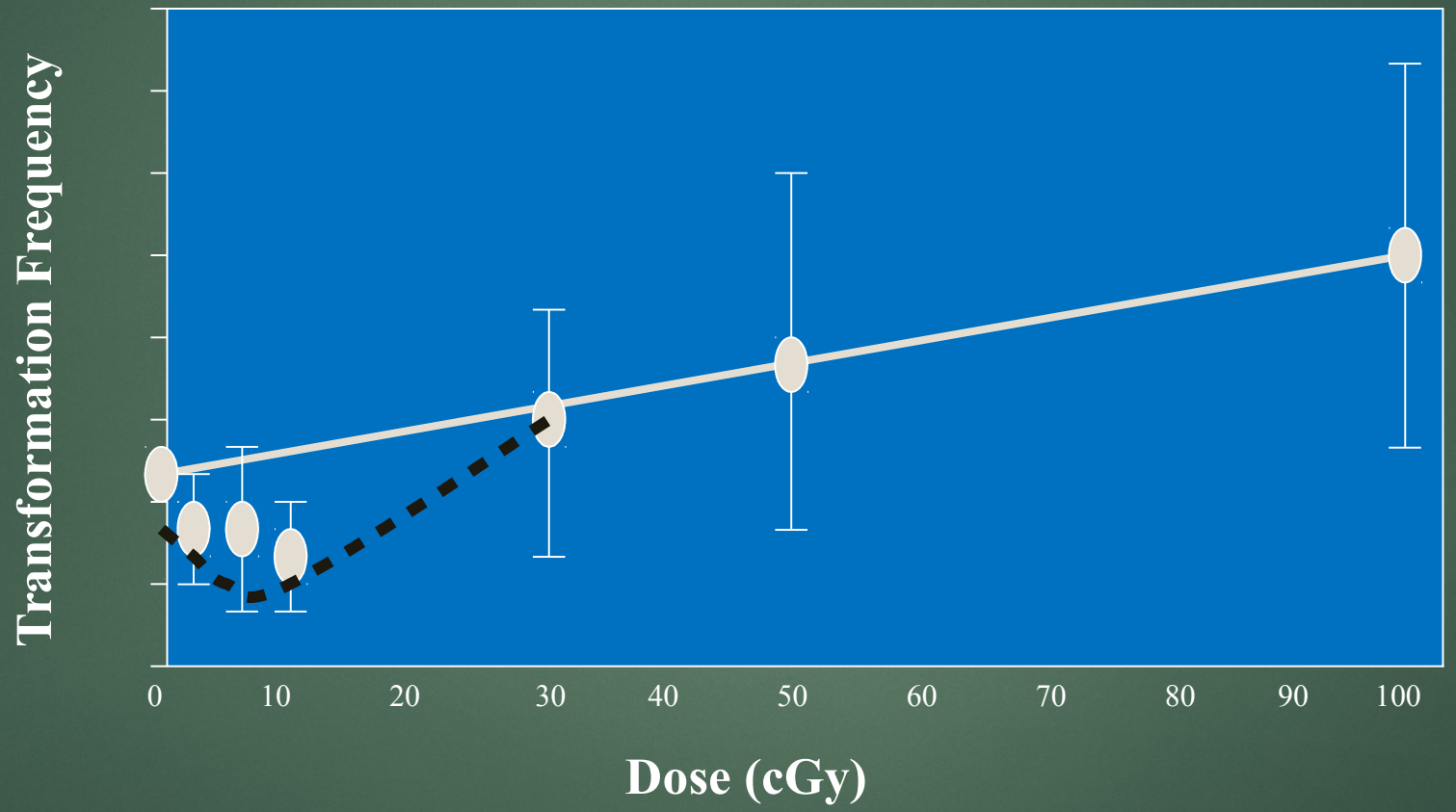
- Small tickle dose followed by a large challenge dose results in a decrease in response (Wolff 1998)
- Small dose results in a decrease in the background level of damage (Sykes 2006, Redpath 2006)

Adaptive Response in Human Lymphocytes



Shadley and Wolff 1987

Adaptive Response
Sub-linear Dose Response

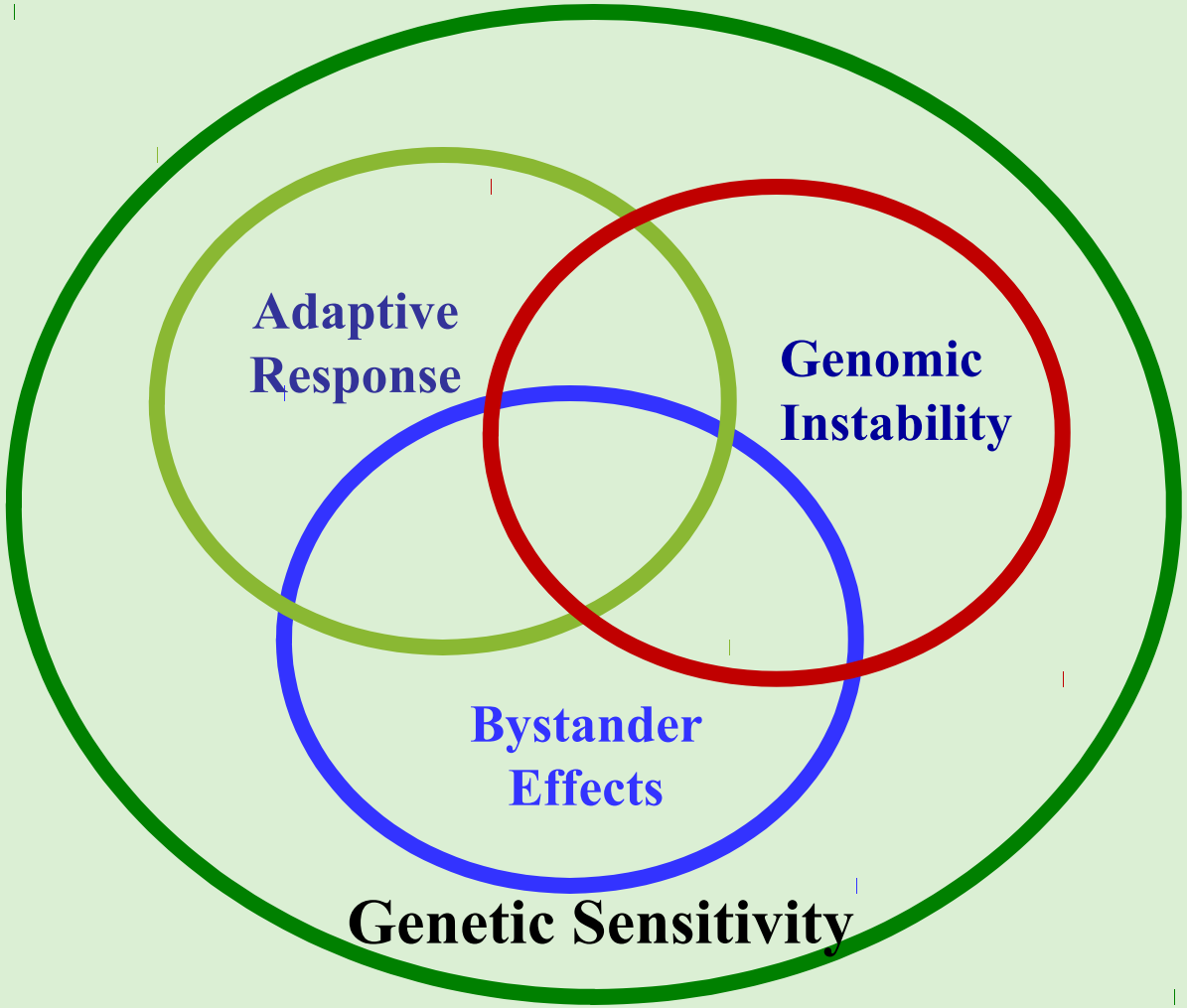


Redpath et al. 2001

Decision Making Value *(Adaptive Response)*

- The response to low doses of radiation is different than the response to high doses.
- Further support the need for a Dose/Dose Rate Effectiveness (DDREF) and Dose Rate Effectiveness Factor (DREF) factor greater than one.
- Demonstrate that radiation responses can be modified by post-radiation treatment.
- Adaptive responses support low dose protection and high dose damage, non-linear dose-response relationships, and suggest that standards extrapolated from the high dose regions are more than adequately conservative.

Biological Responses Induced by Low Doses of Radiation

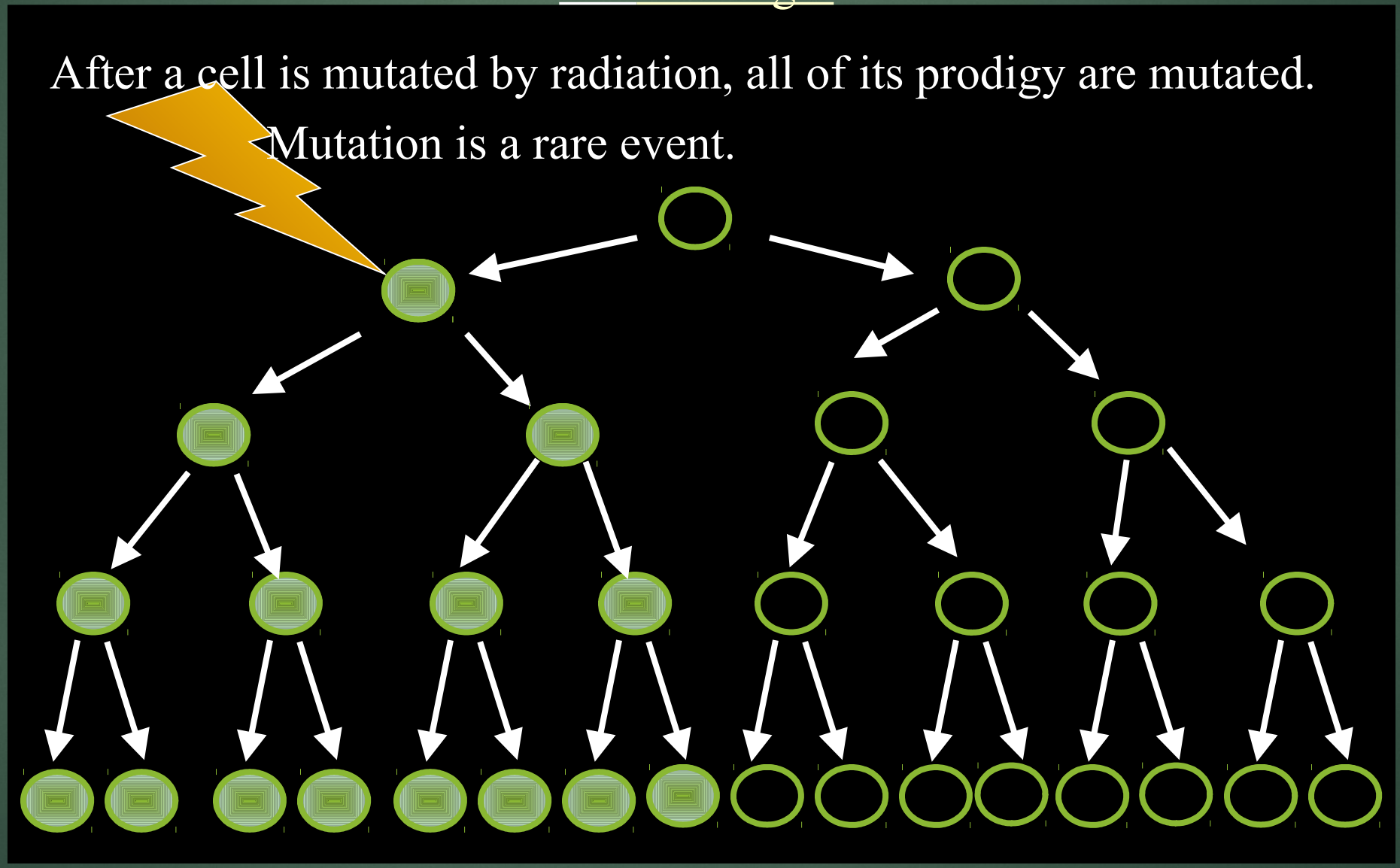


Radiation-induced Genetic Damage

Old Paradigm

After a cell is mutated by radiation, all of its prodigy are mutated.

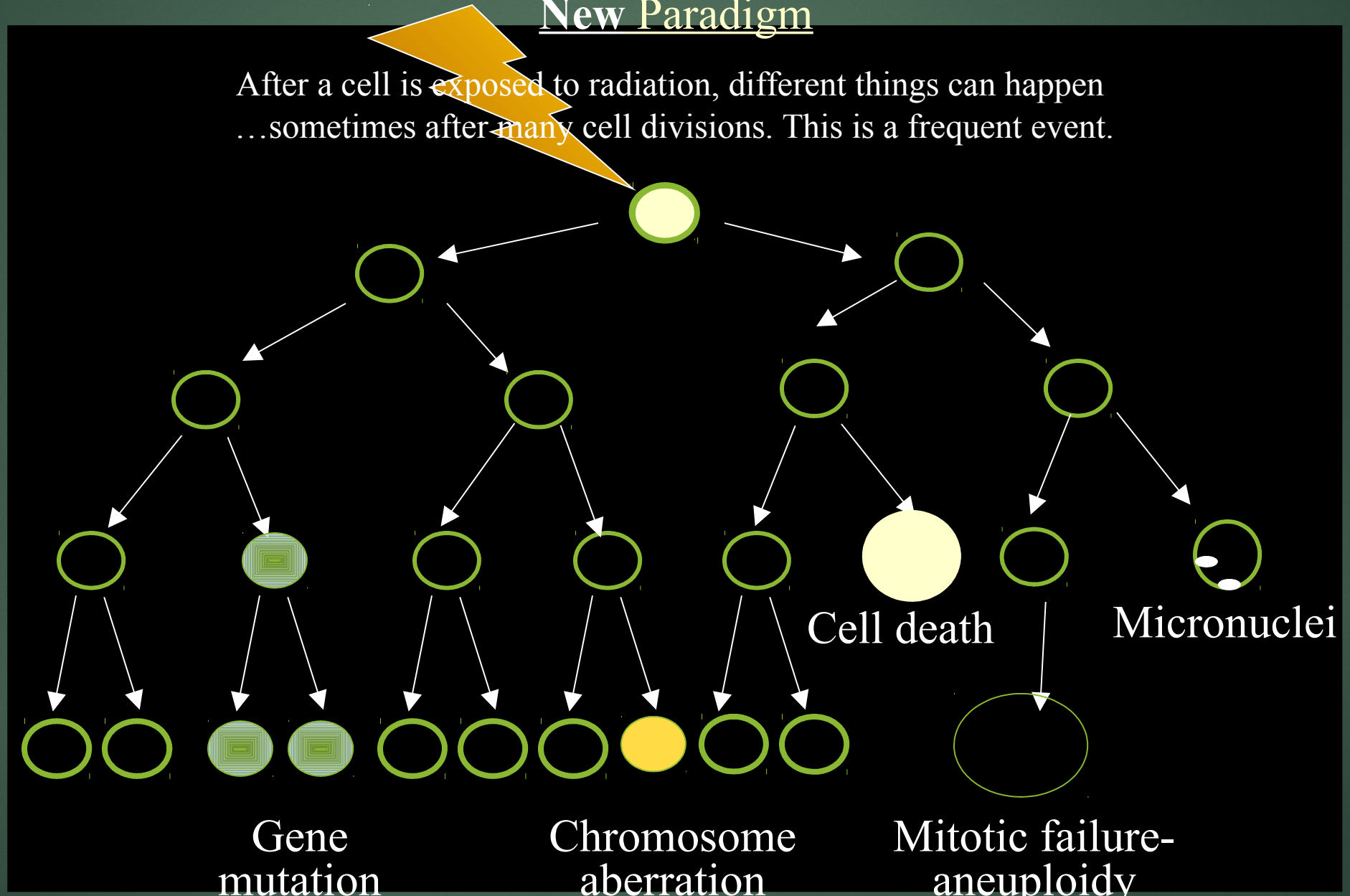
Mutation is a rare event.



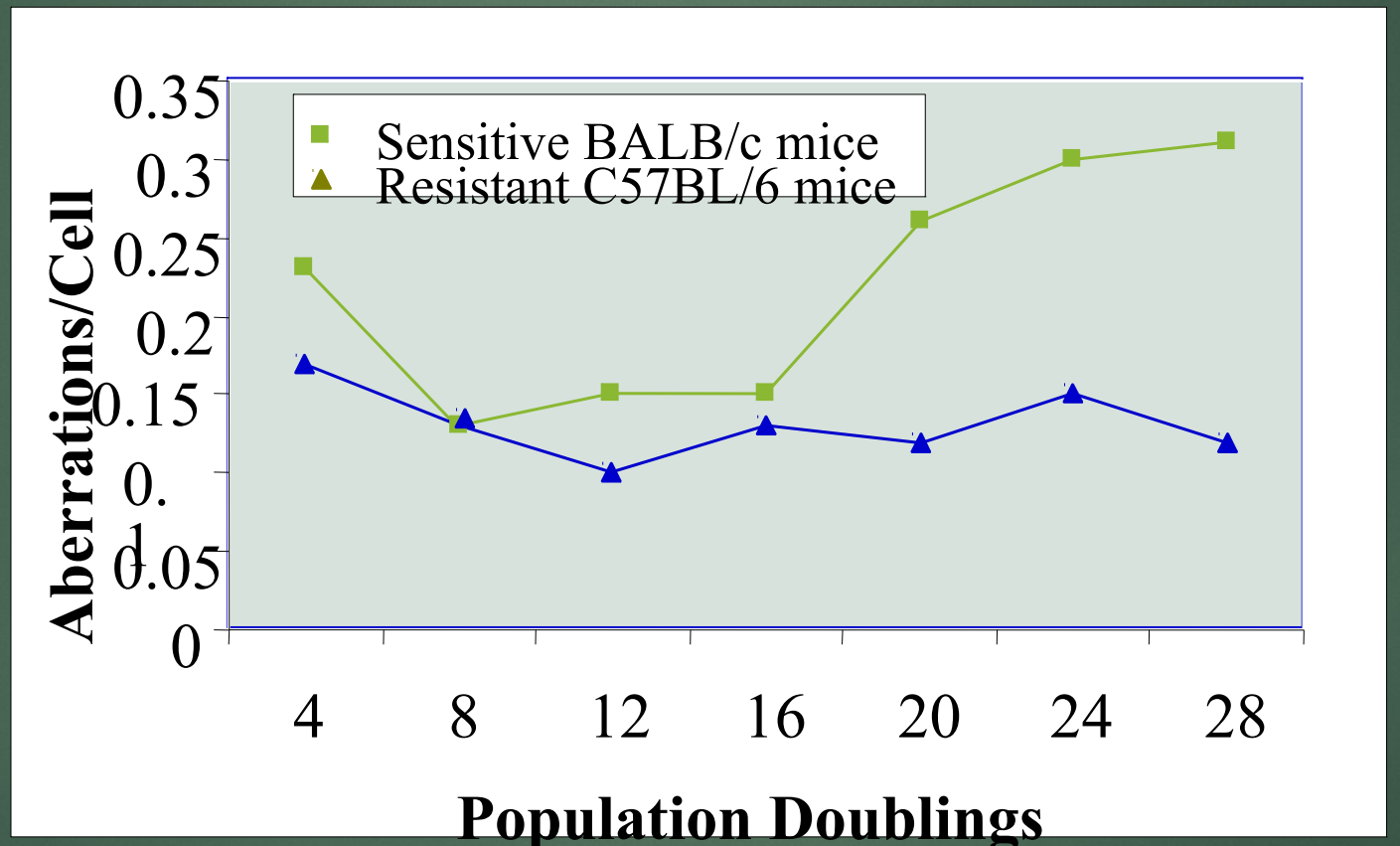
Genomic Instability

New Paradigm

After a cell is exposed to radiation, different things can happen
…sometimes after many cell divisions. This is a frequent event.



Genomic Instability in Mice (Role of Genetic Background)



B. Ponnaiya & R.L. Ullrich, 1998

Decision Making Value *(Genomic Instability)*

- Genomic instability a frequent event following high doses.
- Nucleus the target for genomic instability.
- Genetic background influences the frequency of genomic instability.
- Genomic instability present both *in vitro* and *in vivo*.
- Genomic instability suggests that single mutations may not be the major mechanism of action at high doses.
- Genomic instability supports LNT in the high dose region.

Research in Low Dose Region

- Extensive research on biological effects of low dose radiation resulted in many new observations making paradigm shifts in radiation biology essential.
  - Hit theory vs Bystander and tissue effects
  - Linear dose-responses vs Protective adaptation
  - Mutation theory vs Genomic instability
- The mechanisms of action of these phenomena are being carefully documented and understood.

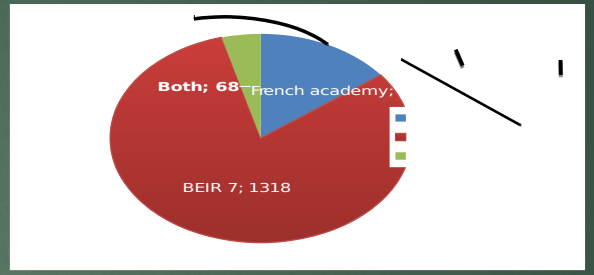
BEIR VII and DOE Low dose Program

- ***Bystander Effects***: Until molecular mechanisms of the bystander effects are elucidated….”

- ***Adaptive Response***: “Such data have not yet been obtained, particularly those explaining the molecular and cellular mechanisms for the adaptive response.”

- ***Genomic Instability***: However, until the molecular mechanisms responsible for genomic instability and its relationship to carcinogenesis are understood…”

French Academy of Science



- Evaluated a different set of literature.
- Focused on the Adaptive protective Responses
- Used the data widely and determined that LNT is not a valid scientific model in the low dose region.

Low dose and dose rate: Mechanisms of Action

- **Molecular and cellular changes induced by low doses of radiation**
- **Low dose induced metabolic changes**
- **Epigenetic response to low doses of radiation**
- **Whole Animal responses to low dose-rate radiation**
- **Human data after low doses**

Are the mechanisms the same at low vs. high doses?

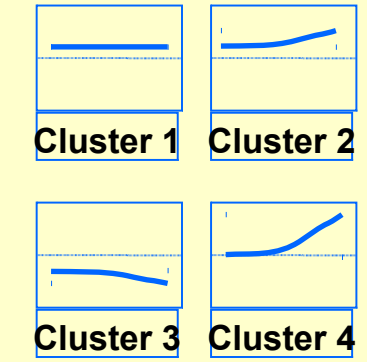
Three lines of evidence point to a transition in transcript expression profiles in the range of 10-25 cGy

All gene data (n = 22283)

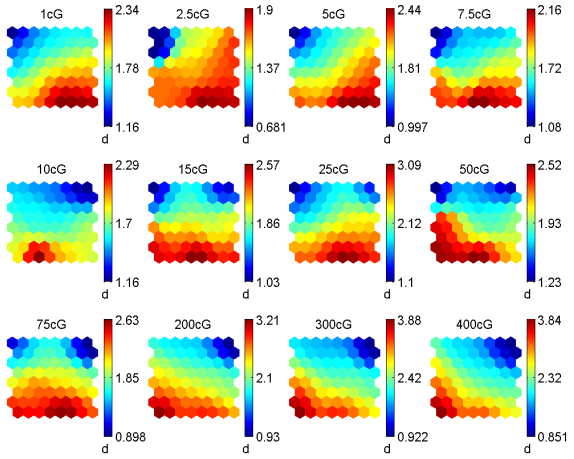
Filter for differential expression (FDR < 0.10)

Combine into one dataset N=420 genes

Cluster analyses



Self Organizing Maps



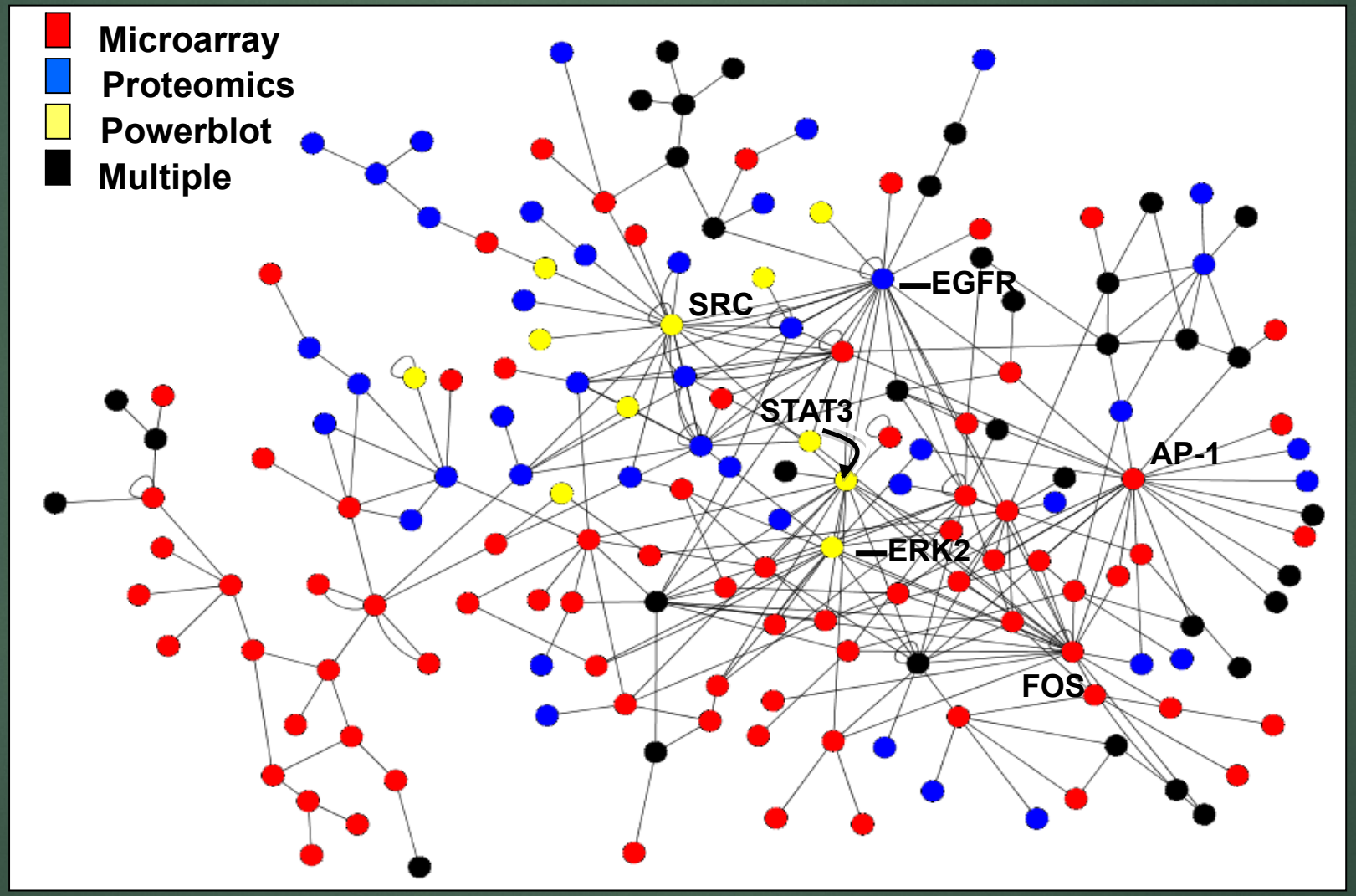
Row																					Uniqu
1	236		61		184		63		34		52		200		37		68		90		116		113	420
2		49		52		58		21		16		44		30		23		39		68		82		156
3			47		36		20		12		15		25		22		21		36		59			96
4				35		19		12		12		13		19		21		21		30				51
5					19		12		12		12		12		19		21		18					29
6						12		12		12		11		12		19		18						21
7							12		12		11		11		12		17							19
8								12		11		11		11		11								13
9									11		11		11		10									11
10										11		11		10										11
11											11		10											11
12												10												10
Dose/cGy	1.0		2.5		5.0		7.5		10		15		25		50		75		200		300		400	

Figure 1

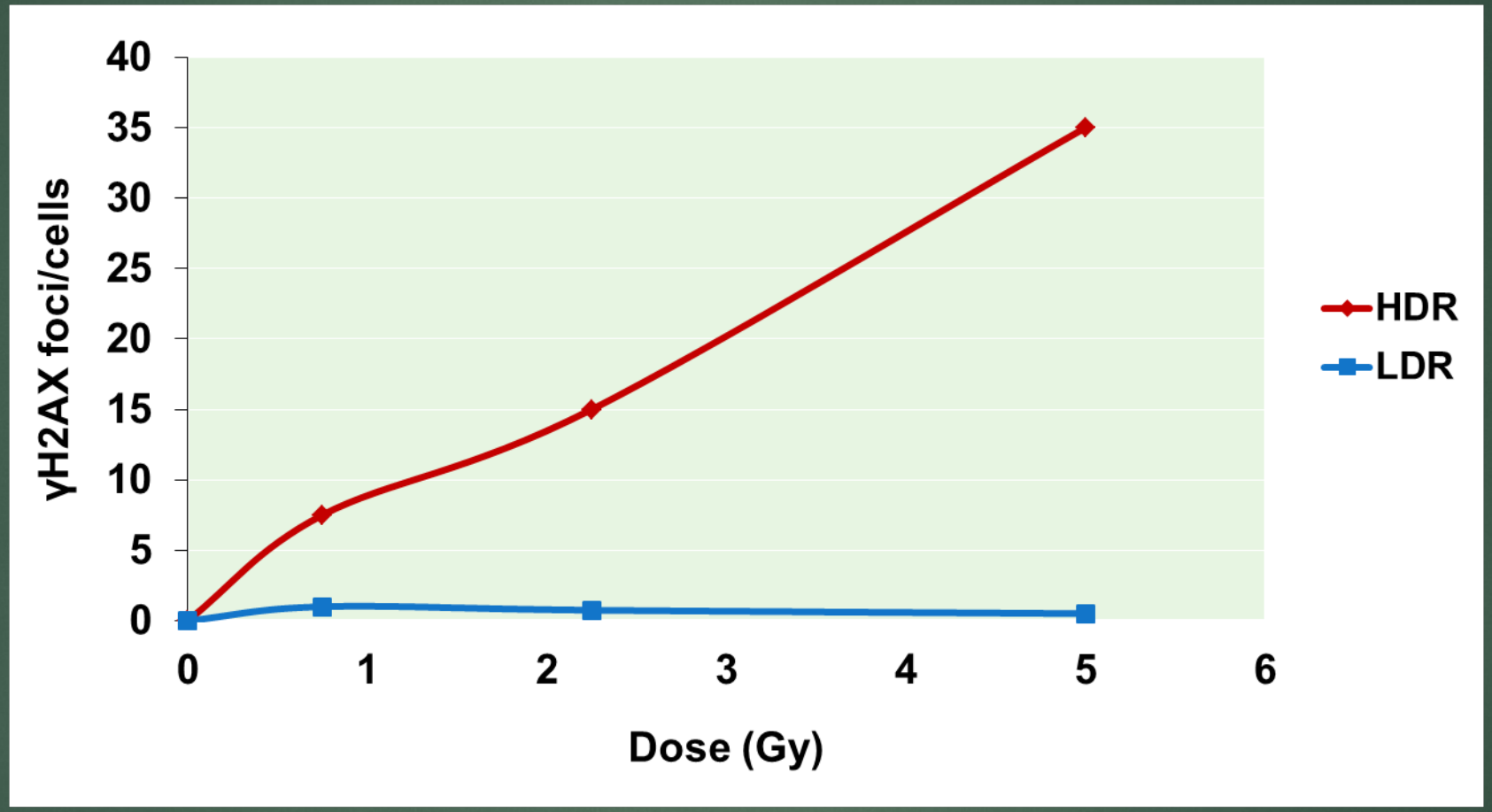
In collaboration with D. Nelson, K. Krishnan

(Wyrobek, et al., LLNL)

Network reconstruction using Integrated data are more comprehensive and accurate

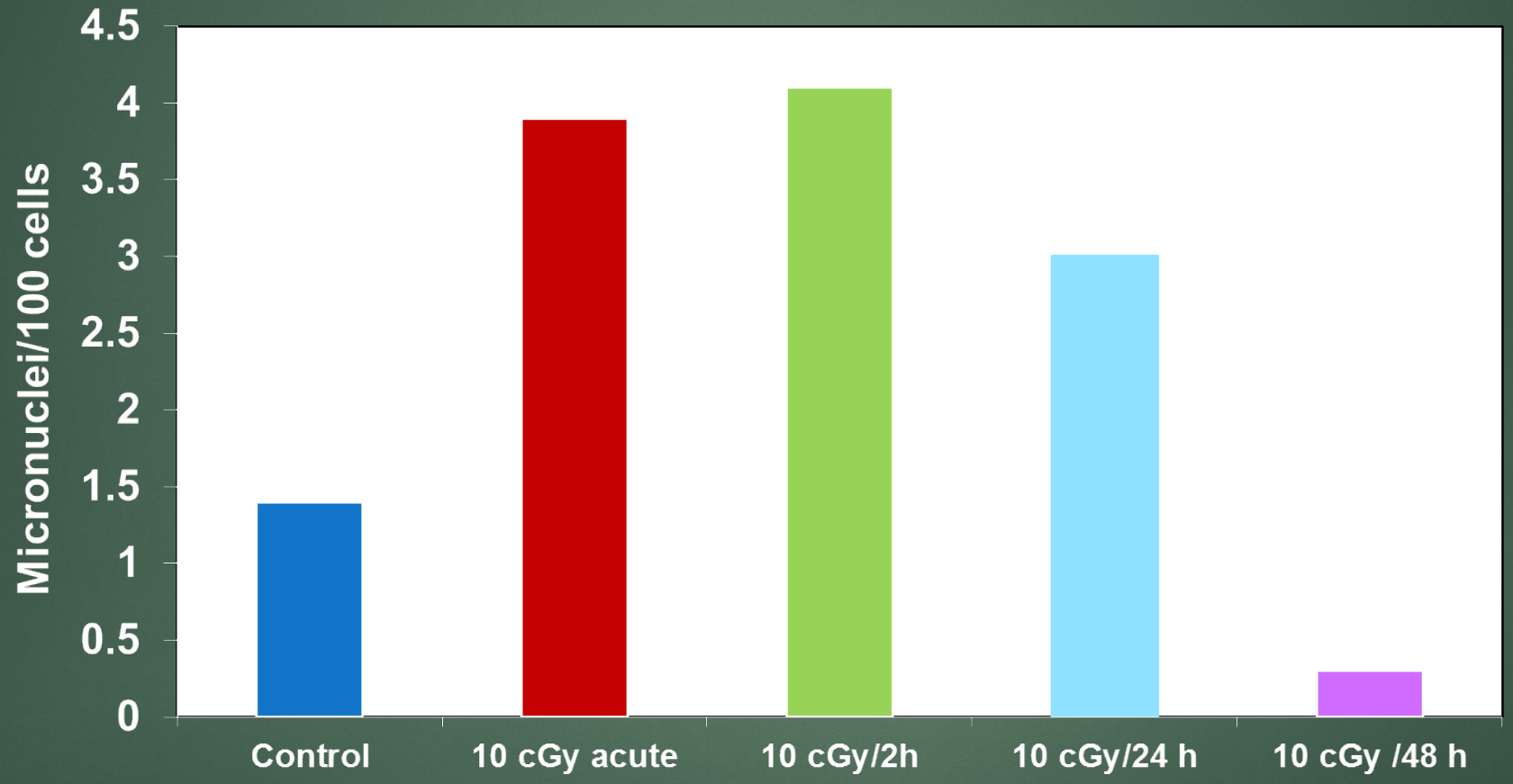


γH2AX



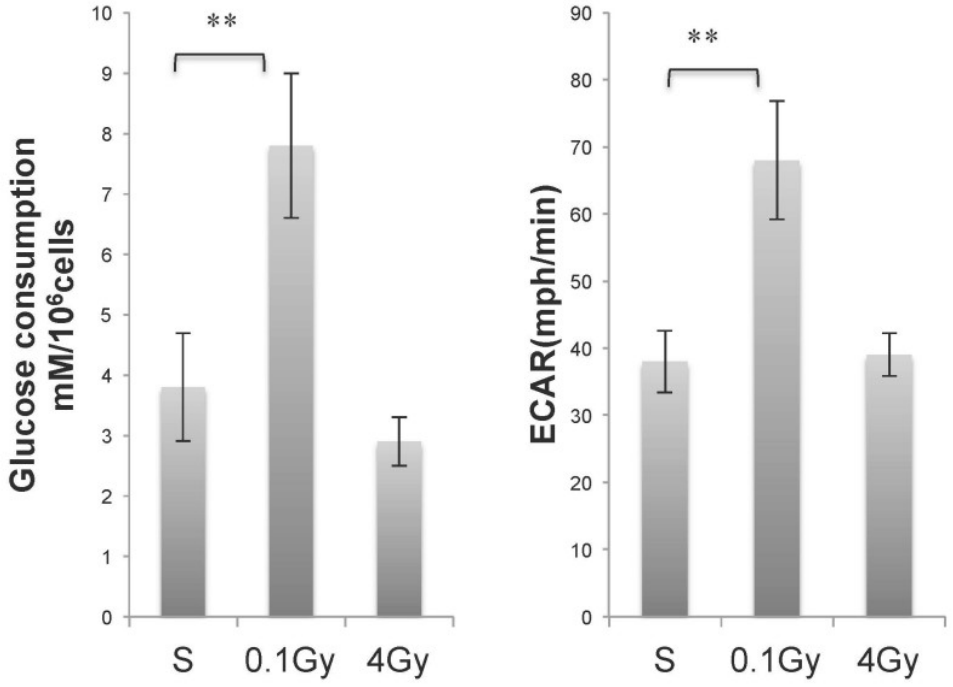
Ishizaki et al. 2004

Influence of Dose-rate on Chromosome Damage



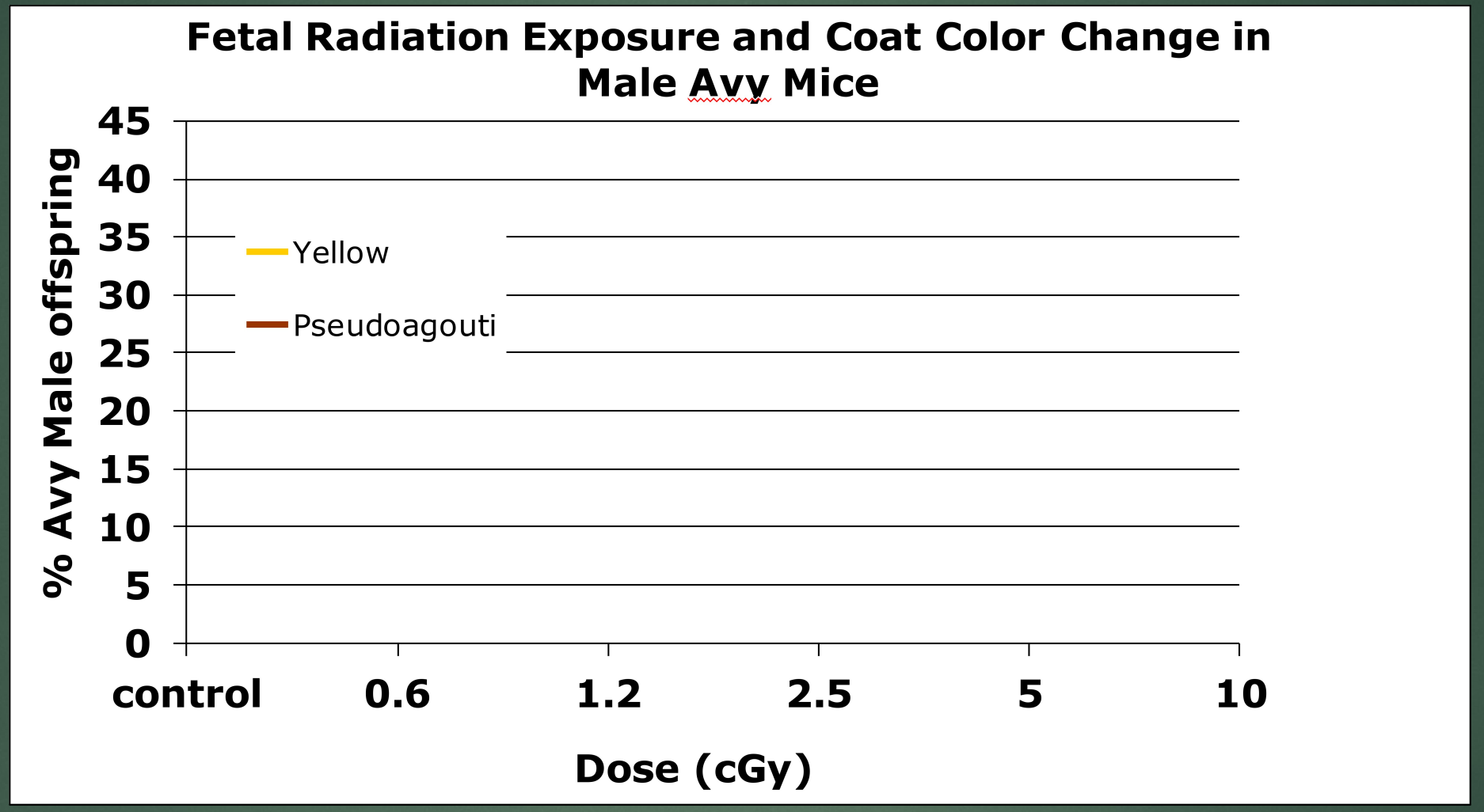
de Toledo et al. 2006

Low-dose irradiation induces glycolysis



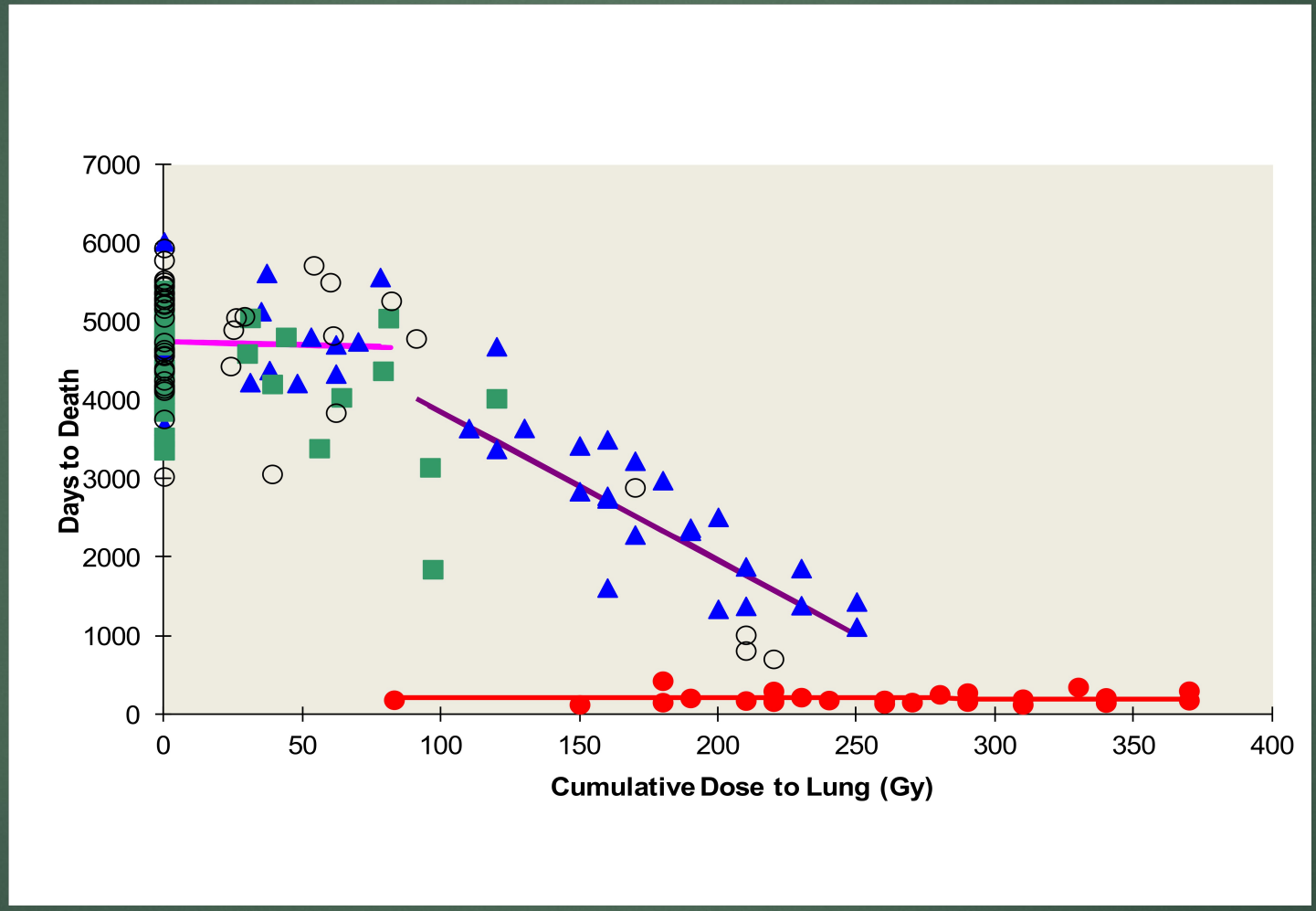
HARVARD | SCHOOL OF PUBLIC HEALTH

Zin-Min Yuan
Harvard School of Public Health

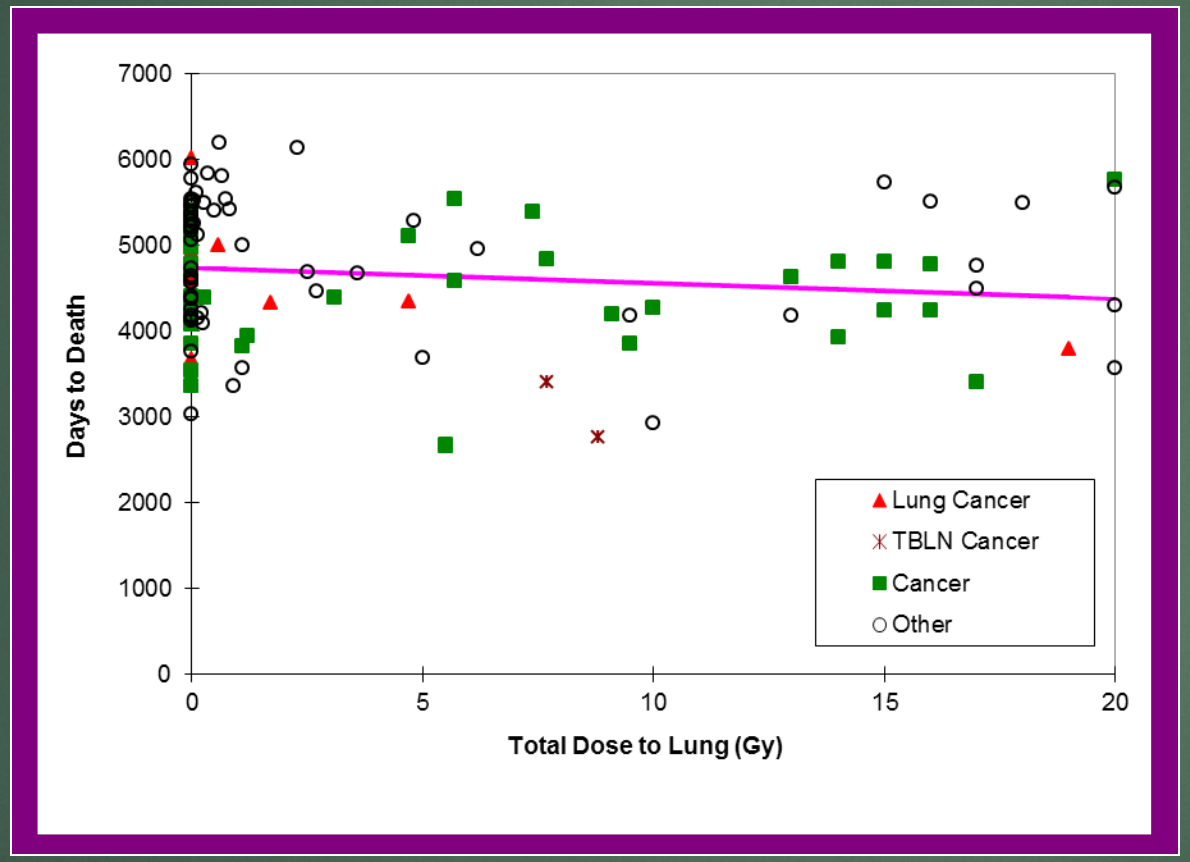


Bernell and Jirtle 2011

Life Shortening Response to Cumulative Dose to Lung Following Inhalation of 91-Yttrium FAP



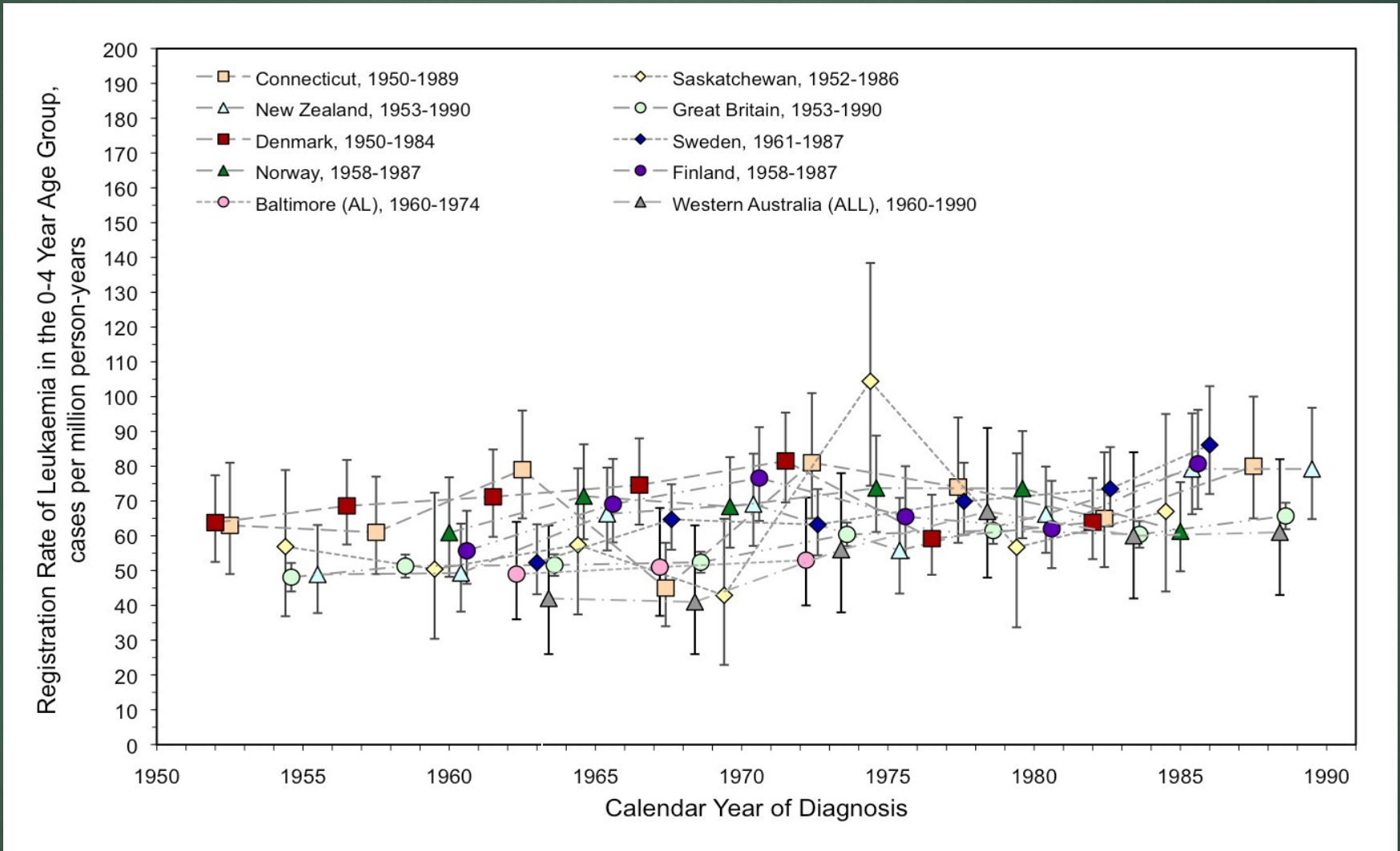
Dogs < 20 Gy Dose to Lung After Inhalation of FAP



	Lung Cancer	Total Cancer
Control	8/54= **15%**	26/54= **48%**
Exposed	4/64= **6%**	29/64= **45%**

20 Gy results in 20,000 "hits/cell"

Human Data: World-wide Rate of Childhood Leukemia as a Function of Time



End Above Ground Weapons Testing

Wakeford

Differences between High- and Low-Dose Radiation Responses

High Dose > 0.2 Sv

Cell killing high
DNA damage high
Gene Expression (Damage?)
Epigenetic Effects?
Free Radical Increased
Direct Action

↑ Apoptosis (Increased)
↑ Mutation Frequency
↑ Cell Transformation
Immune response (-)
Cancer increased (5%/Sv)

Low Dose < 0.2 Sv

Cell killing low
DNA damage low/not detected
Gene Expression (Protective?)
Epigenetic Effects (Protective)
Free Radicals decreased
Indirect Action
MnSOD
Glutathione

↑ Selective Apoptosis
↓ Mutation Frequency
↓ Cell Transformation
Immune response? (+)
Cancer (mSv)?

Summary

- DOE Low Dose Radiation Biology Program made it necessary to change several radiation paradigms which helps us understand radiation risk.
- The Program helped define the mechanisms of action. The mechanisms change as a function of dose and dose-rate.
- Data from all levels of biological organization indicate that low doses may be protective while high doses increase risk.
- Cancer risks using LNTH useful for limiting exposures but do not reflect low dose biological mechanisms. LNTA is overly conservative.

Why Expand and Continue Low Dose Research?

We must invest in research on this critical problem!!

- Potential for treatment of disease with low dose and dose-rate exposures
- Medicine, the fear of needed diagnostic tests can cost many lives.
- The needed use of nuclear power can be limited by fear of radiation

Why Expand and Continue Low Dose Research?

We must invest in research on this critical problem!!

- Nuclear waste clean-up, Billions spent to clean up below background levels
- Terrorist can use the fear of low dose responses to cause economic destruction
- Nuclear accidents or war can put large populations at risk from exposure, decisions on action must be based on the best possible science