

History of the U.S. Department of Energy Research Program

Gilbert W. Beebe Symposium

**The Future of Low-Dose Radiation
Research**

in the United States

**National Academy of Sciences Washington DC,
May 8-9, 2019**

**Dr. Antone L. Brooks
(Tony)**



Goals and Expectations: Low dose Program (Senator Pete Domenici)

“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.”



Knowledge (Before Low Dose Program) (BLD)

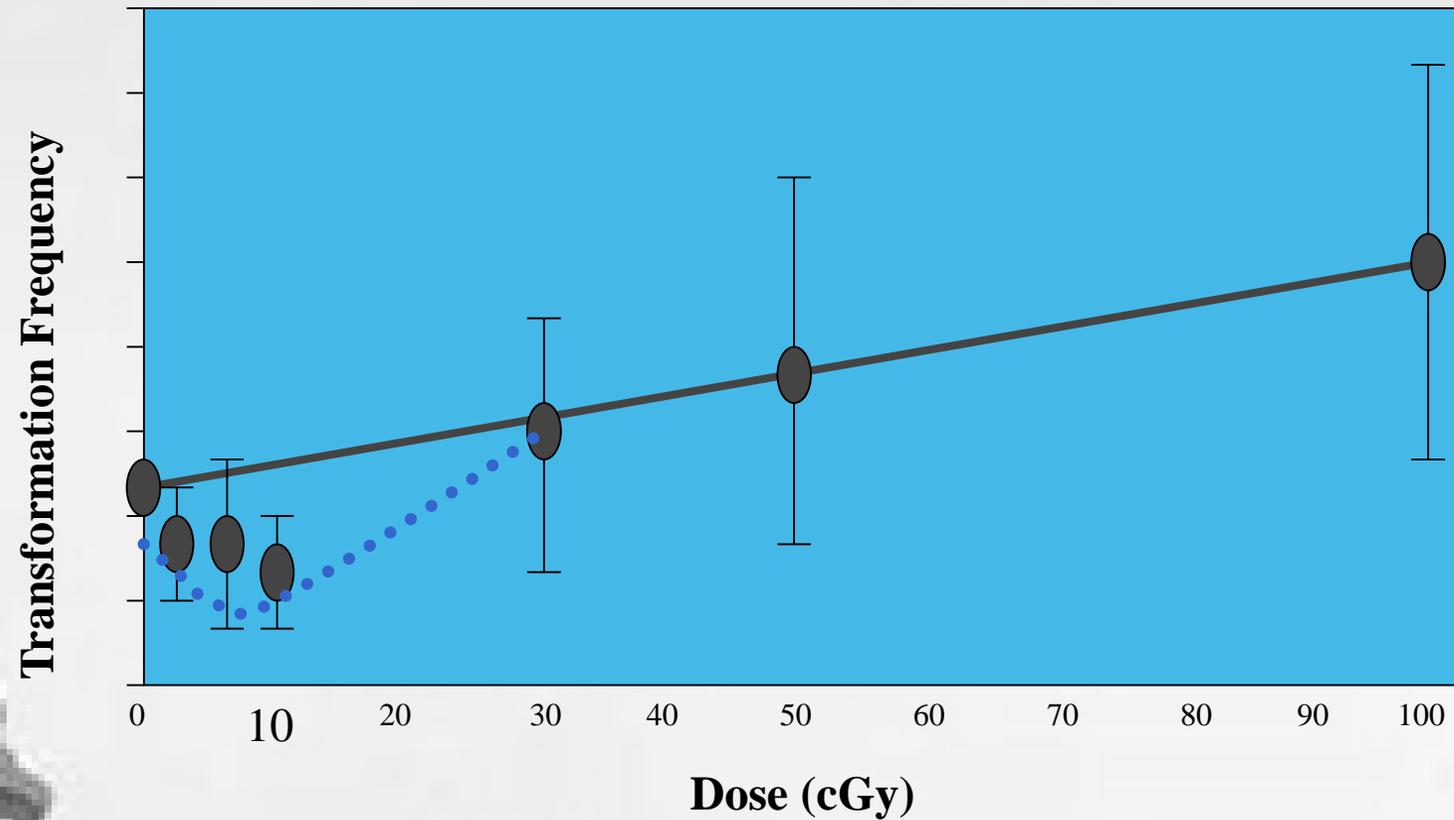
- Acute effects carefully defined for multiple syndromes and species.
- Cancer effects defined in animals for multiple exposure modes, external, acute, chronic, internally deposited radioactive materials.
- Human data from A-Bomb (whole body acute), Radium dial painters (bone), Thorotrast (liver), Uranium miners (lung).
- Cellular markers of radiation exposure and dose (chromosome aberrations)
- Adaptive response human lymphocytes (tickle dose/challenge dose).
- Hit theory (Explain cell survival curves dose, radiation type and dose rate).

Knowledge (After Low Dose Program) (ALD)

- Adaptive Protective Responses
- Bystander Effects
- Genomic Instability
- Defined Molecular pathways activated by low dose radiation
- Gene expression as a function of dose and dose rate.
- Epigenetic effects
- Systems biology applied for complex responses link to humans.
- Helped spark and trigger interest and research world wide.

Adaptive Protective Response

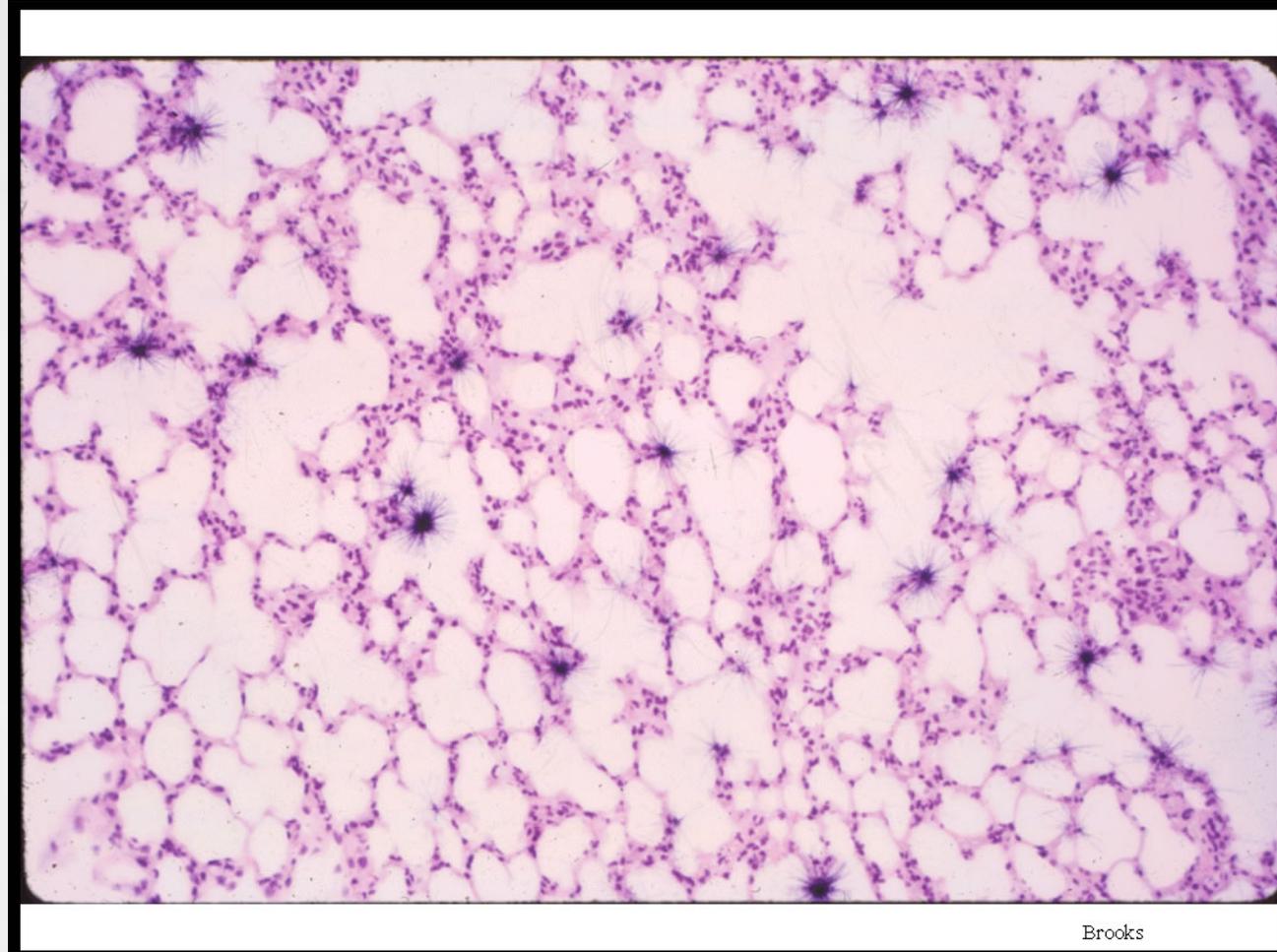
Sub-linear dose response



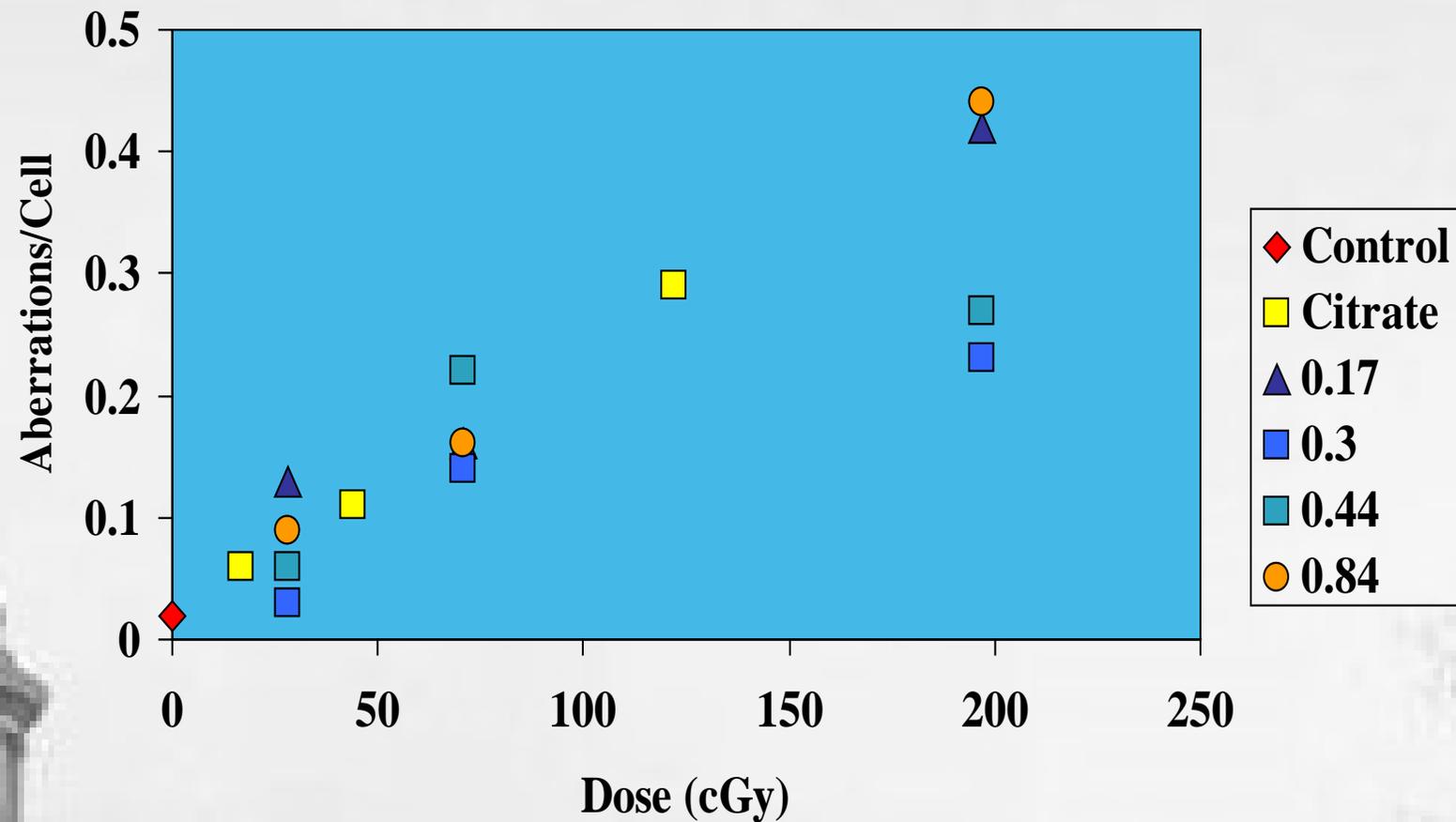
Bystander effects Vs. Hit Theory

- In vitro studies using the newly developed microbeam technology (Columbia U, PNNL, Gray Lab) for both high and low LET radiation.
- Cell/cell and cell/tissue communication and response. The organ responding rather than single cells responding.
- “It takes a tissue to make a tumor”, Barcellos-Hoff)
- In vivo studies using internally deposited Plutonium particles (ITRI).

Non-Uniform Dose Distribution from Plutonium Inhalation



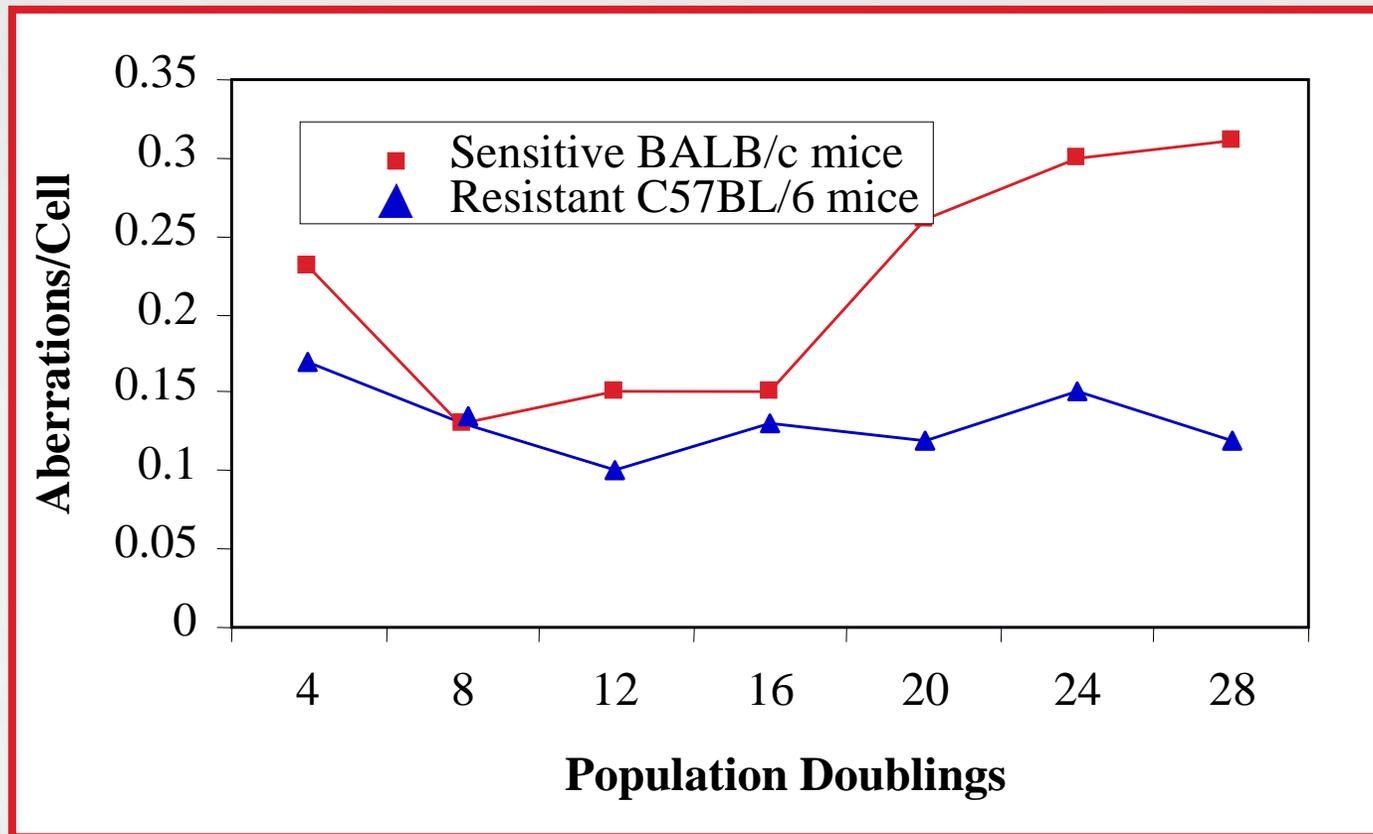
The Influence of ^{239}Pu Dose-Distribution on Chromosome Aberration Frequency



Genomic Instability

- Acute cell and molecular responses followed by repair
- Late occurring cell and molecular changes
- Changes induced both *in vitro* and *in vivo* highly dependent on genetic background

Genomic Instability can be demonstrated in some strains of mice



BEIR VII and Low Dose Research

- **Genomic Instability**

“Until molecular mechanisms responsible for genomic instability and its relationship to carcinogenesis are understood, extrapolation of dose-response data for genomic instability to radiation-induced cancers in the low dose range <100 mGy is not warranted.”

- **Bystander Effects**

“...both beneficial and detrimental effects may result from bystander effects.”

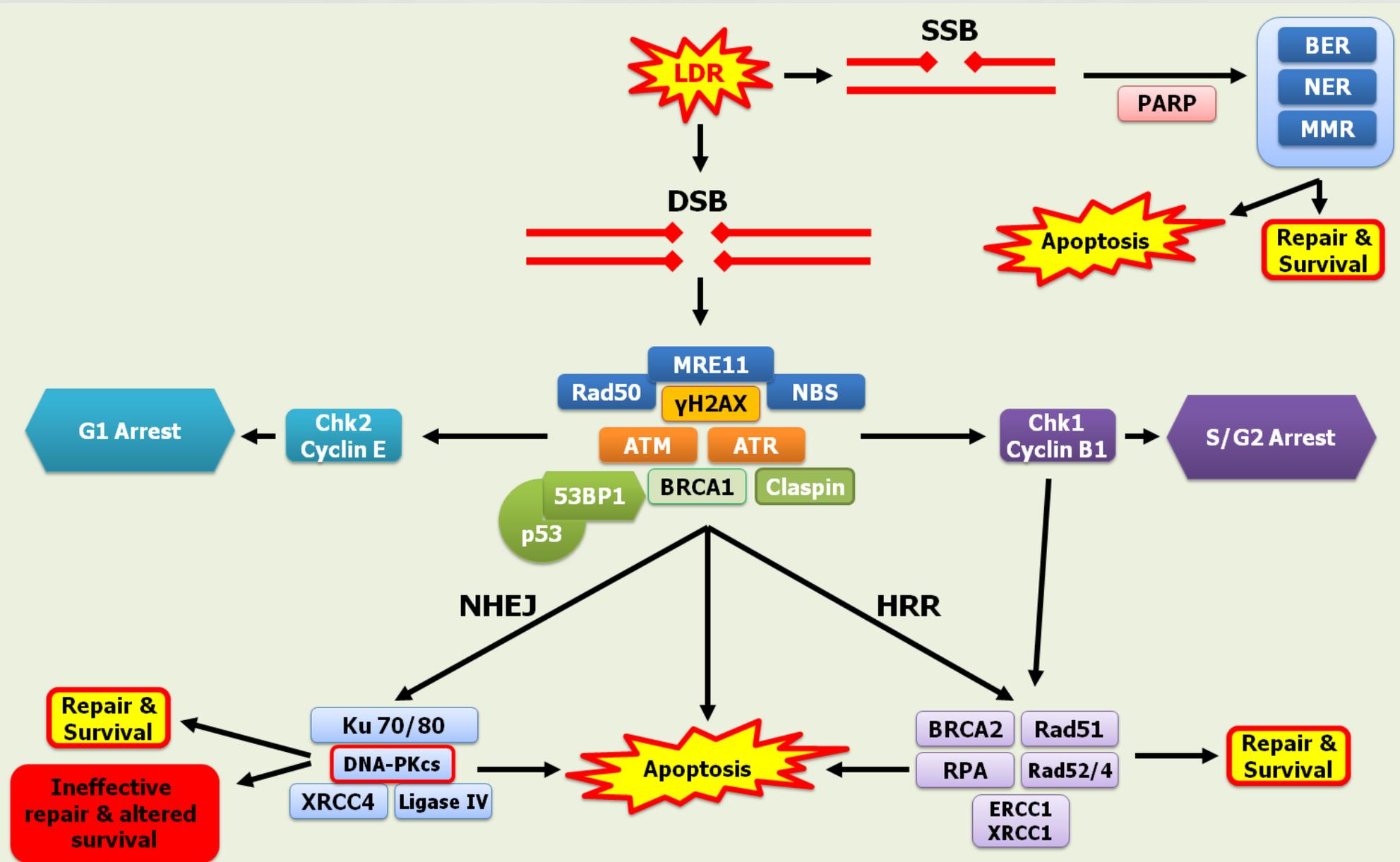
- **Adaptive Response**

“ Relevant endpoints should include not only chromosome aberrations and mutations but also genomic instability and if possible tumor induction.”

Systems biology to link molecular biology to human studies

- Apply new mechanistic biology to well defined human populations.
- Continue to develop mechanistic understanding of biological responses to radiation, need for carefully controlled human studies on potential protective effects.
- Help define key events in critical pathways as cells are transformed from normal to cancer.
 - The role of mutations, inflammatory disease, immune system, abnormal metabolic pathways, mitochondrial alterations, epigenetics, alterations in gene expression.
- Determine risks or benefits in low dose region taking into account all the biological data available.

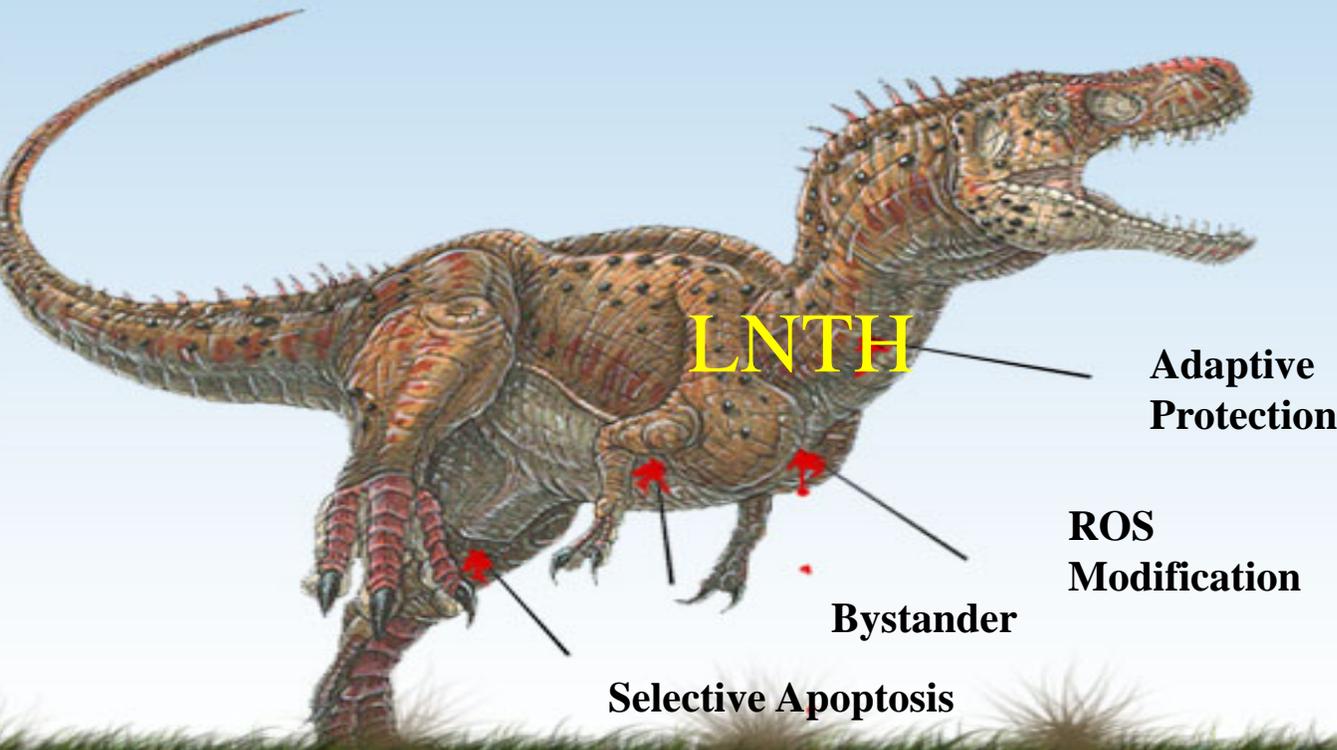
Low Dose Radiation & DNA Damage



The dinosaur of **LNTH** is scientifically dead for low-dose risk assessment but remains used and is useful for regulations:

- Radiation is a poor mutagen and carcinogen and may even be protective.
- Low dose and dose rate radiation cancer risk is very small and very difficult to detect.
- Fear of low dose radiation and radiation protection kills people and is very expensive.

Cell and molecular responses seem to be radio-protective !!!



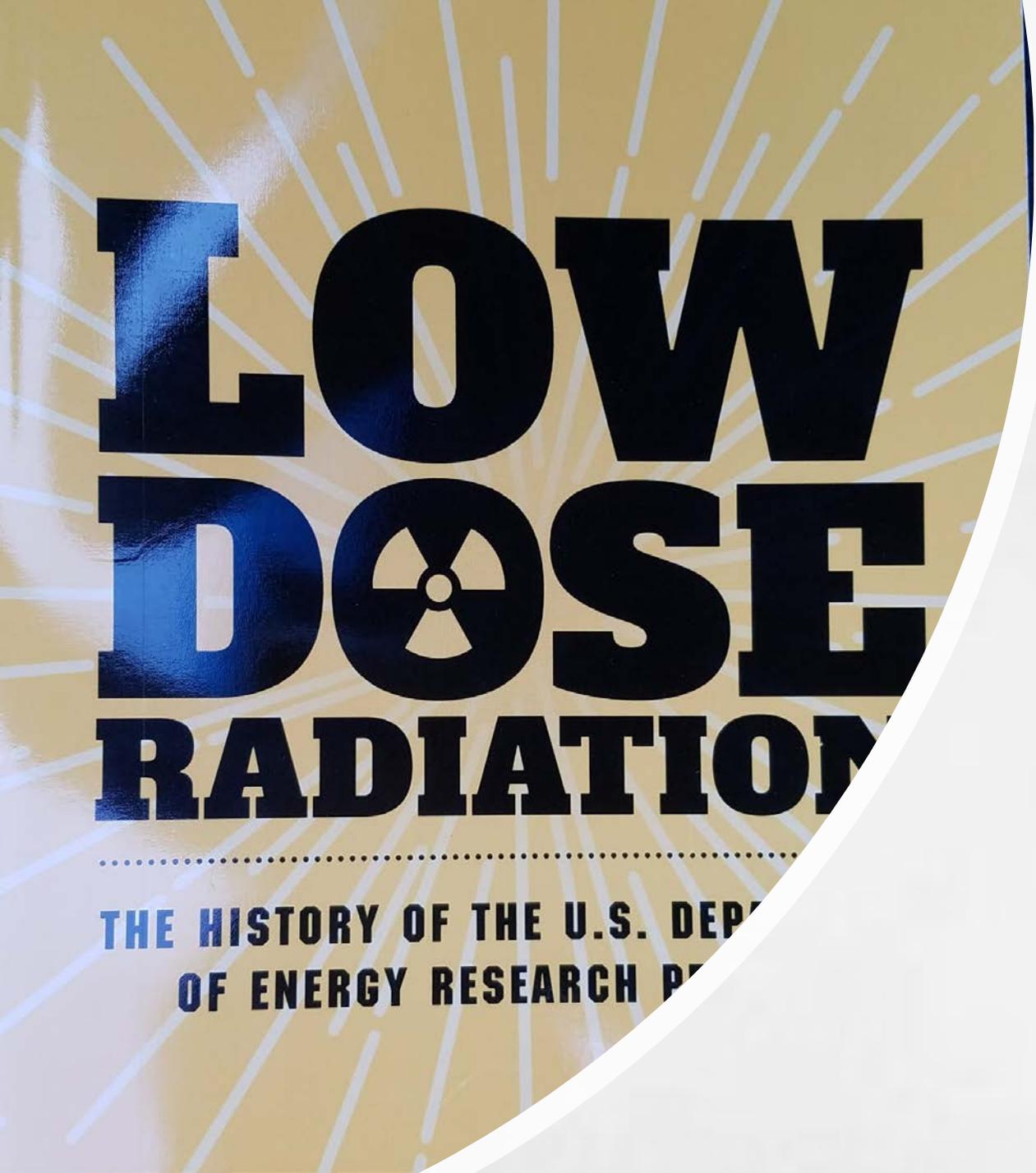
Systems Biology

Genomics
Epigenomics

Proteomics

Metabolomics





LOW DOSE RADIATION

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**THE HISTORY OF THE U.S. DEPT.
OF ENERGY RESEARCH PROGRAMS**

**History of the
DOE Program**
AL Brooks

How can a new Low Dose Research Program get started?

- GAO told congress that we must have such a program to address national needs.
- Congress pass bills telling DOE to start a program!!
- Yes, but where is the money?
 - DOE take it out of your hide.
 - Hanford Clean-up estimated to take 600+ Billion dollars, Perhaps some crumbs off the table from that program (not likely Brian Vance Manager Office of River Protection and Richland Operations Office).
 - We need a new Senator Domenici!!! **To continue research and make regulations based on Science.**

Summary

- With modern biology paradigm shifts in Radiation Biology are needed.
 - Bystander effects vs “hit theory”. Single mutation theory of cancer vs Systems approach. LNTH vs Thresholds. Damage vs Benefits.
- Research needed to extend knowledge from the molecular to human experience, (Link mechanistic studies to molecular epidemiology, risk, potential for protection against and cure of cancer).
 - (NIH human trials needed to generate these important links).
- Low doses stimulate immune system, increase DNA repair, upregulate many other protective mechanisms.
 - (Glutathione, MnSOD, Apoptosis, Metabolic pathways, immune system, mitochondrial changes)
- The LNTH continues to be useful to control human exposure and protect the public. When combined with collective dose, ALARA and LNTH risk calculations; the cost, fear and damage caused by over protective regulations far outweigh the minimal protection gained.
- There is no question as to the need to understand the impact and risk of low doses of radiation. DOE or some other agency needs to step up and get a research program in place to address this need.