

DOE's Low Dose Radiation Research Program

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L'Enfant Plaza Hotel**

6 December 2012



U.S. DEPARTMENT OF
ENERGY

Office
of Science

Office of Biological
and Environmental Research

DOE's Low Dose Program:

Is unique within the U.S. government in focusing on low dose biological research aimed at informing current and future national radiation risk policy for the public and the workplace

- **DOE** focuses on worker and public safety from very low dose x- and gamma-ray exposures encountered in energy production and environmental cleanup

In contrast:

- **NASA** focuses on astronaut safety from high energy particulate radiation exposures encountered in space flight (*low doses, HZE particles*)
- **NCI** (National Cancer Institute) focuses on patient health from high dose clinically-relevant exposures (*200 rads and higher*)
- **NIOSH** Program Area: Radiation dose reconstruction for workers

DOE's Low Dose Program:

Supports basic research to decrease the uncertainties and shrink the confidence intervals around the central estimate of risk

- DOE uses RISK as a basis for radiation protection, but it is not used directly to define radiation protection standards
- Standards are generally defined as a function of dose, or the directly measurable quantities of exposure, activity, or concentration
- Levels are consistent with USNRC and EPA, and with recommendations from NCRP, ICRP
- The risk uncertainty rises drastically in the low dose regime (where we regulate)

Regulation at the upper confidence limit of risk is a policy decision

Outline

- **History:** *Research to develop a better scientific basis for understanding exposures and risks to humans*
- **Biology:** old assumptions, new paradigms
- **The Low Dose Program today**
- **Million U.S. Worker Study**
(John Boice, next presentation)

But first -- What is Low Dose?

X- or Gamma- rays:

One photon track/cell ~ 2 mSv = 200 mrem
~ 2 mGy = 0.20 rads

1 MeV γ -ray; $(20\mu\text{m})^3$ cell volume; = 0.14 rads
500 keV x-ray; $(20\mu\text{m})^3$ cell volume; = 0.19 rads

Alpha particles:

One particle track/cell ~ 200 mSv = 20,000 mrem
~ 200 mGy = 20 rads

Background radiation:

~ 15 ion pairs / cm^3 air / sec

Over land mass, approximately 10 to 20 ion pairs per cubic centimeter in air are formed every second.

This ionization rate decreases with altitude to 500 meters, after which it slowly rises with altitude, reaching the ground level rate at 1500 meters.

The Low Dose Program was initiated in 1999 with a workshop:

Bridging Radiation Policy and Science

An international meeting of experts

Airlie House Conference Center

1 – 5 December 1999

“The lowest dose at which a statistically significant radiation risk has been shown is ~ 100 mSv (10 rem) of x-rays.”

Other Programs are now supported:

- **MELODI** (**M**ultidisciplinary **E**uropean **L**ow **D**ose **I**nitiative)
- **Japan**
- **Other** (China, Korea, India,...)

The Low Dose Program was initiated :

- **To provide mechanistic data for the development of a scientific basis for radiation standards in the low dose region**
- **Possible in 1999 because of**
 - **Extensive biological advances associated with**
 - sequencing of the genome
 - the development of gene expression arrays
 - the expansion of information on cell-cell and cell matrix communication
 - **Technologies such as single cell irradiators**
 - (The first research program to emphasize whole tissue responses using these advances)

Historic Animal Studies

- Historic mega-mouse and -dog studies were conducted from 1970s – '90s (49,000 mice, 17,000 beagle dogs)
- Historic (and newer) studies have shown
 - A pronounced dose-rate effect for cancer
 - Strong low dose “sparing” effect
 - Data and tissue archives
- To determine if cellular and molecular observations influence disease outcome
- Animal data still provide a link between cell and molecular mechanisms and human epidemiological data for risk assessment.

In 1999, five research needs were identified:

- **Understanding biological responses to low dose radiation exposures**
- **Low dose radiation versus endogenous oxidative damage**
- **Thresholds for low dose radiation**
- **Genetic factors affecting individual susceptibility**
- **Communication of research results**

**The real challenge: to do research
at 10 rads or less**

Twelve years later – 2012

Radiation physics (*energy deposition*) dictates a linear induction of initial events as a function of dose

Radiation biology shows us that the subsequent biological response is much more complex

DNA repair

Cell apoptosis

Cell/tissue growth and replacement

Immune system surveillance

Twelve years later – 2012

Program Research Results

- Biological systems can actually detect and respond to very low doses of radiation
- Cells not directly exposed can show a biological response to the low dose radiation exposure of neighboring cells
- Cell-cell and cell-matrix communication are critical in the total response to radiation, resulting in whole tissue or organism responses as compared to individual cell responses
- Qualitatively different molecular-level responses result after low doses of radiation vs. high doses of radiation
- Many cellular and tissue-level responses demonstrate non-linear responses with respect to radiation dose
- In addition to radiation-induced DNA damage, other processes are induced by low dose radiation that participate in either increasing or deterring carcinogenesis

Twelve years later – 2012

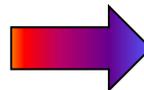
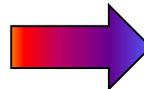
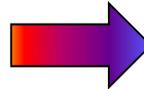
Old Assumptions

Qualitatively similar radiation effects occur at high and low dose exposures

All radiation effects contribute to the process of carcinogenesis

DNA damage is the only mechanism responsible for increasing cancer risk

These assumptions have been prevalent since World War II



New Paradigms

Qualitatively different processes are induced by high vs. low doses/dose-rates

Many radiation effects do not contribute to the process of carcinogenesis

In addition to DNA damage, cancer risk is highly dependent on the cell microenvironment

We now know much more about biology and radiobiology

2000-2012 – Evolution of the Program:

- **NASA joint-funded research**
- **Strong appreciation for cell microenvironment**
- **Added mouse systems genetics**
- **Additional low dose / low dose-rate effects:**
 - Proteomic responses
 - Immune system
 - Epigenetic regulation
 - Aging effects – cell/molecular endpoints
- **Mathematical/risk modeling projects** incorporating new radiobiology
- **Funding of integrated program projects**

2000-2012 – Evolving Research Focus Areas:

- **Systems biology / tissue microenvironment**
 - Regard the tissue / organ / organism as the primary responder
 - Allows rational study of homeostatic mechanisms
 - Will resolve issues and bring about scientific consensus
- **Adaptive responses**
 - Small “priming” dose can stimulate protective effects that are seen in response to a subsequent stress
- **Epigenetic regulation**
 - Heritable changes in gene expression or cell phenotype caused by mechanisms other than changes in the DNA sequence
- **Mouse systems genetics**
- **Low dose epidemiology**

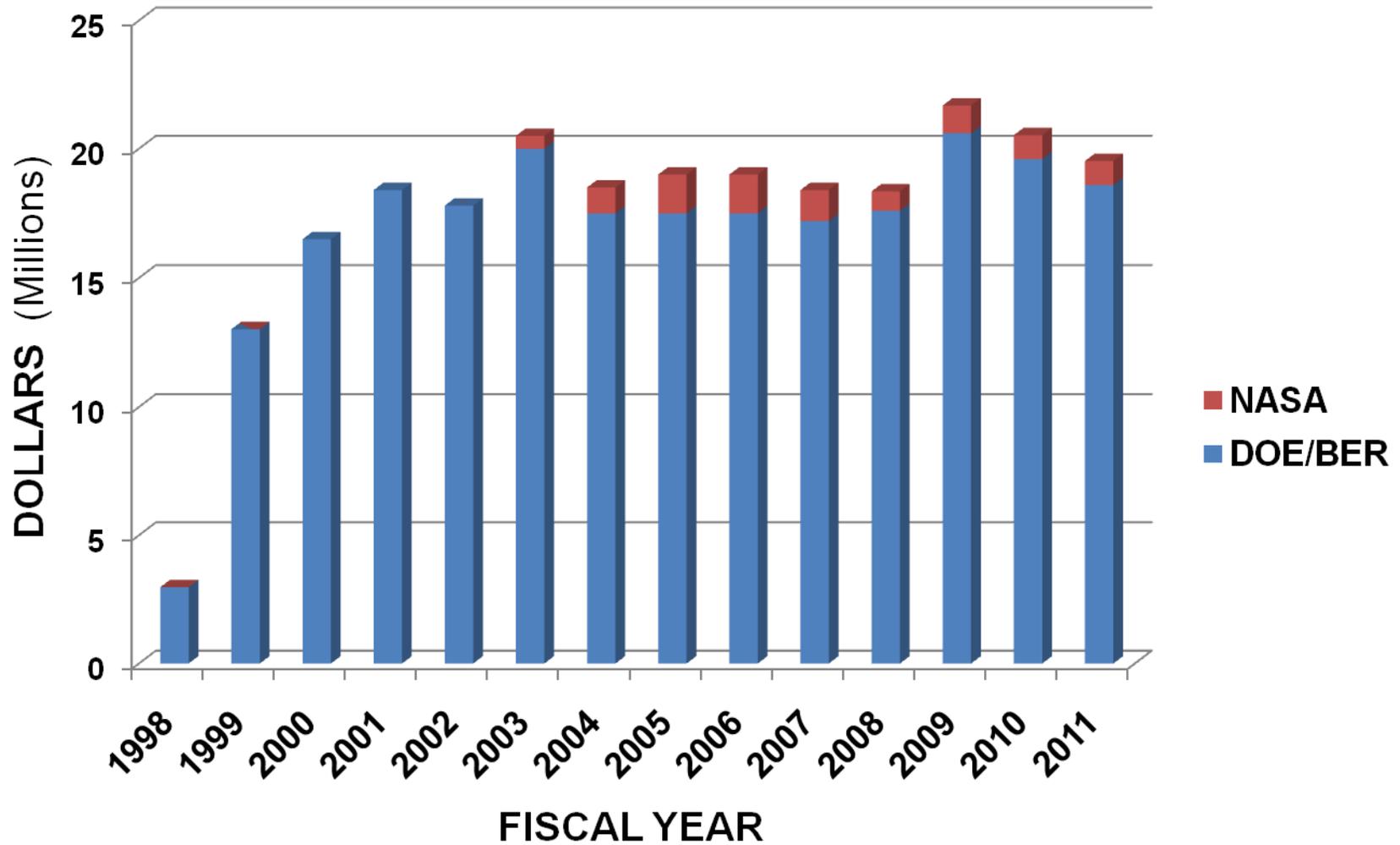
The Low Dose Program Today (1)

- **12th year of Program**
- **Joint funding of research with NASA's Space Radiation Research Program**
 - Cellular and molecular responses in normal tissues
 - After high LET radiation exposures
 - At fluences approximating the space environment (high single-cell doses but low tissue doses)
- **Re-analysis of Radiobiology Tissue Archive data at Northwestern University**
 - The Woloschak laboratory hosts several radiobiology archives containing data and tissues from radiobiology very large (mouse, dog) studies conducted in the second half of the 20th century
- **Research to enable mechanism-based models that incorporate both radiobiology and epidemiology**

The Low Dose Program Today (2)

- **Currently funded projects:**
 - **University-based**
 - Three 5-yr Program Projects in 5th year
 - 21 radiobiology projects in 3rd (last) year or no-cost extensions—
 - 7 of these are joint NASA-DOE projects
 - **Million U.S. Worker Study**
 - **National Lab SFAs: LBNL, PNNL**
- **Communication links with the public; science to inform public debate**
 - Website
 - Workshops
 - Dose ranges charts
- **>700 peer-reviewed publications (www.lowdose.doe.gov)**
- **New public awareness:**
 - **Medical diagnostic doses (CT scans)**
 - **Fukushima – evacuation/relocation**

Low Dose Radiation Research Program



“There is a need for a more complete view of the relationships that exist between low dose radiation exposure and the cancer process. Without a complete systems approach, it will not be possible to apply the current research to radiation protection.”

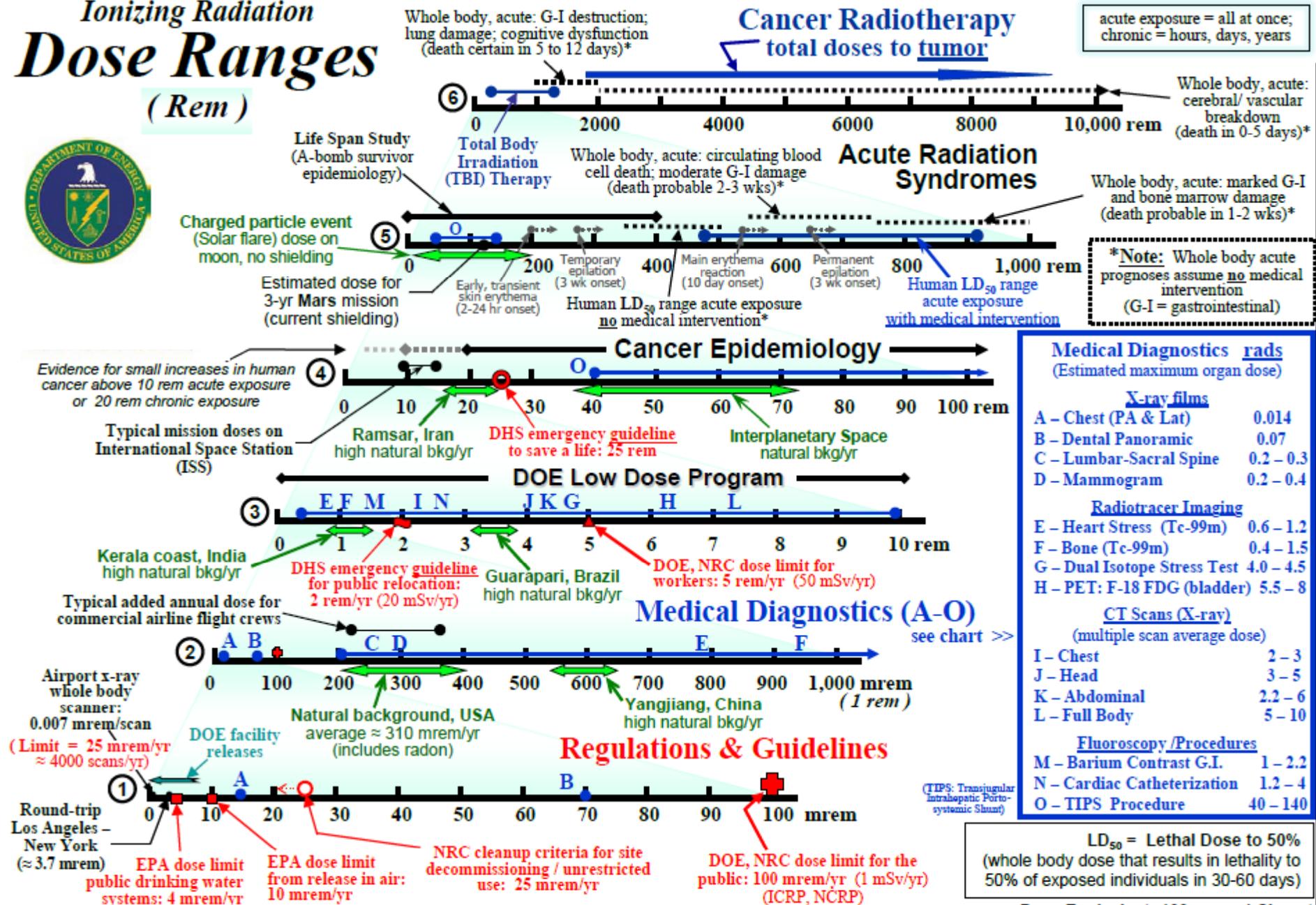
**A History of the
United States Department of Energy (DOE)
Low Dose Radiation Research Program:
1998-2008**

Dr. Antone L. Brooks
tbrooks@tricity.wsu.edu
September 2012 Review Draft

www.lowdose.energy.gov

Ionizing Radiation Dose Ranges

(Rem)



acute exposure = all at once;
chronic = hours, days, years

Whole body, acute:
cerebral/vascular
breakdown
(death in 0-5 days)*

Whole body, acute: marked G-I
and bone marrow damage
(death probable in 1-2 wks)*

*Note: Whole body acute
prognoses assume **no** medical
intervention
(G-I = gastrointestinal)

Medical Diagnostics rads (Estimated maximum organ dose)

X-ray films	
A - Chest (PA & Lat)	0.014
B - Dental Panoramic	0.07
C - Lumbar-Sacral Spine	0.2 - 0.3
D - Mammogram	0.2 - 0.4
Radiotracer Imaging	
E - Heart Stress (Tc-99m)	0.6 - 1.2
F - Bone (Tc-99m)	0.4 - 1.5
G - Dual Isotope Stress Test	4.0 - 4.5
H - PET: F-18 FDG (bladder)	5.5 - 8
CT Scans (X-ray) (multiple scan average dose)	
I - Chest	2 - 3
J - Head	3 - 5
K - Abdominal	2.2 - 6
L - Full Body	5 - 10
Fluoroscopy /Procedures	
M - Barium Contrast G.I.	1 - 2.2
N - Cardiac Catheterization	1.2 - 4
O - TIPS Procedure	40 - 140

LD₅₀ = Lethal Dose to 50%
(whole body dose that results in lethality to
50% of exposed individuals in 30-60 days)

Dose Equivalent: 100 rem = 1 Sievert
= (absorbed dose x radiation quality)
Absorbed Dose: 100 rad = 1 Gray

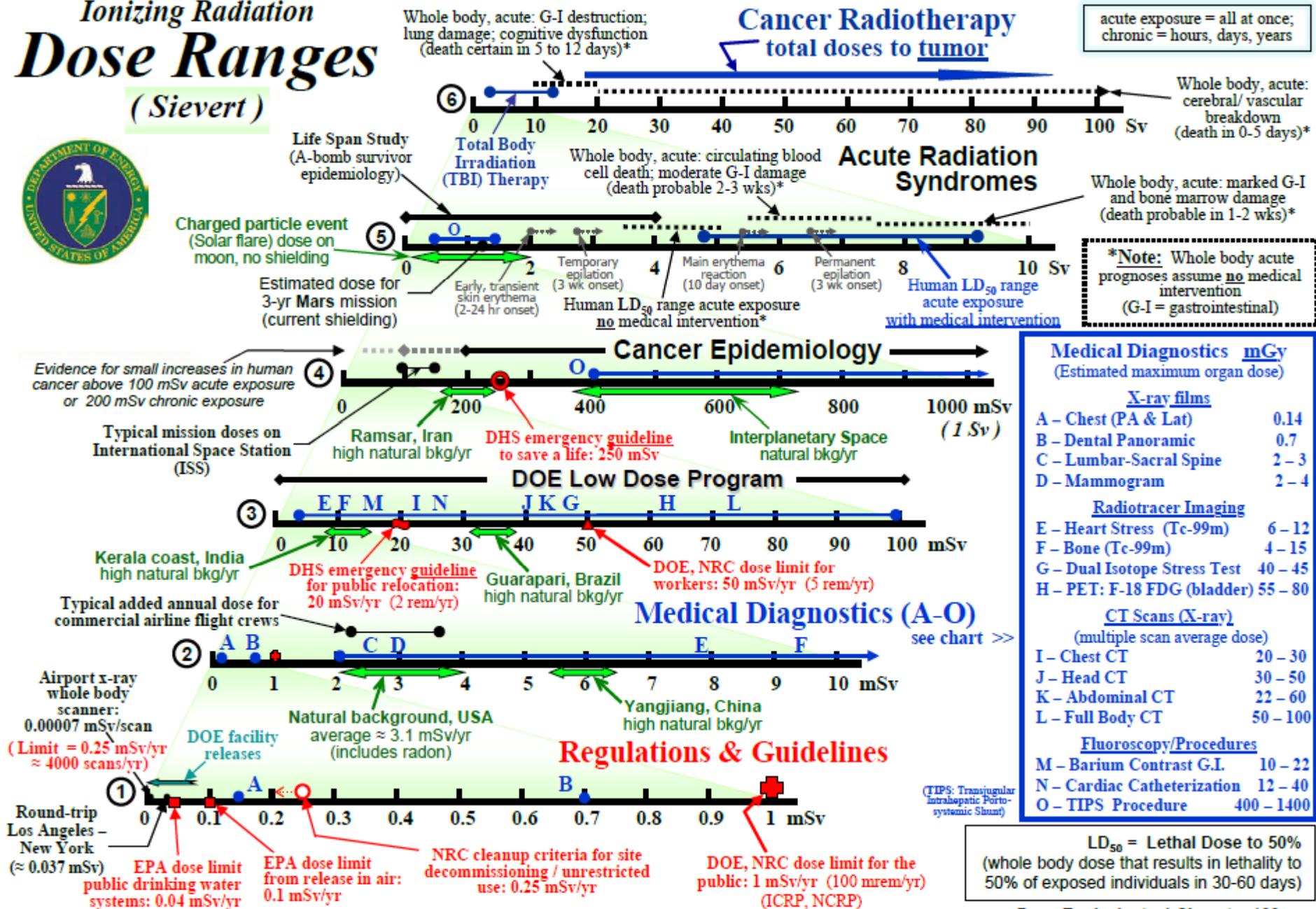
NOTE: This chart was constructed with the intention of providing a simple, user-friendly, "order-of-magnitude" reference for radiation exposures of interest to scientists, managers, and the general public. In that spirit, most quantities are expressed as "dose equivalent" in the more commonly used radiation protection units, the rem and Sievert. Medical diagnostics are expressed as estimated maximum organ dose, as they are not in "effective dose" they do not imply an estimation of risk (no tissue weighting). Dose limits are in effective dose, but for most radiation types and energies the difference is numerically not significant within this context. It is acknowledged that the decision to use these units is a simplification, and does not address everyone's needs. (NRC = Nuclear Regulatory Commission; EPA = Environmental Protection Agency; DHS = Department of Homeland Security)
Disclaimer: Neither the United States Government nor any agency thereof, nor any of their employees, makes any warranty, express or implied, or

Chart compiled by NF Metting, Office of Science,
DOE/BER. "Orders of Magnitude" revised June 2010
<http://www.lowdose.energy.gov/>

Source: Office of Biological and Environmental Research (BER), Office of Science, U.S. Department of Energy

(END...)

Ionizing Radiation Dose Ranges (Sievert)



Medical Diagnostics <u>mGy</u> (Estimated maximum organ dose)	
<u>X-ray films</u>	
A - Chest (PA & Lat)	0.14
B - Dental Panoramic	0.7
C - Lumbar-Sacral Spine	2 - 3
D - Mammogram	2 - 4
<u>Radiotracer Imaging</u>	
E - Heart Stress (Tc-99m)	6 - 12
F - Bone (Tc-99m)	4 - 15
G - Dual Isotope Stress Test	40 - 45
H - PET: F-18 FDG (bladder)	55 - 80
<u>CT Scans (X-ray)</u> (multiple scan average dose)	
I - Chest CT	20 - 30
J - Head CT	30 - 50
K - Abdominal CT	22 - 60
L - Full Body CT	50 - 100
<u>Fluoroscopy/Procedures</u>	
M - Barium Contrast G.I.	10 - 22
N - Cardiac Catheterization	12 - 40
O - TIPS Procedure	400 - 1400

LD₅₀ = Lethal Dose to 50%
(whole body dose that results in lethality to 50% of exposed individuals in 30-60 days)

Dose Equivalent: 1 Sievert = 100 rem = (absorbed dose x radiation quality)
Absorbed Dose: 1 Gray = 100 rad
1 Sv ≈ 1 Gy for x- and gamma-rays

NOTE: This chart was constructed with the intention of providing a simple, user-friendly, "order-of-magnitude" reference for radiation exposures of interest to scientists, managers, and the general public. In that spirit, most quantities are expressed as "dose equivalent" in the more commonly used radiation protection units, the rem and Sievert. Medical diagnostics are expressed as estimated maximum organ dose, as they are not in "effective dose" they do not imply an estimation of risk (no tissue weighting). Dose limits are in effective dose, but for most radiation types and energies the difference is numerically not significant within this context. It is acknowledged that the decision to use these units is a simplification, and does not address everyone's needs. (NRC = Nuclear Regulatory Commission; EPA = Environmental Protection Agency; DHS = Department of Homeland Security)
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Source: Office of Biological and Environmental Research (BER), Office of Science, U.S. Department of Energy

New Paradigm 1

Qualitatively different biological responses are induced by high versus low dose, dose rate

- **Mostly from transcriptomics**

- mRNA gene expression studies
- Many papers, must be fully analyzed

- **Proteomics**

- Yang F, *et al.*, Stenoien DL (2012) [Quantitative phosphoproteomics identifies filaggrin and other targets of ionizing radiation in a human skin model](#) . Experimental Dermatology 21(5): 352–357
- Yang F, *et al.*, Stenoien DL (2010) [Phosphoproteomics Profiling of Human Skin Fibroblast Cells Reveals Pathways and Proteins Affected by Low Doses of Ionizing Radiation](#) . PLoS One 5(11): e14152

- **Metabolomics**

- New research ongoing

New Paradigm 2 (a)

Many radiation effects do not contribute to the process of carcinogenesis

- ***Some low dose-induced biological processes are protective***
- **Robust in normal intact biological systems**
- **Cellular level**
 - Homeostatic balance
 - Cellular apoptotic program
 - Efficient enzymatic repair/replacement systems
- **Whole *organism level***
 - *Homeostatic balance*
 - Immune system surveillance
- **Adaptive response experiments- many, varied**

New Paradigm 2 (b)

Adaptive Response Experiments

- The adaptive response is initiated by very low dose, and a beneficial effect is seen most clearly in normal healthy organisms
- This response is the strongest argument for not extrapolating from high dose effects to low dose risk
- Therefore, we need to know the mechanism(s)
 - **Protection by Selective Deletion of Aberrant Cells**
 - Transformed cells are selectively deleted by signals from normal cells and low dose irradiation augments the efficacy of normal cells (Bauer, 1996; Portess *et al.* 2007; Redpath, 2008)
 - Radiation-induced TGF β mediates surveillance of genomically unstable cells *in vitro* and *in vivo* (Maxwell *et al.*, 2008)
 - If bystander effects for apoptosis occur in spleen after low-dose irradiation *in vivo* then the magnitude of the effect falls within the range of normal homeostatic apoptosis (Sykes, *et al.*, 2010)

New Paradigm 3 (a)

In addition to DNA damage, cancer risk is highly dependent on the cell microenvironment

- Genotype:
 - Is an important determinant of cancer susceptibility in general
 - Influences the cell's ability to cope with DNA damage
 - Influences cooperation of other tissues (vasculature, immune system, etc.)
- Experimental data showing that ionizing radiation:
 - Can alter genomic sequence (DNA damage)
 - Can induce signals that alter multi-cellular interactions & phenotypes that underpin carcinogenesis
- At high doses, the altered cell microenvironment creates a critical context that promotes tumor development

Barcellos-Hoff and Nguyen, 2009, *Radiation Carcinogenesis in Context: How Do Irradiated Tissues Become Tumors?* Health Phys. 97(5):446-457 (from NCRP annual meeting, 2008)

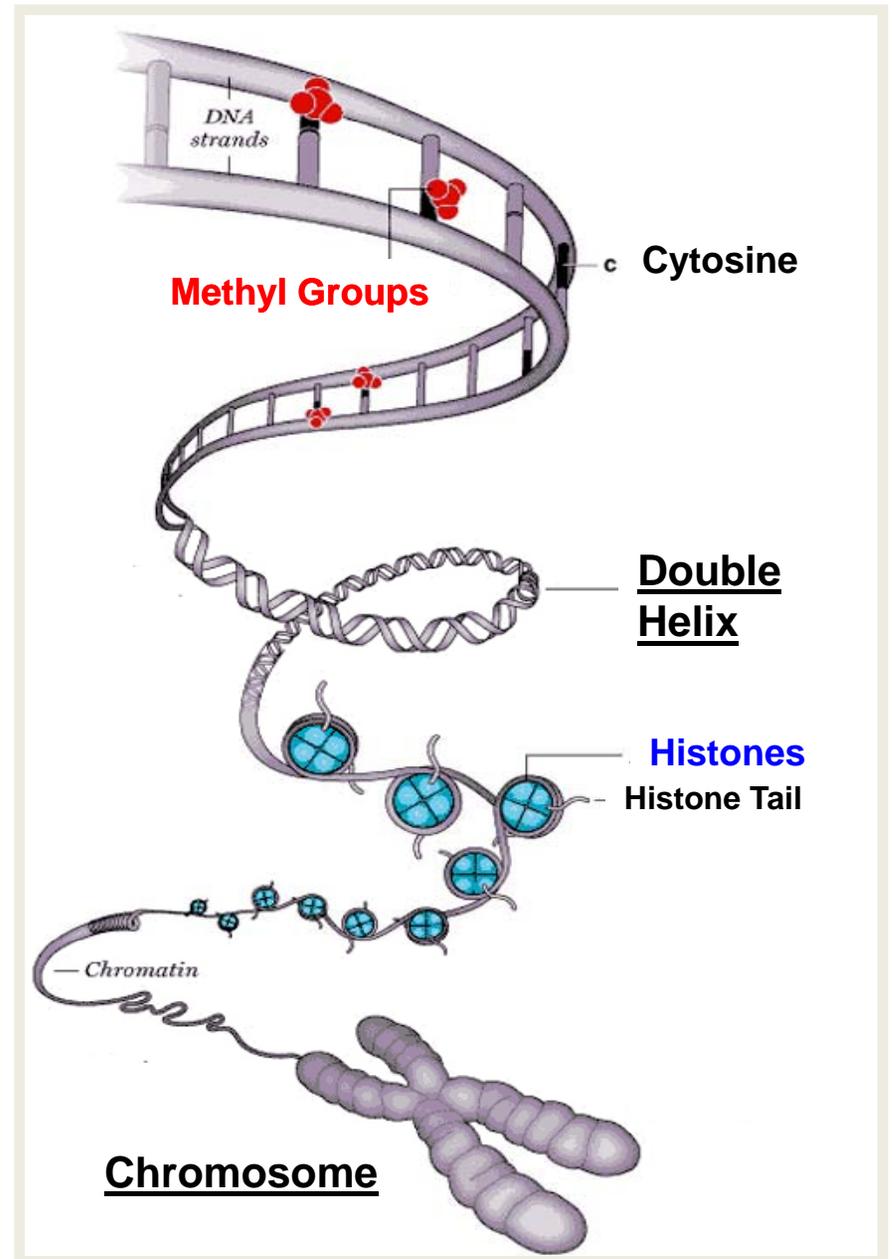
New Paradigm 3 (b)

There are multiple levels of regulation

Epigenetics research refers to the study of heritable changes in gene function that occur without a change in the sequence of the DNA. (i.e. DNA methylation & chromatin structure)

Components of the epigenetic code:

- **DNA methylation**
- **Histone modifications**
- **siRNA, other**



(Models should reflect the biology)

Radiation physics (energy deposition) dictates a linear induction of initial events as a function of dose

Radiation biology shows us that the subsequent biological response is much more complex

DNA repair

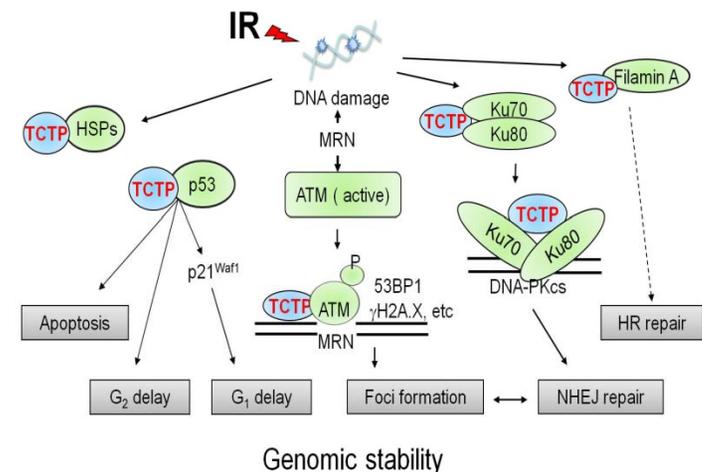
Cell apoptosis

Cell/tissue growth and replacement

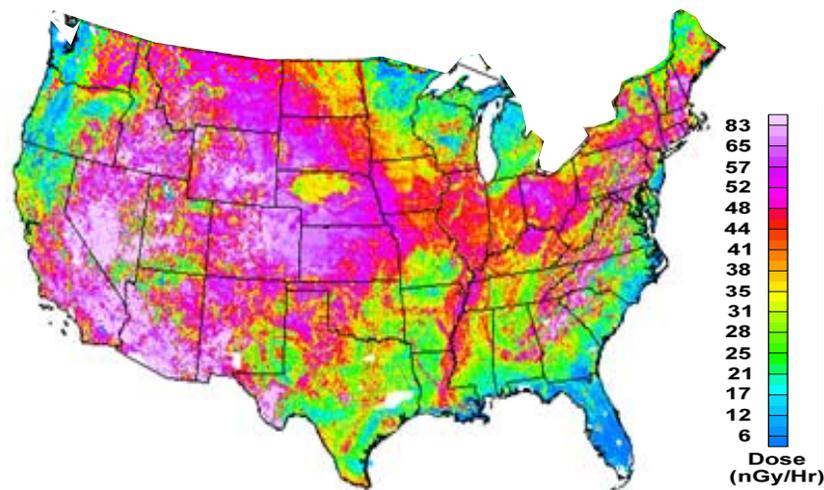
Immune system surveillance

(etc.)

Role of the Translationally Controlled Tumor Protein in DNA Damage Sensing and Repair



Zhang et al., *PNAS*, 109: E926-33, 2012



Gamma-Ray Absorbed Dose

Duval, J.S., Carson, J.M., Holman, P.B., and Darnley, A.G., 2005, *Terrestrial radioactivity and gamma-ray exposure in the United States and Canada*

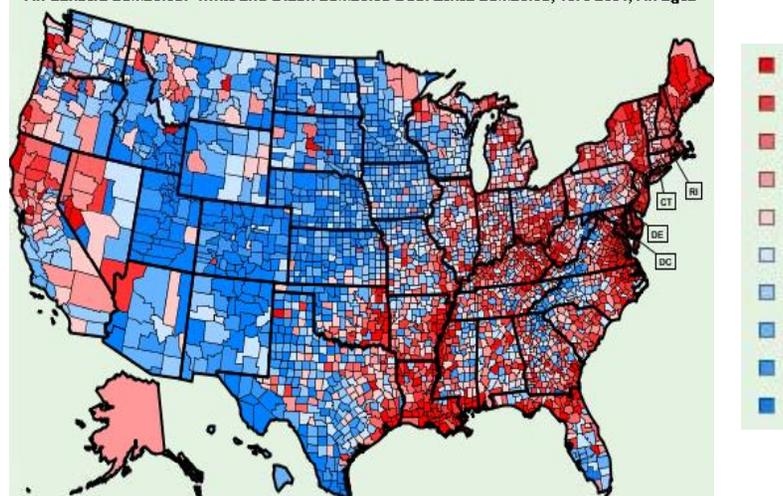
U.S. Geological Survey

(0.1 - 0.7 mGy/yr)

Open-File Report 2005-1413.

<http://pubs.usgs.gov/of/2005/1413/>

Cancer mortality rates by county (age-adjusted 2000 US population)
All Cancers Combined: White and Black Combined Both Sexes Combined, 1970-2004, All ages

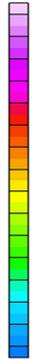
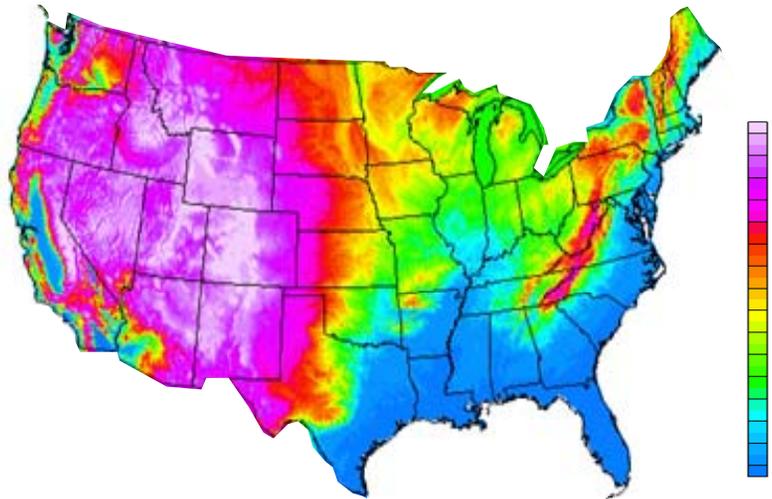


Cancer Mortality Rates by County

All Cancers, male + female, all ages
1970-2004

Deaths per 100,000 person-years

<http://ratecalc.cancer.gov/ratecalc/index.jsp>

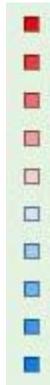
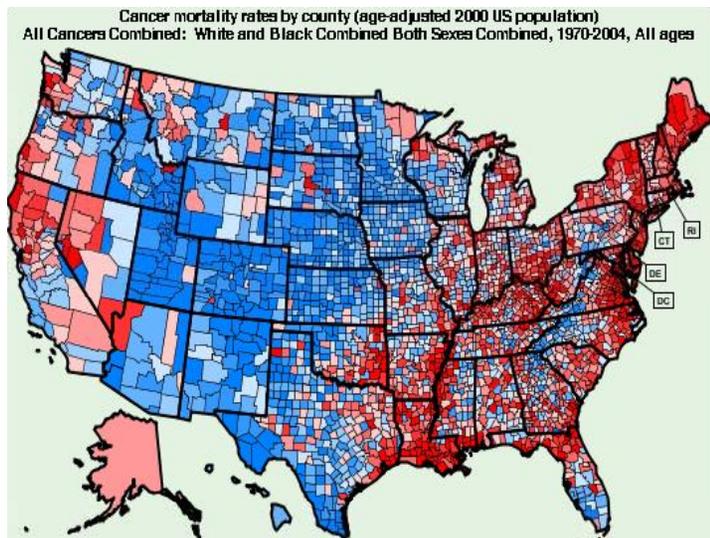


Cosmic-ray Exposure
 (calculated from the topography)

U.S. Geological Survey
 Open-File Report 2005-1413.

(0.4 - 0.8 mGy/yr)

<http://pubs.usgs.gov/of/2005/1413/>



Cancer Mortality Rates by County

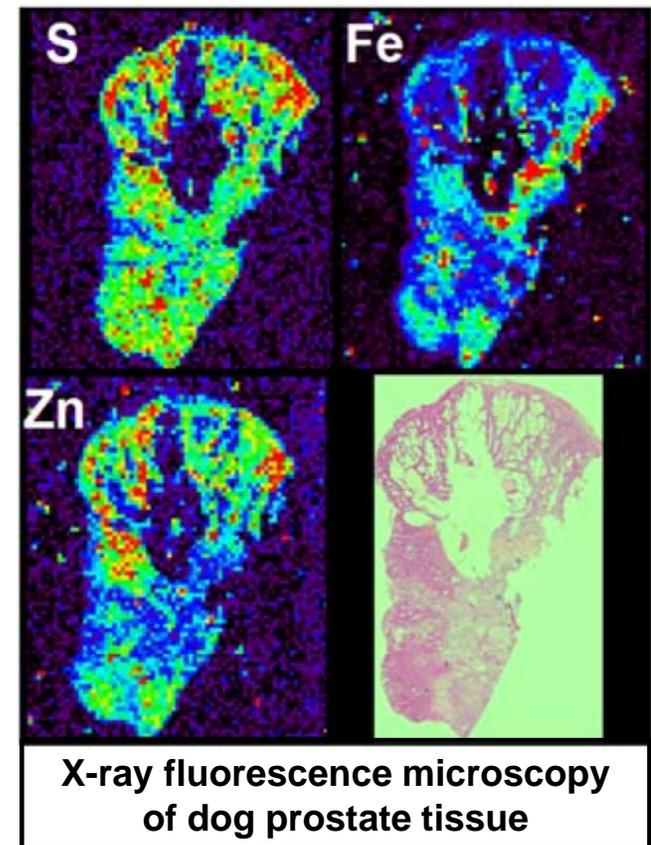
All Cancers, male + female, all ages
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 Deaths per 100,000 person-years

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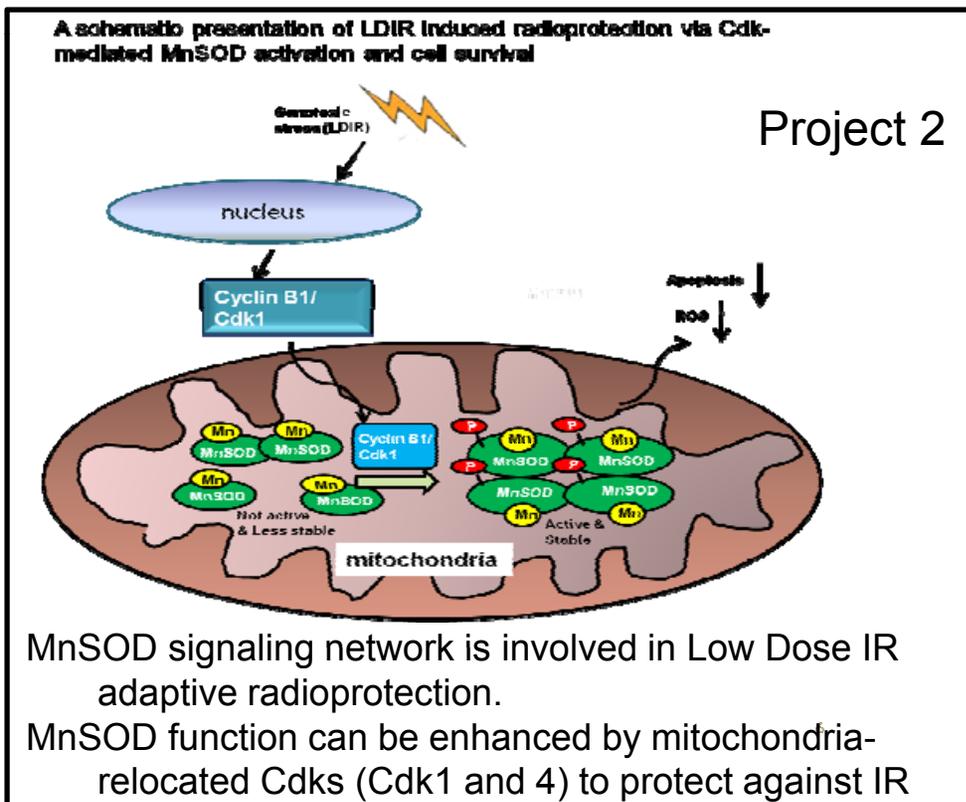
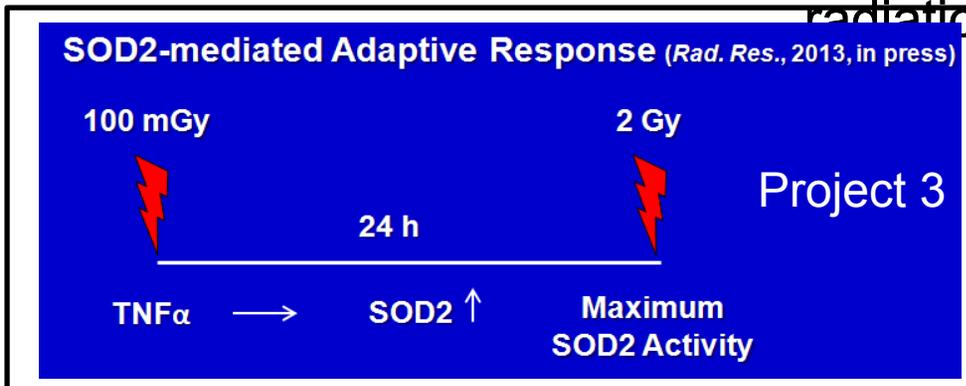
<http://ratecalc.cancer.gov/ratecalc/index.jsp>

Irradiated Tissue Archives Featured in *Nature*

- A recent news article in *Nature*
- Archived data and materials from radiation studies performed between 1952 and 1992: U.S., Europe, etc....
- Relevance to DOE's Low Dose Program
- "[Radiation risks: Raiders of the lost archive](#)"
- Quoted in the article: Dr. Gayle Woloschak, Professor at Northwestern University



Three parts of the program project focus on mitochondria and unite around findings of the role of protein MnSOD in adaptive responses to



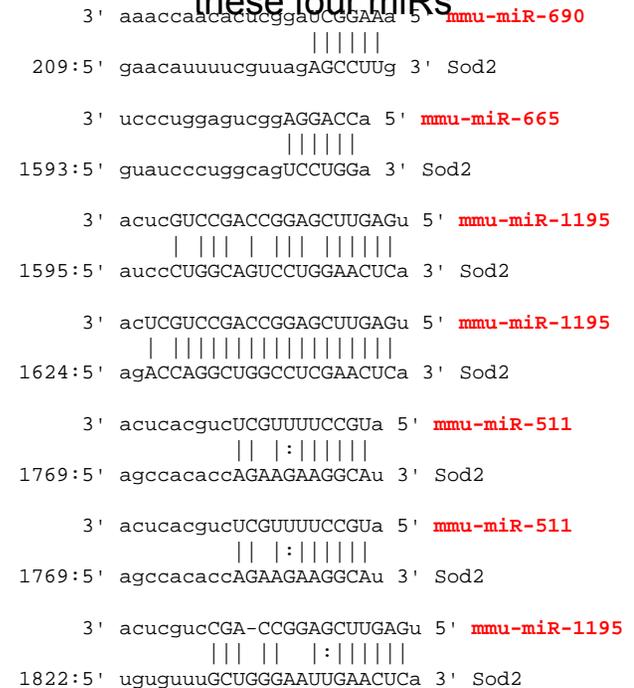
MnSOD signaling network is involved in Low Dose IR adaptive radioprotection.
MnSOD function can be enhanced by mitochondria-relocated Cdks (Cdk1 and 4) to protect against IR injury.

Archival tissue samples are investigated with a custom array of 40 micro RNAs. Four miRs: 665, 690, 1195 and 511 are found in spleens of mice as late as one year after irradiation.

Project 1



Both TNF-alpha and MnSOD are targets of these four miRs



Janus Tissue Archive

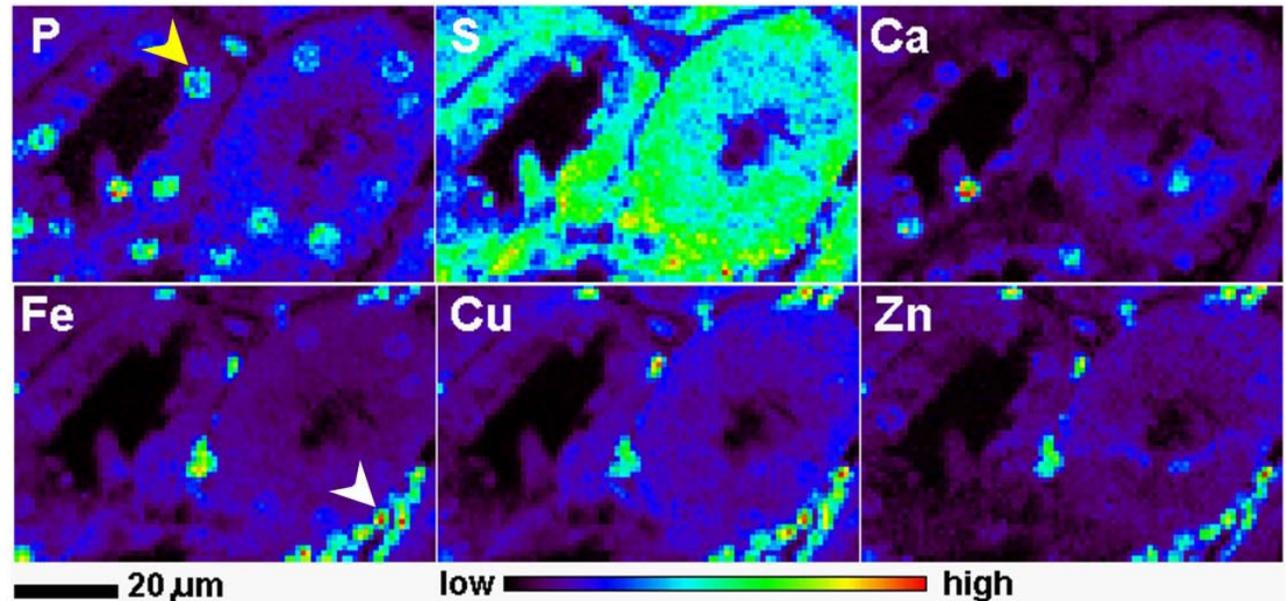
Mega tissue and data archive contains collection of data and tissues from irradiated animals:

- >50,000 mice,
- >10,000 rats
- >17,000 dogs

The data are publicly available at website [//janus.northwestern.edu](http://janus.northwestern.edu)



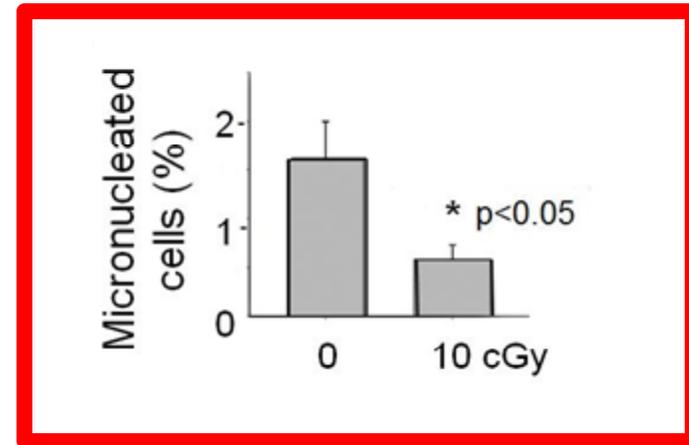
A typical research project includes (1) study of the data archive, (2) selecting the tissues to be sectioned and processing them for (2.a) regular histopathology, (2.b) high throughput X-ray fluorescence elemental microscopy, or (2.c) subjecting them to a variety of molecular analysis techniques focusing on proteins, DNA or micro RNAs.



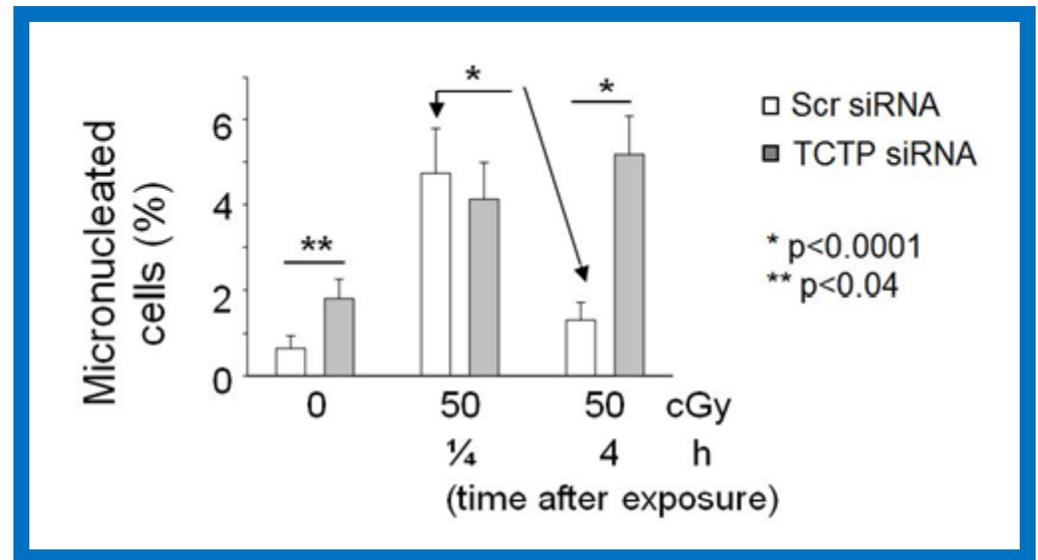
Paunesku T, Wanzer MB, Kirillova EN, Muksinova KN, Revina VS, Lyubchansky ER, Grosche B, Birschwilks M, Vogt S, Finney L, Woloschak GE. X-ray fluorescence microscopy for investigation of archival tissues. *Health Phys.* **2012** 103(2):181-6.

Role of the protein TCTP in DNA damage sensing and repair after low dose exposure

- **Low dose/Low dose-rate gamma-rays reduce DNA damage to a level below the spontaneous rate in normal human cells (protects against micronuclei formation, a marker of DNA damage)**



- **The TCTP protein participates in this protective process through a role in DNA damage sensing and repair (Scrambled vs. TCTP-siRNA knockdown experiment)**

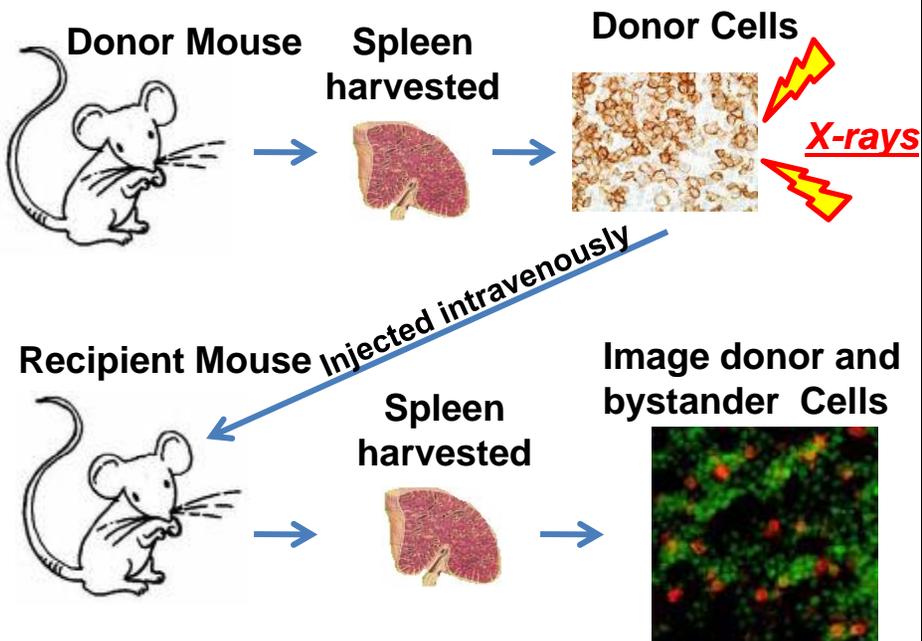
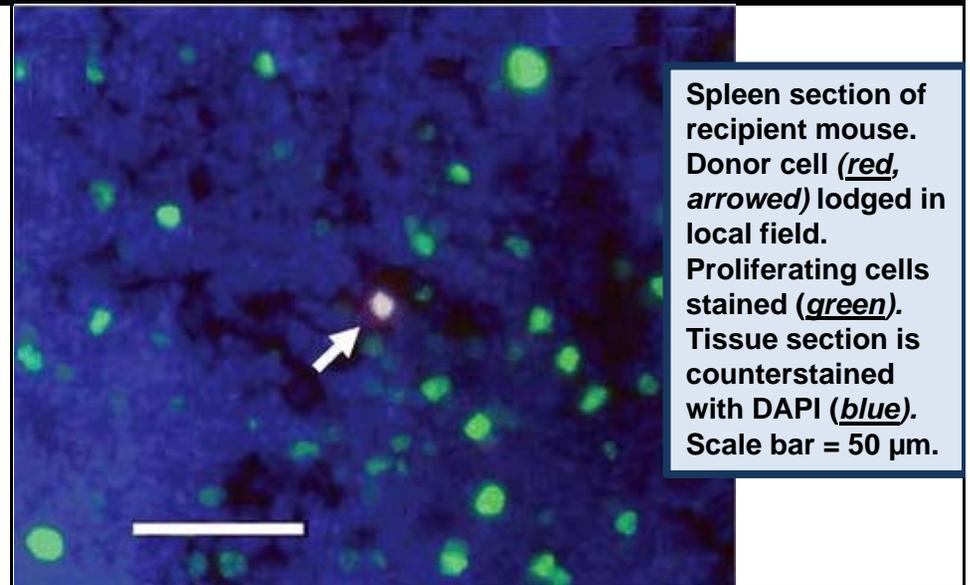


J Zhang, BN Pandev, G Guo, D Pain, H Li, and El Azzam. 2012. "Role of the translationally controlled tumor protein in DNA damage sensing and repair." *PNAS* 109(16):E926-E933.

An Adoptive Transfer Method to Detect Low-Dose Radiation-Induced Bystander Effects *In Vivo*

Objectives

- Develop a method for studying low-dose and low-dose-rate radiation-induced bystander effects *in vivo* in an intact non-irradiated organ of a physiologically normal animal
- Test whether bystander effects are the same as seen in low-dose *in vitro* studies



Results/Impact

- The novel method is robust, reproducible and allows study of variations in exposure time, dose rate, radiation source, etc.
- Neither the local area surrounding lodged donor cells nor the spleen as a whole showed a change in apoptosis or proliferation
- These results suggest that if bystander effects are occurring *in vivo*, they may not pose as large a concern to radiation risk estimation as *in vitro* studies might predict.

(Staudacher, et al., 2010; Blyth and Sykes, 2011)

DNA repair center formation is greater at lower doses than at higher doses

Objective

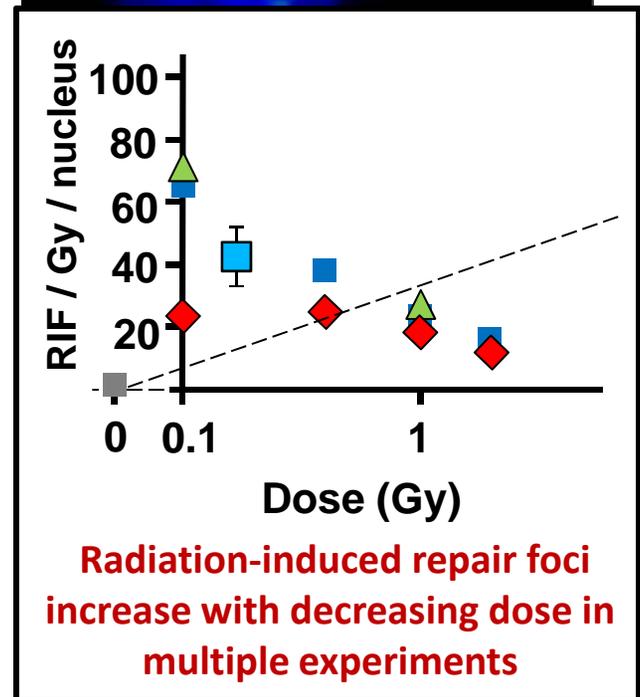
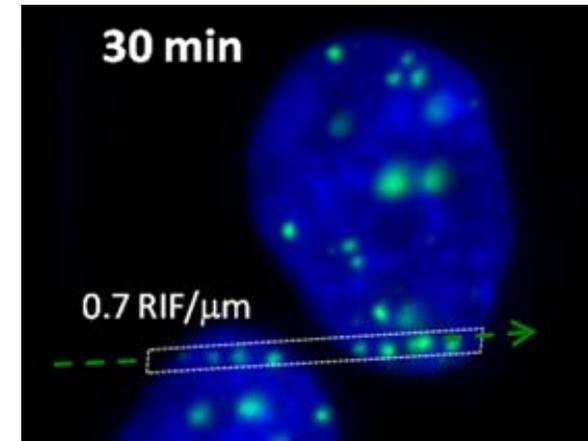
A critical question in radiation biology is how efficiently radiation-induced damage is repaired as a function of dose. This study investigates the kinetics of radiation-induced DNA damage and repair in human cell cultures

Approach

- Human breast epithelial cells were exposed to increasing doses of X-rays or heavy ions
- Cells were immuno-stained for markers of DNA damage forming radiation-induced foci(RIF) in the nucleus after exposure to ionizing radiation: i.e. repair centers

Results/Impact

- The absolute number of repair centers (RIFs) is 3-fold higher at lower doses than at higher doses
- Since there is a set number of DNA breaks per unit dose, we concluded that at low dose there is on average 1 DNA break per RIF whereas at high doses there are 3 breaks per RIF.
 - Complex chromosomal rearrangements (hallmark of cancer) require two breaks in close proximity. Therefore they will primarily or exclusively happen at high doses.
 - DNA damage repair at low radiation doses is more efficient than at higher doses.
- Cancer risk from exposure to ionizing radiation may not be proportional to dose.



Epithelial-to-Mesenchymal Transition is Induced as a Non-Linear Function of Radiation Dose

Objective:

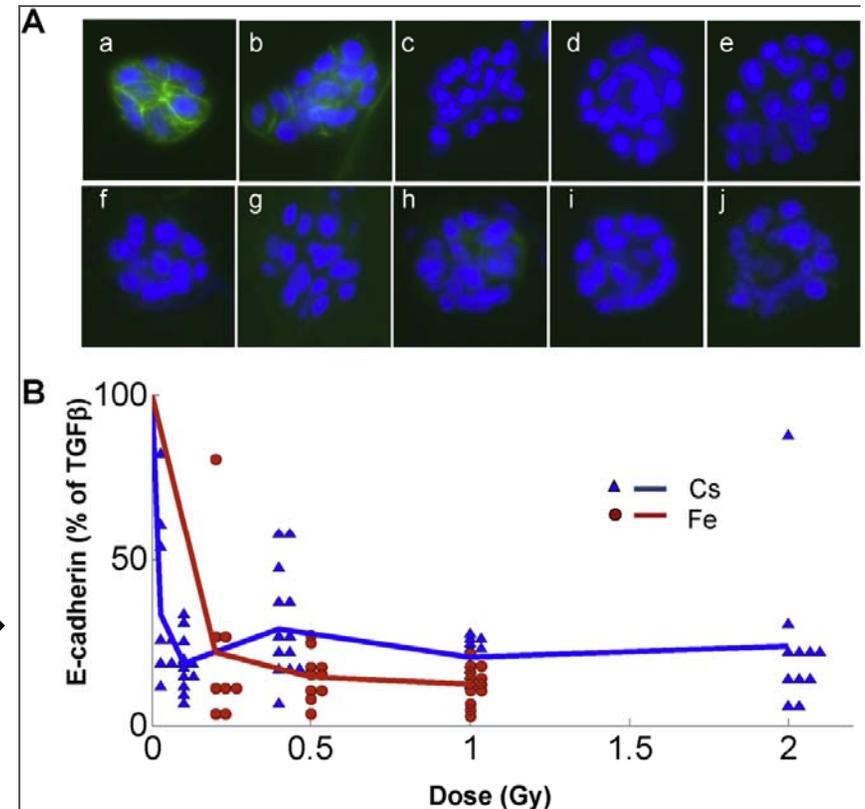
Study the dose-dependent kinetics of a radiation-induced biological effect important in cancer risk by determining whether radiation dose affects the $TGF-\beta$ -mediated epithelial-to-mesenchymal transition (EMT)

Approach:

- Human mammary epithelial cultures were exposed to **cesium gamma-rays** or **high energy iron particles** in the presence of $TGF-\beta$
- **Image analysis** measured membrane-associated EMT markers such as E-cadherin protein

Results/Impact:

- Radiation **acts as a switch** to prime human mammary epithelial cells to undergo $TGF-\beta$ -mediated EMT (- a relatively abrupt transition or threshold, followed by saturation or a plateau)
- These results do not support the LNT model for predicting cancer risks at low doses



Anarawewa K, Costes S, Fernandez-Garcia I, Chou W, Ravani S, Park H, and Barcellos-Hoff MH, 2011. *Int J Radiation Oncology Biol. Phys.*

Cell type dependent gene transcription profiling in a skin tissue model following low dose radiation exposures

Objective: To examine low dose radiation induced temporal responses of an *in vitro* three dimensional human skin tissue model using microarray-based transcriptional profiling.

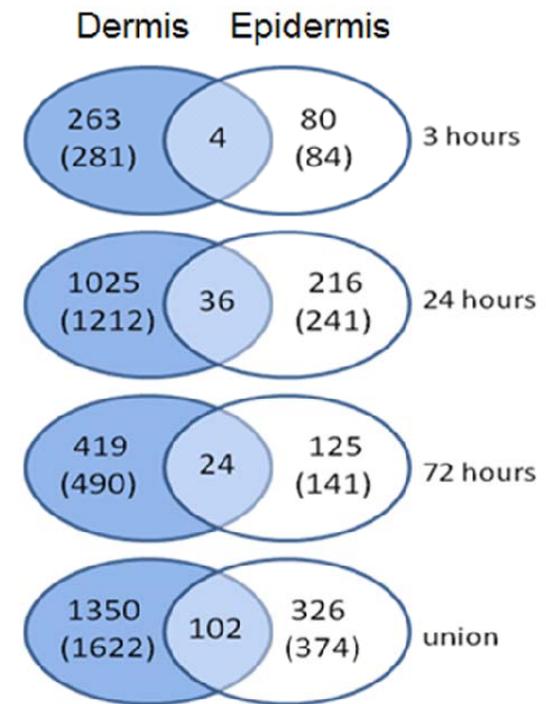
Approach:

- Human skin equivalents were irradiated with 10 cGy of X-rays. Cell type specific temporal changes in the gene expression profile were measured using DNA microarrays and validated using qRT-PCR.
- The effect of low dose radiation exposure on proliferation was correlated with observed changes in gene expression.

Results:

- Exposure to 10 cGy of X-rays regulates key pathways including: cell cycle, DNA damage repair, reactive oxygen signaling, immune responses, wound healing, and individual genes involved in extracellular matrix remodeling
- The induced transcriptional changes are highly context dependent with many more changes occurring in the dermis

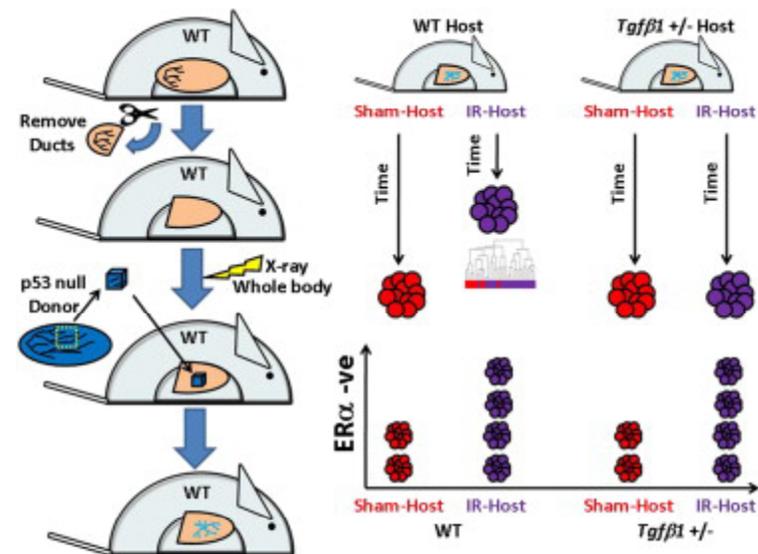
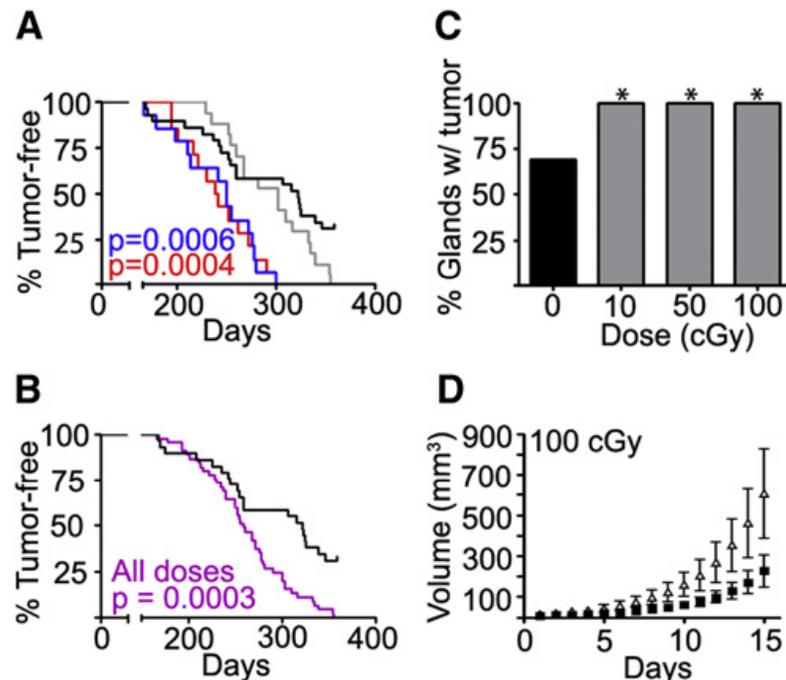
von Neubeck, CH, *et al.*, Environ. Mol. Mut. 53 245-59 (2012)



Venn-diagrams of the number of differentially expressed probes depending on cell context and time

Radiation Acts on the Microenvironment to Affect Breast Carcinogenesis by Distinct Mechanisms

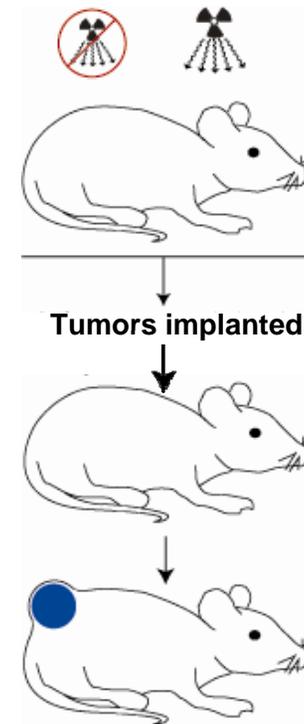
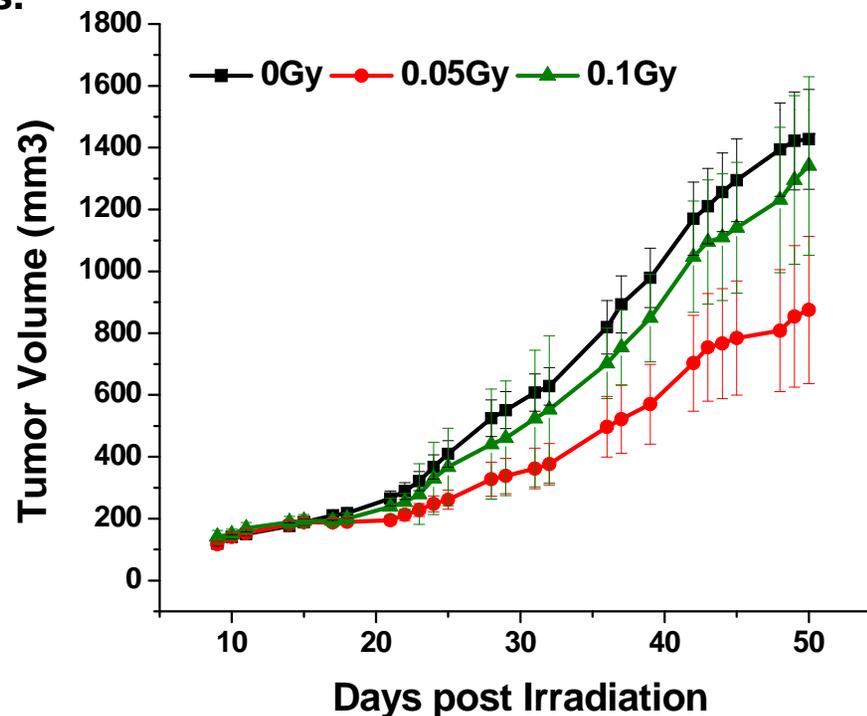
- The mammary gland of host mice is cleared of endogenous epithelium; host is irradiated and then transplanted orthotopically with non-malignant *Trp53 null* mammary tissue
- Tumor latency decreased and tumor growth rate increased with the earlier host irradiation. Unexpectedly, host irradiation also increased the proportion of ER-negative tumors.
- Expression profiles of *Trp53 null* tumors arising in an irradiated host compared to those arising in non-irradiated hosts were distinct, reflecting the biology imposed by radiation on the microenvironment during tumor development
- **Low-dose findings NOT predicted from standard LNT thinking are observed.**
- **Results also demonstrate that radiation does not act ONLY on the initiation step in carcinogenesis.**



Nguyen, N.H et al., Barcellos-Hoff, M.H. (2011). *Cancer Cell* 19, 640-651.

Tumor Progression Shows a Nonlinear Dependence on Prior Low-Dose Whole-Body Irradiation

- Human A549 lung cancer cells were implanted in mice PREVIOUSLY irradiated with acute 0Gy, 0.05Gy and 0.1Gy doses.
- Goal was to determine if prior low-dose irradiation affects tumor progression.
- Low-dose findings NOT predicted from standard LNT thinking are observed.
- Results also demonstrate that radiation does not act ONLY on the initiation step in carcinogenesis.



Summary:

- 1) *The carcinogenesis "Progression" step is significantly inhibited after a single low dose to the host*
- 2) *Not significant for 0.1Gy, showing response is non-linear in dose*