Ionizing Radiation
Dose Ranges
(Rem)

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

Cancer Radiotherapy
total doses to tumor

Whole body, acute: G-I destruction; lung damage; cognitive dysfunction (death certain in 5 to 12 days)*

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

⑥ 0 — 2000 — 4000 — 6000 — 8000 — 10,000 rem

Total Body Irradiation (TBI) Therapy

Acute Radiation Syndromes

Life Span Study (A-bomb survivor epidemiology)

Whole body, acute: circulating blood cell death; moderate G-I damage (death probable 2-3 wks)*

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

Charged particle event (Solar flare) dose on moon, no shielding

Estimated dose for 3-yr Mars mission (current shielding)

⑤ 0 — 200 — 400 — 600 — 800 — 1,000 rem

Early, transient skin erythema (2-24 hr onset)

Temporary epilation (3 wk onset)

Main erythema reaction (10 day onset)

Permanent epilation (3 wk onset)

Human LD_{50} range acute exposure no medical intervention*

Human LD_{50} range acute exposure with medical intervention

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

Cancer Epidemiology

Evidence for small increases in human cancer above 10 rem acute exposure or 20 rem chronic exposure

④ 0 — 10 — 20 — 30 — 40 — 50 — 60 — 70 — 80 — 90 — 100 rem

Typical mission doses on International Space Station (ISS)

Ramsar, Iran high natural bkg/yr

DHS emergency guideline to save a life: 25 rem

Interplanetary Space natural bkg/yr

DOE Low Dose Program

③ 0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10 rem

E F M I N J K G H L

Kerala coast, India high natural bkg/yr

DHS emergency guideline for public relocation: 2 rem/yr (20 mSv/yr)

Guarapari, Brazil high natural bkg/yr

DOE, NRC dose limit for workers: 5 rem/yr (50 mSv/yr)

Typical added annual dose for commercial airline flight crews

Medical Diagnostics (A-O)
see chart >>

② 0 — 100 — 200 — 300 — 400 — 500 — 600 — 700 — 800 — 900 — 1,000 mrem (1 rem)

A B C D E F

Airport x-ray whole body scanner: 0.007 mrem/scan

Natural background, USA average ≈ 310 mrem/yr (includes radon)

Yangjiang, China high natural bkg/yr

Regulations & Guidelines

(Limit = 25 mrem/yr ≈ 4000 scans/yr)

DOE facility releases

① 0 — 10 — 20 — 30 — 40 — 50 — 60 — 70 — 80 — 90 — 100 mrem

A B

Round-trip Los Angeles – New York (≈ 3.7 mrem)

EPA dose limit public drinking water systems: 4 mrem/yr

EPA dose limit from release in air: 10 mrem/yr

NRC cleanup criteria for site decommissioning / unrestricted use: 25 mrem/yr

DOE, NRC dose limit for the public: 100 mrem/yr (1 mSv/yr) (ICRP, NCRP)

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

(TIPS: Transjugular Intrahepatic Porto-systemic Shunt)

LD_{50} = 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
1 rem ≈ 1 rad for x- and gamma-rays
(" ≈ " stands for "approximately equal to")

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

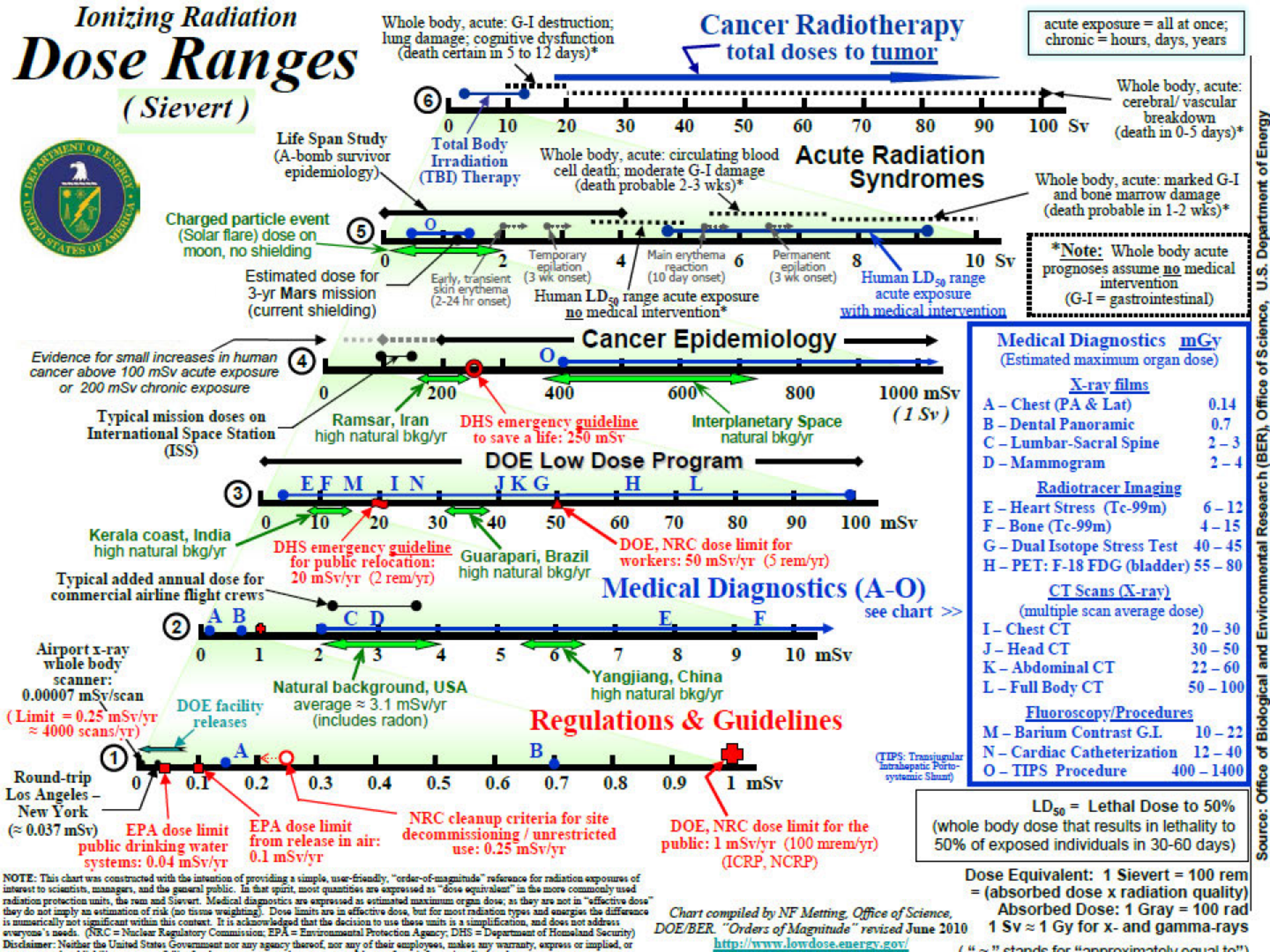
Chart compiled by NF Metting, Office of Science, DOE/BER. "Orders of Magnitude" revised June 2010
http://www.lowdose.energy.gov/

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

(END…)

Ionizing Radiation
Dose Ranges
(Sievert)

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



Medical Diagnostics mGy
(Estimated maximum organ dose)

X-ray films	
A – Chest (PA & Lat)	0.14
B – Dental Panoramic	0.7
C – Lumbar-Sacral Spine	2 – 3
D – Mammogram	2 – 4
Radiotracer Imaging	
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
CT Scans (X-ray) (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
Fluoroscopy/Procedures	
M – Barium Contrast G.I.	10 – 22
N – Cardiac Catheterization	12 – 40
O – TIPS Procedure	400 – 1400

LD_{50} = 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)
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/

("≈" stands for "approximately equal to")

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**
  - Yuan paper – metabolic shift after low dose exposure

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

New Paradigm 2 (b)

Adaptive Response

- 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 TGFβ 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)
  - **Protection by Metabolic Reprogramming**
    - Low dose radiation exposure induces a HIF-1-mediated adaptive and protective metabolic response (Lall, *et al.,* Yuan, 2014)

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)

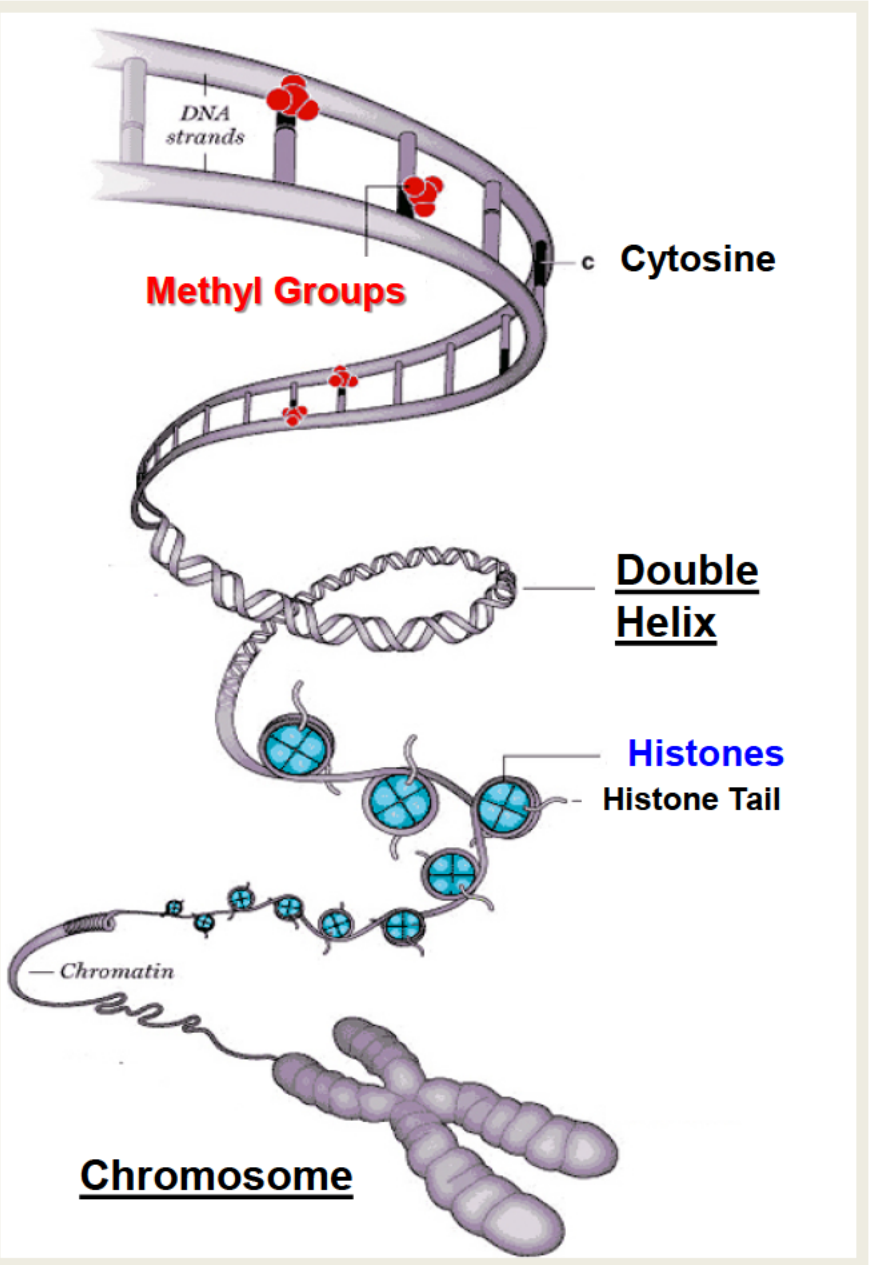
New Paradigm 3 (b)

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

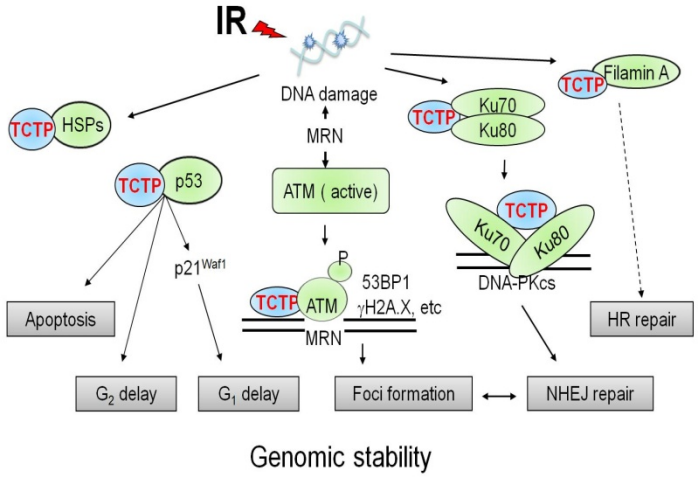
Cell apoptosis

Cell/tissue growth and replacement

Immune system surveillance

(etc.)

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



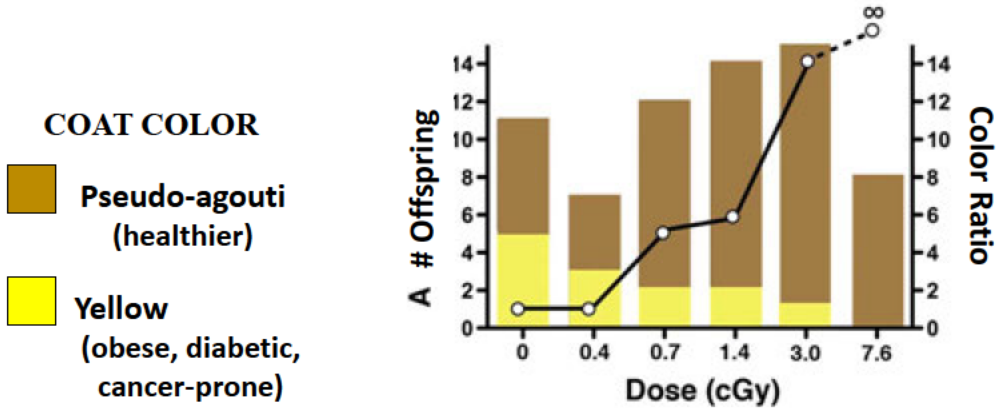
Zhang et al., *PNAS*, 109: E926-33, 2012

Low Dose Science Highlight

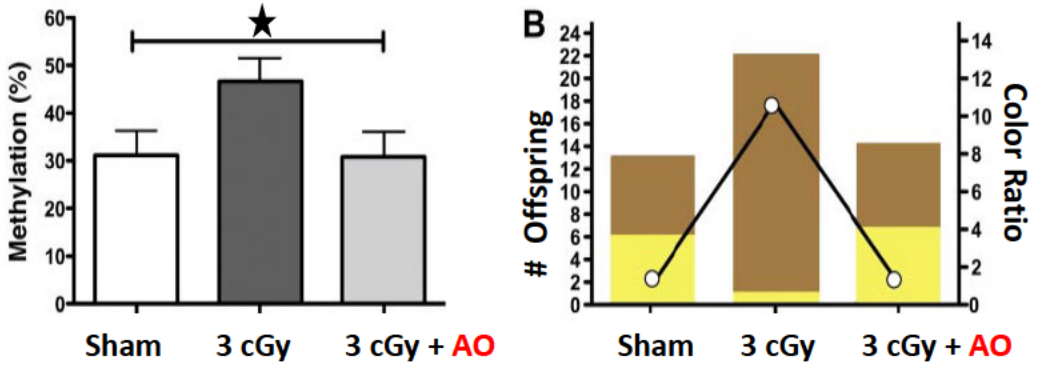
Low dose radiation-induced epigenetic alterations in the A^{vy} yellow agouti mouse model

- Irradiation of pregnant mouse mothers in gestational day 4 increased methylation of agouti gene in the offspring
- DNA sequence of the A^{vy} gene locus was not altered
- Larger numbers of offspring were darker brown as a function of dose, with concomitant better health
- Anti-oxidant supplementation of mouse mothers reduced locus methylation, and the ratio of brown /yellow mice to near control levels
- **Conclusion:** In this isogenic mouse model, low dose-induced epigenetic changes play a role in radiation hormesis

Very low doses of radiation induce epigenetic alterations



Adaptive radiation-induced epigenetic alterations are mitigated by antioxidants (AO)



Bernal, A. J., Dolinoy, D. C., Huang, D., Skaar, D. A., Weinhouse, C., Jirtle, R. J. *Adaptive radiation-induced epigenetic alterations mitigated by antioxidants*. ***FASEB J.*** **27; 665-671 (2013).** www.fasebj.org

Combining Predictive Models with Experiments to Understand Radiation Effects in Skin Tissue

Objective

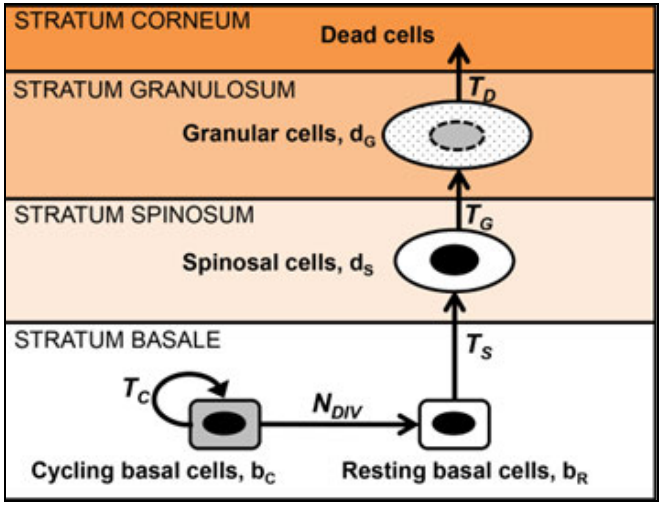
- To understand and predict risks from heavy ion radiation by studying effects on molecular, cellular and tissue-level processes in relevant experimental systems

Approach

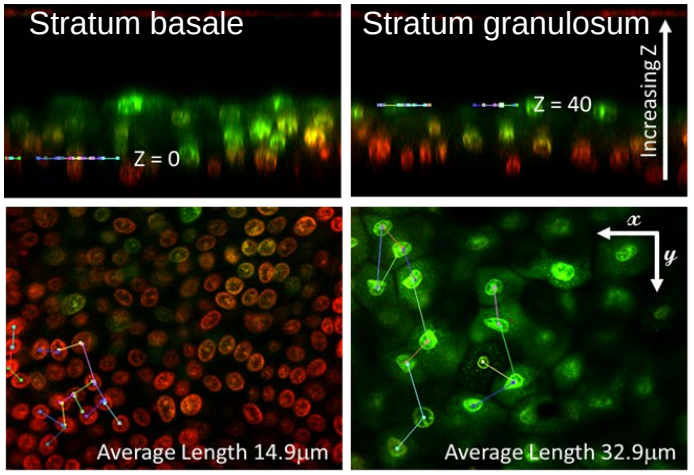
- Engineered 3D human skin tissues were exposed to neon ion irradiation, then several tissue-level properties were measured
- A mathematical model was developed to simulate the complex homeostatic changes in cell division, differentiation, and proliferation that were induced by the neon ion exposures

Impact

- This integrated approach provides a framework to understand responses of multicellular systems and can be adapted to other epithelial tissues and radiation exposure scenarios



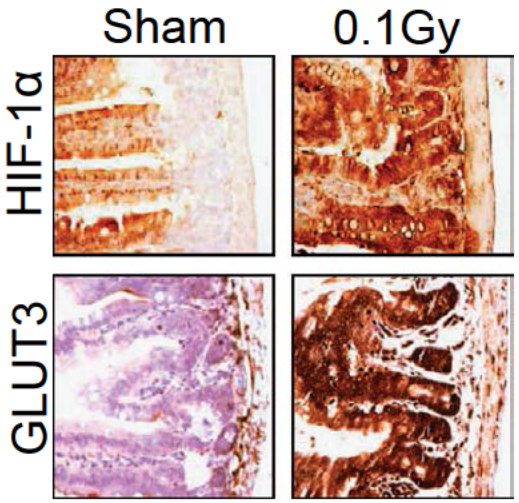
Schematic descriptions of the mathematical models for unirradiated and neon irradiated skin tissue



Confocal images to spatially characterize cell density in the tissue

von Neubeck C, H Shankaran, MJ Geniza, PM Kauer, RJ Robinson, WB Chrisler, and MB Sowa, "Integrated Experimental and Computational Approach to Understand the Effects of Heavy Ion Radiation on Skin Homeostasis." *Integrative Biology* (Accepted).

Low-dose irradiation induces a metabolic shift and radiation resistance *in vivo*

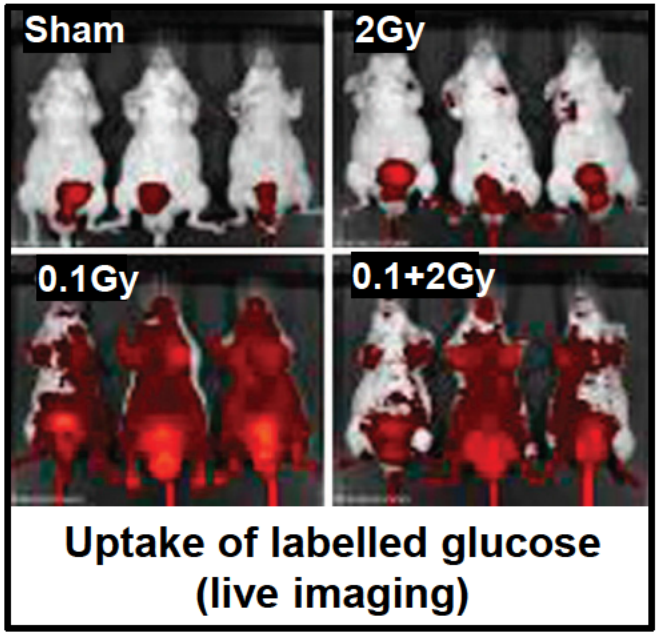


Objective

Studies have shown the existence of adaptive dose–response relationships with low doses being protective and high doses causing detrimental effects. This study addresses a novel metabolic mechanism underlying the adaptive stress response.

Results / Impact

- Treatment of normal human cells with low-dose radiation induces a metabolic shift from oxidative phosphorylation to aerobic glycolysis, resulting in increased radiation resistance.
- Importantly, these findings are also observed systemically in mice.
- This metabolic change represents a previously unknown cellular response to low-dose radiation.

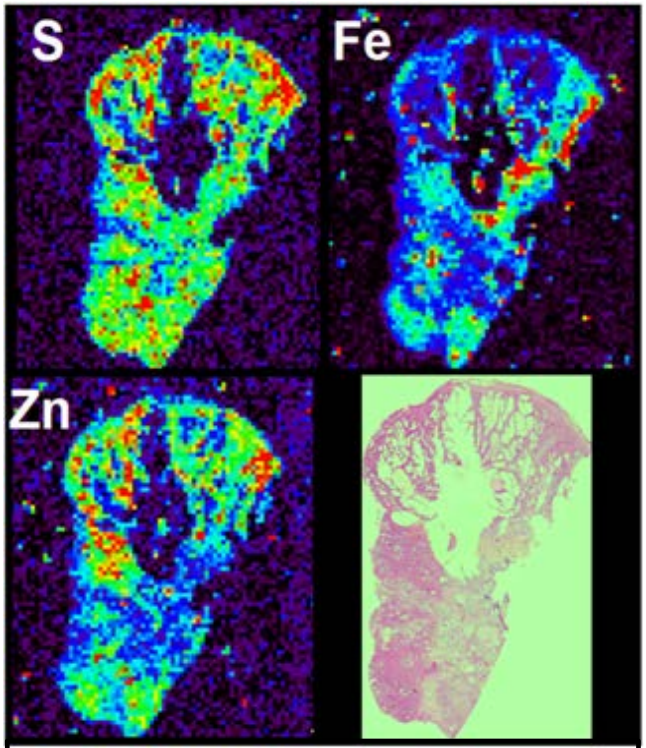


Uptake of labelled glucose (live imaging)

R Lall, *et al.*, Z-M Yuan, "Low-dose radiation exposure induces a HIF-1-mediated adaptive and protective metabolic response", *Cell Death and Differentiation* 28 February 2014; doi:10.1038/cdd.2014.24

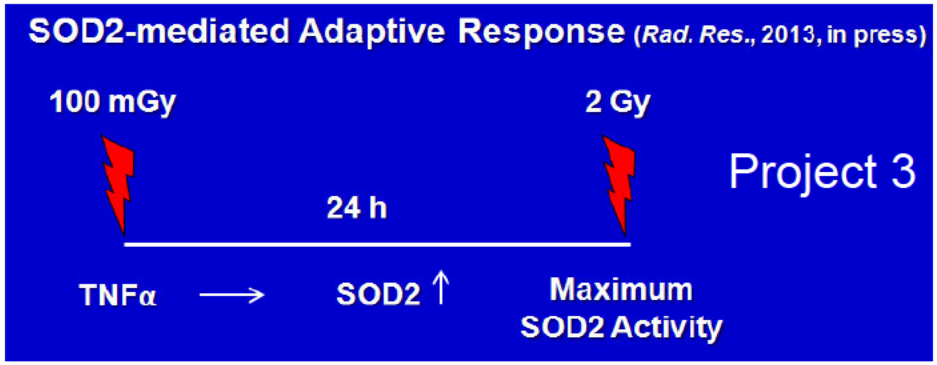
Irradiated Tissue Archives Featured in *Nature*

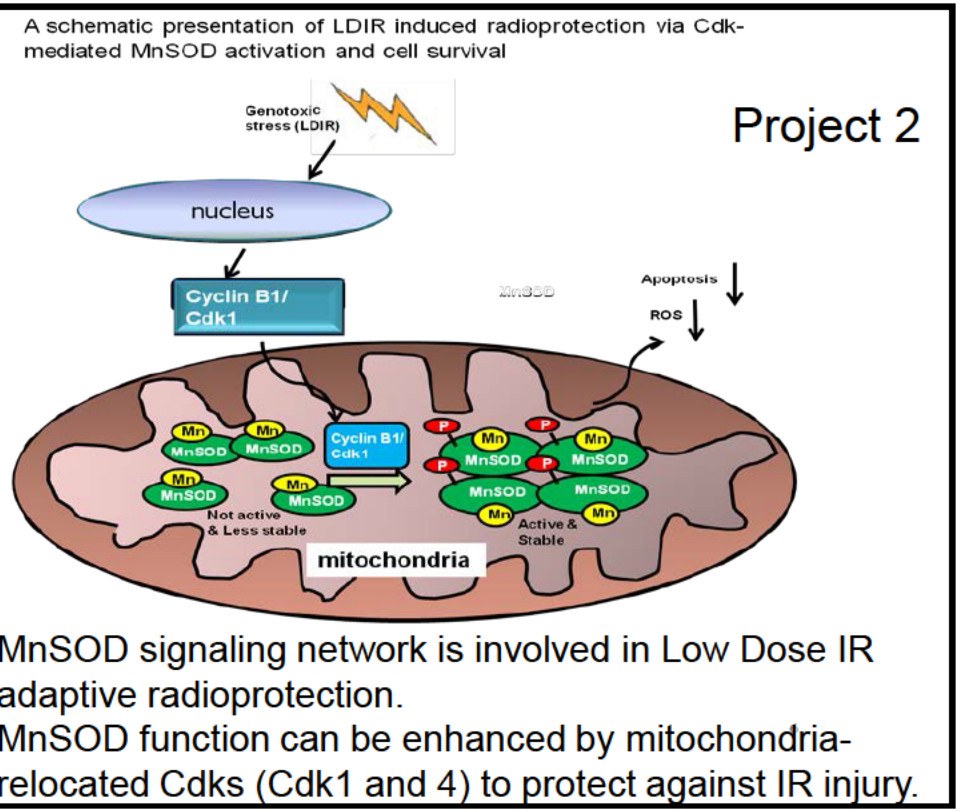
- A recent news article in ***Nature***
- Archived data and materials from radiation studies performed between 1952 and 1992: U.S., Europe, etc….
- Relevance to DOE's Low Dose Program
- "**Radiation risks: Raiders of the lost archive**"
- Quoted in the article: Dr. Gayle Woloschak, Professor at Northwestern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



X-ray fluorescence microscopy of dog prostate tissue

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





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.

Project 1

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.

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

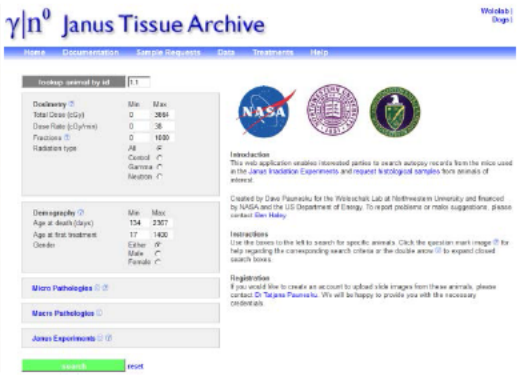
```
     3' aaaccaacactcggaUCGGAAa 5' mmu-miR-690
                       ||||||
209:5' gaacauuuucguuagAGCCUUg 3' Sod2

     3' ucccuggagucggAGGACCa 5' mmu-miR-665
                      ||||||
1593:5' guaucccuggcagUCCUGGa 3' Sod2

     3' acucGUCCGACCGGAGCUUGAGu 5' mmu-miR-1195
         | ||| | ||| ||||||
1595:5' auccCUGGCAGUCCUGGAACUCa 3' Sod2

     3' acUCGUCCGACCGGAGCUUGAGu 5' mmu-miR-1195
       | ||||||||||||||||||
1624:5' agACCAGGCUGGCCUCGAACUCa 3' Sod2

     3' acucacgucUCGUUUUCCGUa 5' mmu-miR-511
               || |:||||||
1769:5' agccacaccAGAAGAAGGCAu 3' Sod2

     3' acucacgucUCGUUUUCCGUa 5' mmu-miR-511
               || |:||||||
1769:5' agccacaccAGAAGAAGGCAu 3' Sod2

     3' acucgucCGA-CCGGAGCUUGAGu 5' mmu-miR-1195
              ||| ||  |:||||||
1822:5' uguguuuGCUGGGAAUUGAACUCa 3' Sod2
```

Janus Tissue Archive

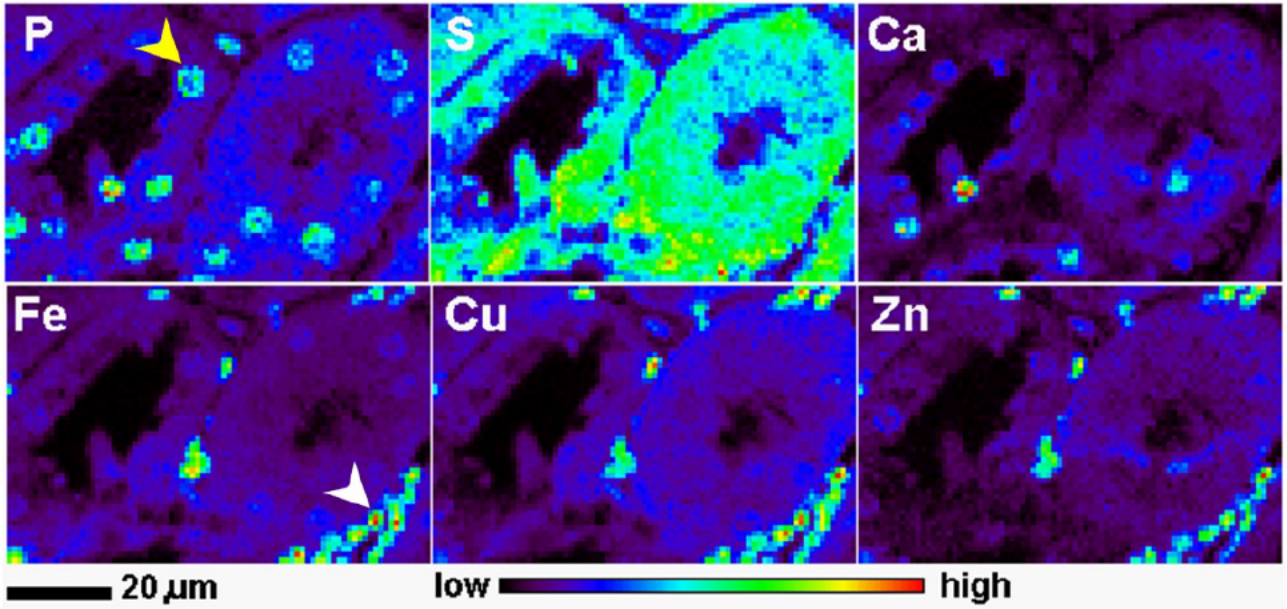
Mega tissue and data archive contains collection of data and tissues from irradiated animals:

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

The data are publicly available at website
//janus.northwestern.edu



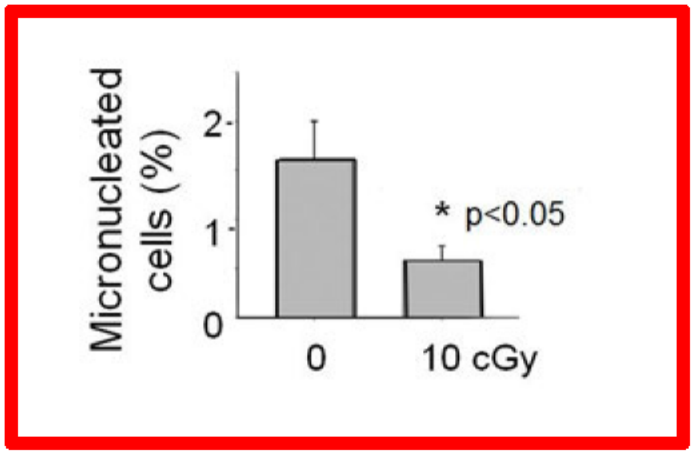
A typical research project includes (1) study of the data archive, (2) selecting the tissues to be sectioned and processing them for (2.a) regular histopathology, (2.b) high throughput X-ray fluorescence elemental microscopy, or (2.c) subjecting them to a variety of molecular analysis techniques focusing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



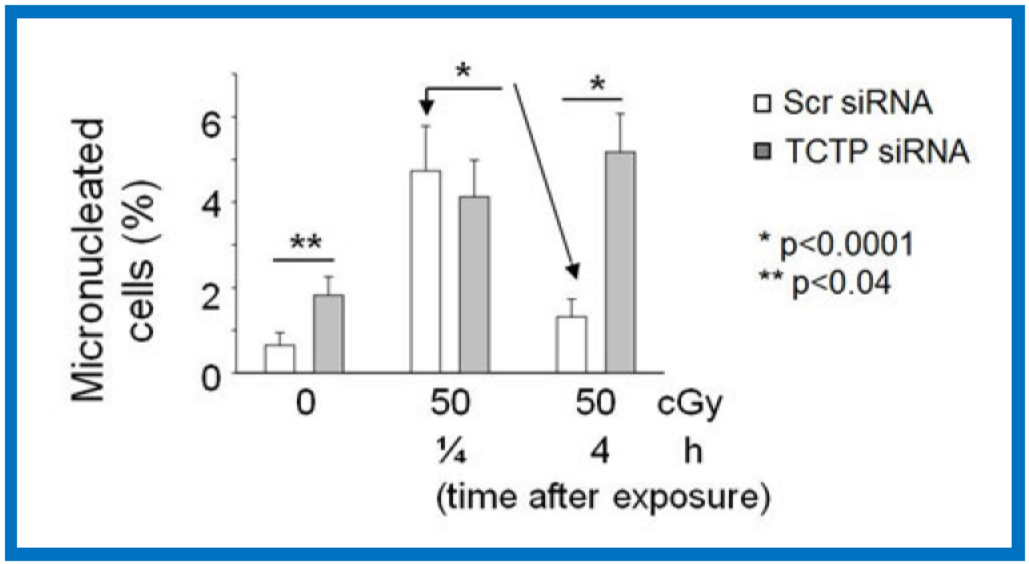
Paunesku T, Wanzer MB, Kirillova EN, Muksinova KN, Revina VS, Lyubchansky ER, Grosche B, Birschwilks M, Vogt S, Finney L, Woloschak GE. X-ray fluorescence microscopy for investigation of archival tissues. *Health Phys*. **2012** 103(2):181-6.

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** (10 cGy exposure 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)**

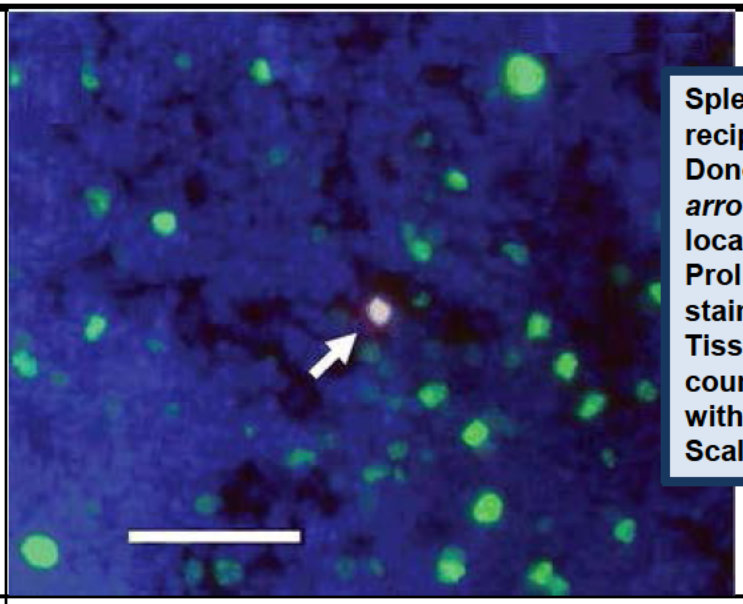


J Zhang, BN Pandev, G Guo, D Pain, H Li, and EI Azzam. **2012.** "Role of the translationally controlled tumor protein in DNA damage sensing and repair." ***PNAS*** 109(16):E926-E933.

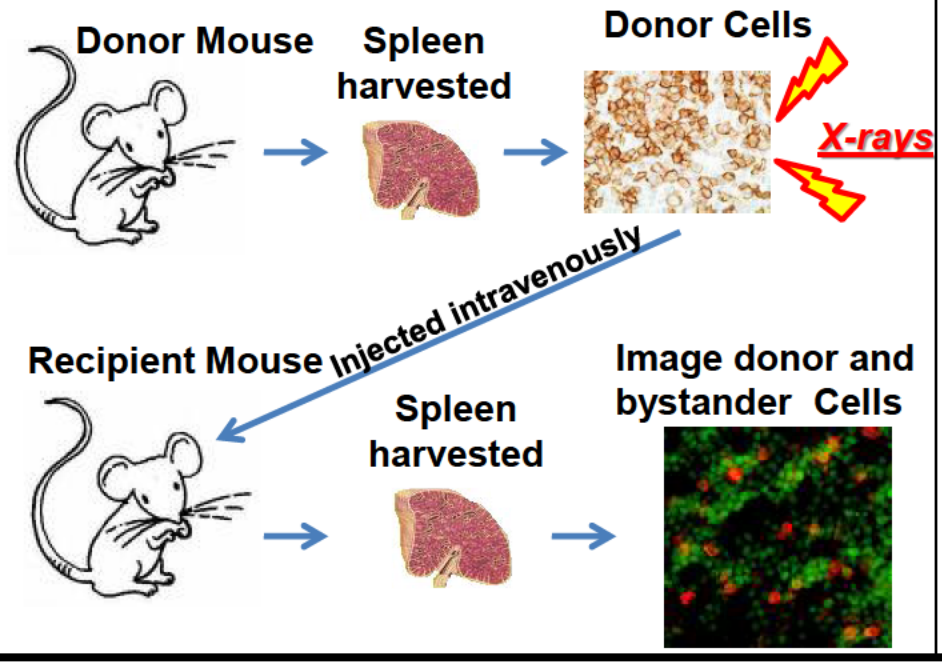
An Adoptive Transfer Method to Detect Low-Dose Radiation-Induced Bystander Effects *In Vivo*

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



Spleen section of recipient mouse. Donor cell *(red, arrowed)* lodged in local field. Proliferating cells stained *(green)*. Tissue section is counterstained with DAPI *(blue)*. Scale bar = 50 µm.



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

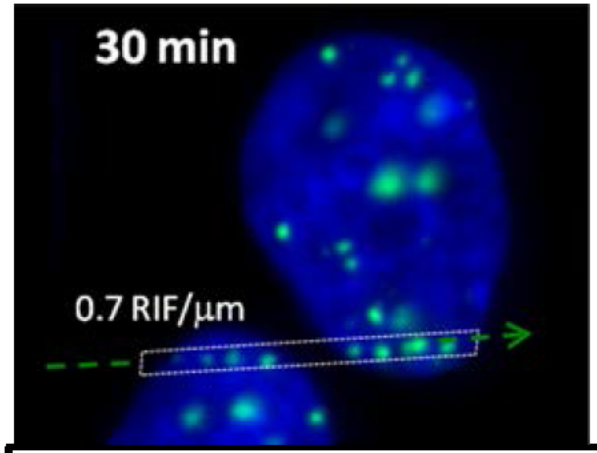
A critical question in radiation biology is how efficiently radiation-induced damage is repaired as a function of dose. This study investigates the kinetics of radiation-induced DNA damage and repair in human cell cultures

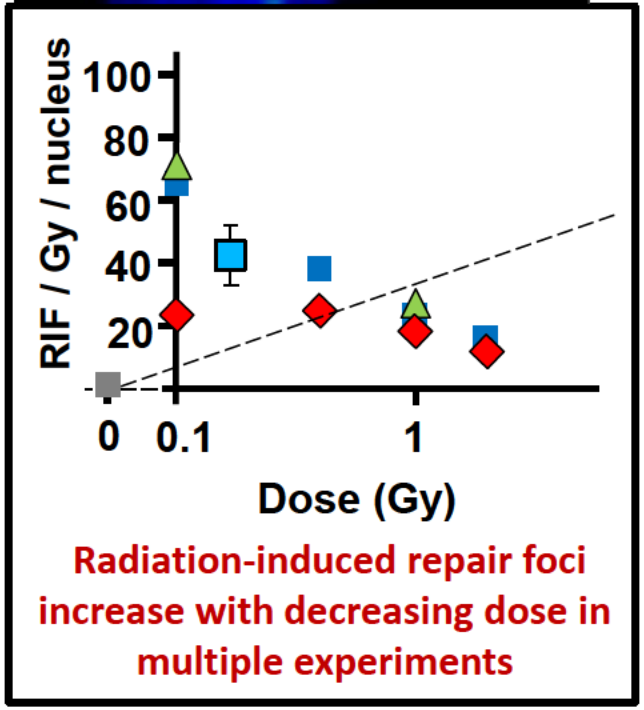
Approach

- 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.





Radiation-induced repair foci increase with decreasing dose in multiple experiments

Neumaier, et al. *2011, Evidence for formation of DNA repair centers and dose-response nonlinearity in human cells.* ***Proc Natl Acad Sci.*** doi: 10.1073/pnas.1117849108

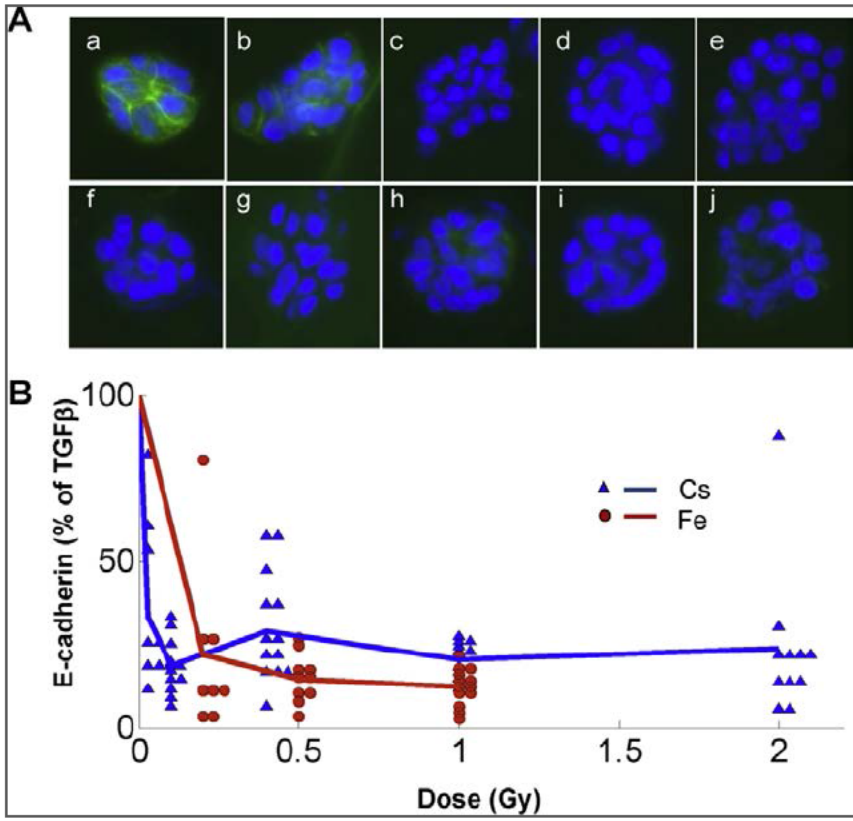
Epithelial-to-Mesenchymal Transition is Induced as a Non-Linear Function of Radiation Dose

Objective:

Study the dose-dependent kinetics of a radiation-induced biological effect important in cancer risk by determining whether radiation dose affects the *TGF*-β–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*-β
- **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-β-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

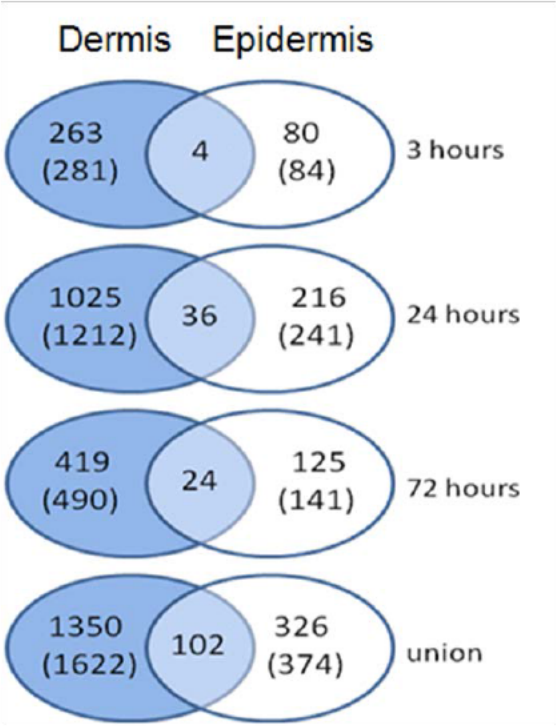
Anarawewa K, Costes S, Fernandez-Garcia I, Chou W, Ravani S, Park H, and Barcellos-Hoff MH, **2011**. ***Int J Radiation Oncology Biol. Phys.***

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.



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

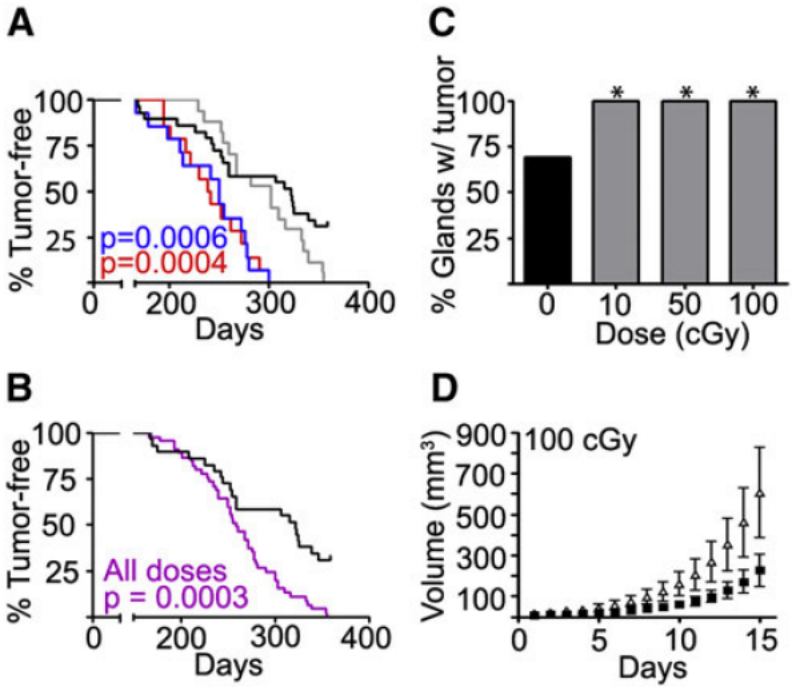
Results:

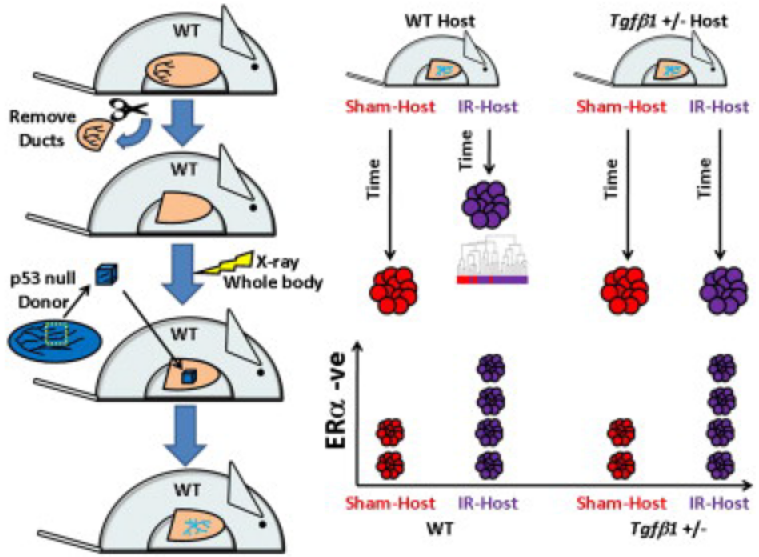
- Exposure to 10 cGy of X-rays regulates key pathways including: cell cycle, DNA damage repair, reactive oxygen signaling, immune responses, wound healing, and individual genes involved in extracellular matrix remodeling
- The induced transcriptional changes are highly context dependent with many more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

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

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.**

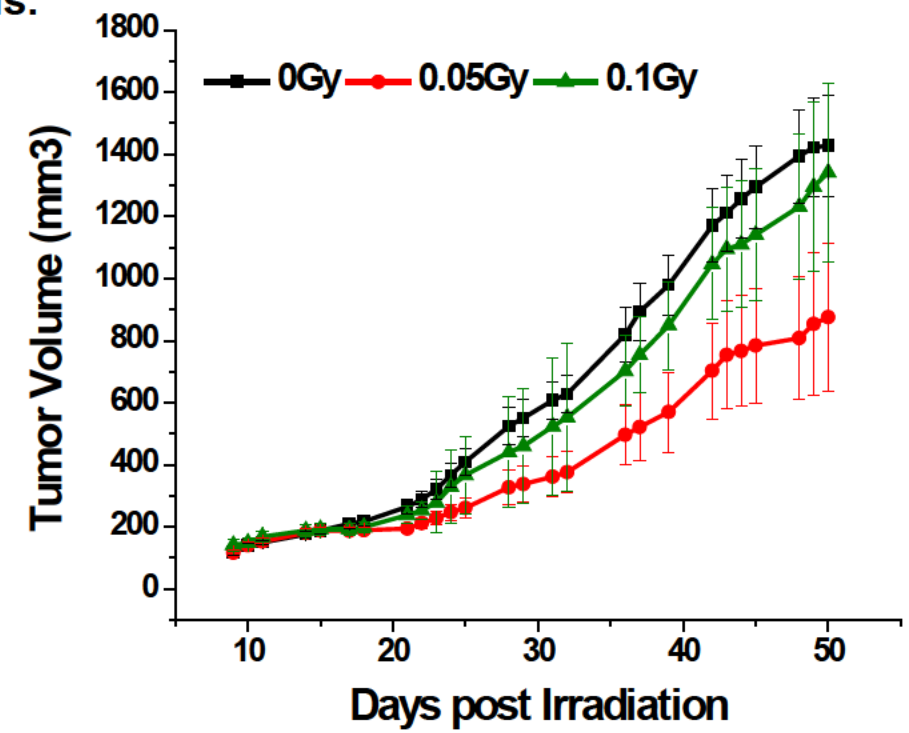


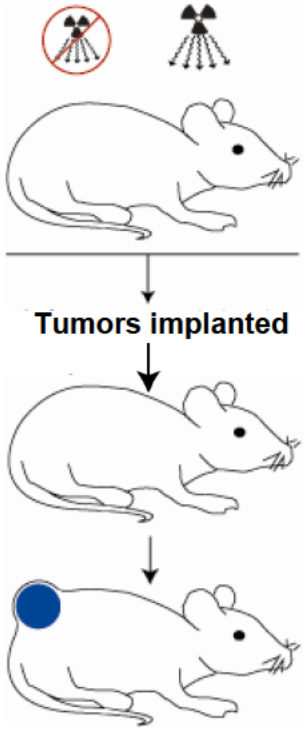


Nguyen, N.H et al., Barcellos-Hoff, M.H. **(2011)**. **Cancer Cell** 19, 640-651.

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.**



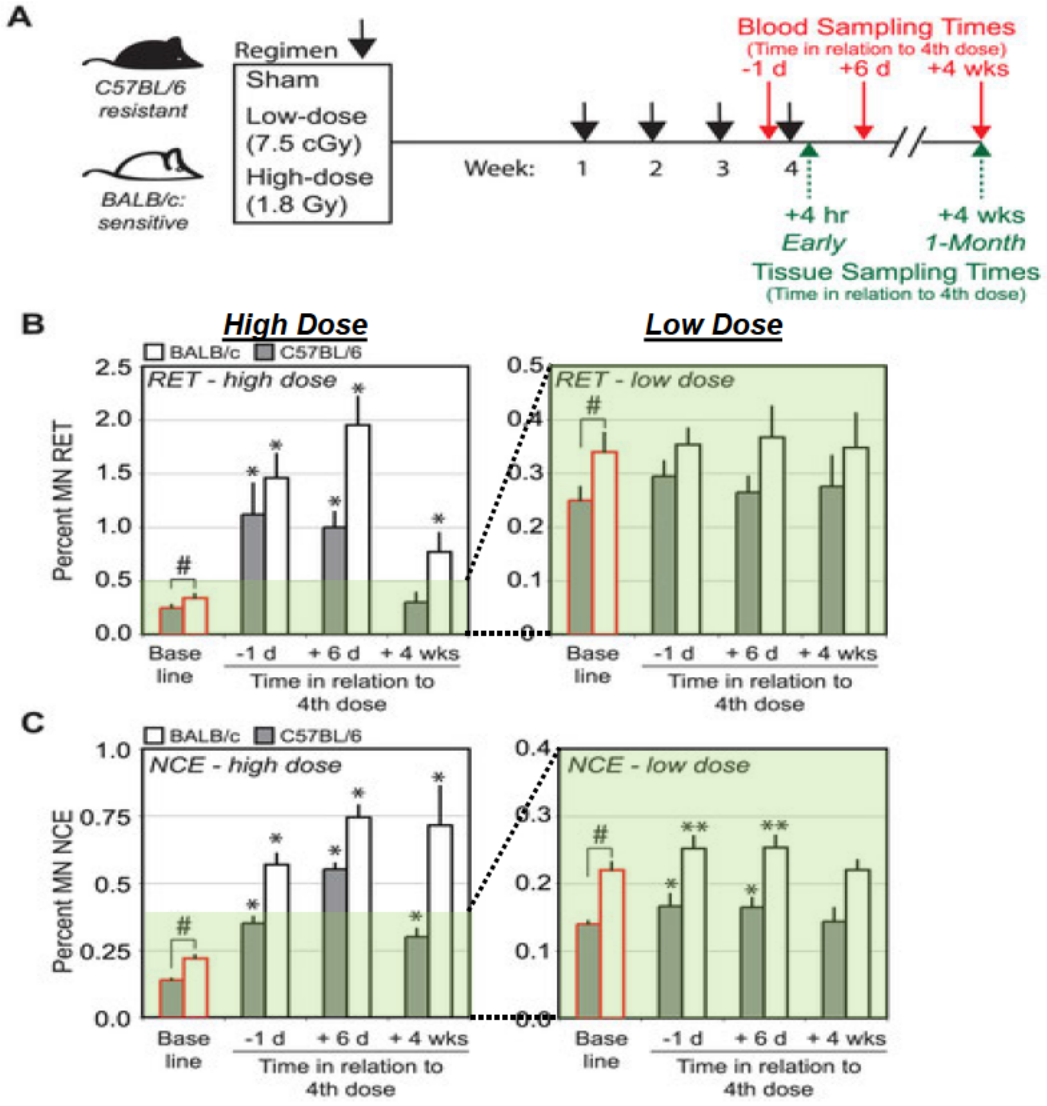


Summary:

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*

Hlatky, private communication

Radiation induced micronuclei in erythrocytes of mice that differ in low dose-induced mammary cancer sensitivity.



Snijders AM, Marchetti F, Bhatnagar S, Duru N, et al. (2012) Genetic Differences in Transcript Responses to Low-Dose Ionizing Radiation Identify Tissue Functions Associated with Breast Cancer Susceptibility. PLoS ONE 7(10): 2012.
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0045394

From: Anderson, Todd
To: Metting, Noelle
Cc: Carruthers, Julie; Huerta, Marcos; Weatherwax, Sharlene
Subject: RE: Update slides
Date: Thursday, October 16, 2014 9:04:00 AM
Attachments: Update Oct 2014.pdf

Noelle,

For brevity, I think we could drop slides 14-15 and 20-22 and still have a good snapshot of the program history and current status. Also, I think everything past slide 25 we could delete bring as a separate backup, if needed.

Also, (slide 4) while I know that many DOE entities would certainly be impacted by a change in radiation protection standards if EPA moved in that direction, NE is the only entity that I know of that has engaged in any substantive dialog with SC about the Low Dose Program.

Also, has the US citizenry been asking for a relaxation of EPA rad protection standards? I suspect not.

I'm copying everyone on this since we will be making modifications to this presentation quickly this morning.

Thanks

Todd

From: Metting, Noelle
Sent: Wednesday, October 15, 2014 6:15 PM
To: Anderson, Todd
Subject: Update slides

Todd,

Here is the update. I still think it is overburdened with science, and unneeded slides, but please take a look. I assume we can change things tomorrow.

Thanks,

Noelle

NF Metting, Sc.D.

Program Manager

Sr. Radiation Biologist

Office of Science/BER

U.S. Department of Energy

Voice: 301-903-8309

Fax: 301-903-0567

noelle.metting@science.doe.gov

<< File: Update Oct 2014.pdf >>

From:	Weatherwax, Sharlene
To:	Anderson, Todd
Cc:	Riches, Mike
Subject:	RE: HR5544
Date:	Thursday, October 09, 2014 2:30:52 PM

That's why you need to brief the Senate folks so they don't develop their own bill. These are technically different staffers than the ones who introduced the bill. Yes, when it was officially introduced it had sponsors.

From: Anderson, Todd
Sent: Thursday, October 09, 2014 2:29 PM
To: Weatherwax, Sharlene
Cc: Riches, Mike
Subject: FW: HR5544

Hmm, new bill now has sponsors.

Note language of within funds support for Lose Dose.

Todd

From: Metting, Noelle
Sent: Thursday, October 09, 2014 2:18 PM
To: Anderson, Todd
Subject: HR5544

Hi Todd,

Today is the first I have heard of House Bill HR5544, introduced 19 Sep. No wonder the staffers want an update.

Noelle

Voice: 301-903-8309

Fax: 301-903-0567

noelle.metting@science.doe.gov

<< File: BILLS-113hr5544ih.pdf >>

From: Anderson, Todd
To: Metting, Noelle
Subject: RE: HR5544
Date: Thursday, October 09, 2014 2:27:00 PM

Hmm, me too. It looks like it was prepared from a similar bill that was floating around this committee for about a year now. Except now it has sponsors.

From: Metting, Noelle
Sent: Thursday, October 09, 2014 2:18 PM
To: Anderson, Todd
Subject: HR5544

Hi Todd,

Today is the first I have heard of House Bill HR5544, introduced 19 Sep. No wonder the staffers want an update.

Noelle

Voice: 301-903-8309

Fax: 301-903-0567

noelle.metting@science.doe.gov

<< File: BILLS-113hr5544ih.pdf >>

From: Carruthers, Julie
To: Dehmer, Patricia
Subject: low dose briefing to hill staffers...
Date: Thursday, October 16, 2014 7:09:00 PM

Noelle did not stick to the discussed scope of the briefing.
Todd is going to write up a summary of the meeting for you and Sharlene, including the discussion that followed after the staffers left, which was highly inflammatory.

Julie Carruthers, Ph.D.
Senior Science and Technology Advisor
Office of Science
U.S. Department of Energy
1000 Independence Ave., SW
Washington, DC 20585
(202) 586-1308

From:	Anderson, Todd
To:	Weatherwax, Sharlene
Subject:	RE: Metting Proposal
Date:	Wednesday, December 03, 2014 2:52:00 PM

Yup. Checking with Rich about today.

From: Weatherwax, Sharlene
Sent: Wednesday, December 03, 2014 2:51 PM
To: Anderson, Todd
Subject: RE: Metting Proposal

We have interviews on Friday. Cannot do it then.

From: Anderson, Todd
Sent: Wednesday, December 03, 2014 2:49 PM
To: Weatherwax, Sharlene
Subject: RE: Metting Proposal

…thinking similarly.

Always knew this would come in at an inconvenient time. Let me check with Rich about today.

From: Weatherwax, Sharlene
Sent: Wednesday, December 03, 2014 2:47 PM
To: Anderson, Todd
Subject: RE: Metting Proposal

I think Friday just puts us another day out, and you and I are not in all next week.

From: Anderson, Todd
Sent: Wednesday, December 03, 2014 2:46 PM
To: Weatherwax, Sharlene
Subject: RE: Metting Proposal

Or Friday morning. Tomorrow is awful with the party and All Hand's meeting.
Not sure if Rich is prepared for today but I could ask.

From: Weatherwax, Sharlene
Sent: Wednesday, December 03, 2014 2:43 PM
To: Anderson, Todd
Subject: FW: Metting Proposal

Should we do it today? Tomorrow is the holiday party--awkward

From: Drury, Rich (CONTR)
Sent: Wednesday, December 03, 2014 2:27 PM
To: Anderson, Todd
Cc: Weatherwax, Sharlene
Subject: Metting Proposal

Todd,

I have an approved final letter back from OGC. I would suggest we deliver it tomorrow if that works for you logistically. Feasible?

Rich

Richard Drury
Senior Advisor, Chickasaw Advisory Services, LLC
Contractor to DOE Office of Science, SC-48
Room E-159, 19901 Germantown Rd
Germantown, MD 20874
Richard.Drury@science.doe.gov
(301) 903-0392/office ◆ 240-422-0079/mobile

From: Carruthers, Julie
To: Huerta, Marcos
Subject: RE: low dose radiation
Date: Tuesday, October 14, 2014 3:18:00 PM

Yes. Adam is the only one that has communicated with directly with us on specific details of the proposed provision.

If you recall, the majority invited Pat to testify on an SC reauthorization hearing and never specifically asked about this provision during the hearing or in the QFRs.

Julie Carruthers, Ph.D.
Senior Science and Technology Advisor
Office of Science
U.S. Department of Energy
1000 Independence Ave., SW
Washington, DC 20585
(202) 586-1308

-----Original Message-----
From: Huerta, Marcos
Sent: Tuesday, October 14, 2014 3:15 PM
To: Carruthers, Julie
Subject: RE: low dose radiation

So who in HSST did we tell we were not excited about a low dose authorization? Just adam? Or did we send this to the majority as well?

-----Original Message-----
From: Carruthers, Julie
Sent: Tuesday, October 14, 2014 3:03 PM
To: Huerta, Marcos
Subject: RE: low dose radiation

Sorry, hit send to soon...left detail unfinished

Yes, Janine should probably know our position (for her information).

1. We had communicated to the HSST several on several occasions when this language was part of the their broader COMPETES Act reauthorization bill that we were not supportive of this emphasis on the low dose program and that follow-on responsibility for further research really belonged to other agencies (EPA and NIH), and that the Academies, which has dedicated Board on this topic, has a self-interest in getting continued Federal funding for additional studies. They were not responsive to our views, noting that some Members like this stuff.

2. When Adam approached us with his stand alone bill this summer, we discussed it internally, and decided because we were categorically against the entire bill, that we would just have Clarence communicate back to Adam that we had no comments.

Our hope is that an in-person meeting will allow us the opportunity to explain to the staff in person our concerns with going forward with this bill. Even though we have communicated these views before, it's new staff on both the House and Senate sides so we see this as an opportunity to educated them.

-Julie

Julie Carruthers, Ph.D.
Senior Science and Technology Advisor
Office of Science
U.S. Department of Energy
1000 Independence Ave., SW
Washington, DC 20585
(202) 586-1308

-----Original Message-----
From: Huerta, Marcos
Sent: Tuesday, October 14, 2014 2:45 PM
To: Carruthers, Julie
Subject: FW: low dose radiation

I recall we had no comments on this to send back to Adam back in Sept/August. Anything about it I should let CI know?

-----Original Message-----
From: Benner, Janine [mailto:Janine.Benner@Hq.Doe.Gov]
Sent: Tuesday, October 14, 2014 2:34 PM
To: Huerta, Marcos
Subject: low dose radiation

FYI, below is the text of legislation introduced last month calling for a National Academy of Sciences study assessing the current status and development of a long-term strategy for low dose radiation research. Were you aware of this? I'm told that maybe Clarence spoke to you about it but I didn't get his notes. Looks pretty innocuous, but would like to know whether it's something that BER supports.

[Congressional Bills 113th Congress]
[From the U.S. Government Printing Office] [H.R. 5544 Introduced in House (IH)]

113th CONGRESS
2d Session

H. R. 5544

To increase the understanding of the health effects of low doses of ionizing radiation.

IN THE HOUSE OF REPRESENTATIVES

September 18, 2014

Mr. Broun of Georgia (for himself, Mr. Smith of Texas, Mr. Bucshon, Mr. Johnson of Ohio, and Mr. Collins of New York) introduced the following bill; which was referred to the Committee on Science, Space, and Technology

---