Current Topics in the Field of Low Dose Radiation Biology

Environmental Radiological Assistance Directory (ERAD) Webinar

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Abstract

The field of low dose radiation biology focuses on biological responses to radiation exposures that are at or near current workplace exposure limits. It was not until the advent of molecular biology that low dose effects could even be measured. Until recently, most molecular studies of radiation effects were carried out using an isolated cell type in monolayer culture, and the responses of those cells were then extrapolated to mammalian tissues and whole organisms. New research indicates that fundamentally different cellular and molecular responses can occur as a function of the level of biological organization (cells, tissues, whole organisms), and that normal, intact tissue responds, in general, differently to radiation than do single cells or monoculture cell populations. Responses of special interest include radio-adaptive responses, systems genetics of inter-individual variation, and low dose and/or low dose-rate effects on proteomic and metabolic responses, the immune system, and epigenetic regulation. Recent progress on several of these topics will be presented.

My Background…

Noelle F. Metting

- Radiation Biologist, U.S. Department of Energy, Office of Science
  - **Manager, DOE's Low Dose Radiation Research Program** (2000-14)
  - Currently on detail to Office of Environment, Health, Safety, and Security, Office of Public Radiation Protection (AU-22)

Education

Sc.D. (1994) **Doctor of Science** (Cancer Biology), Harvard University, Boston, MA; Doctoral dissertation: *"Studies of Radiation-Induced Mutagenesis and Cell Cycle Perturbation"*

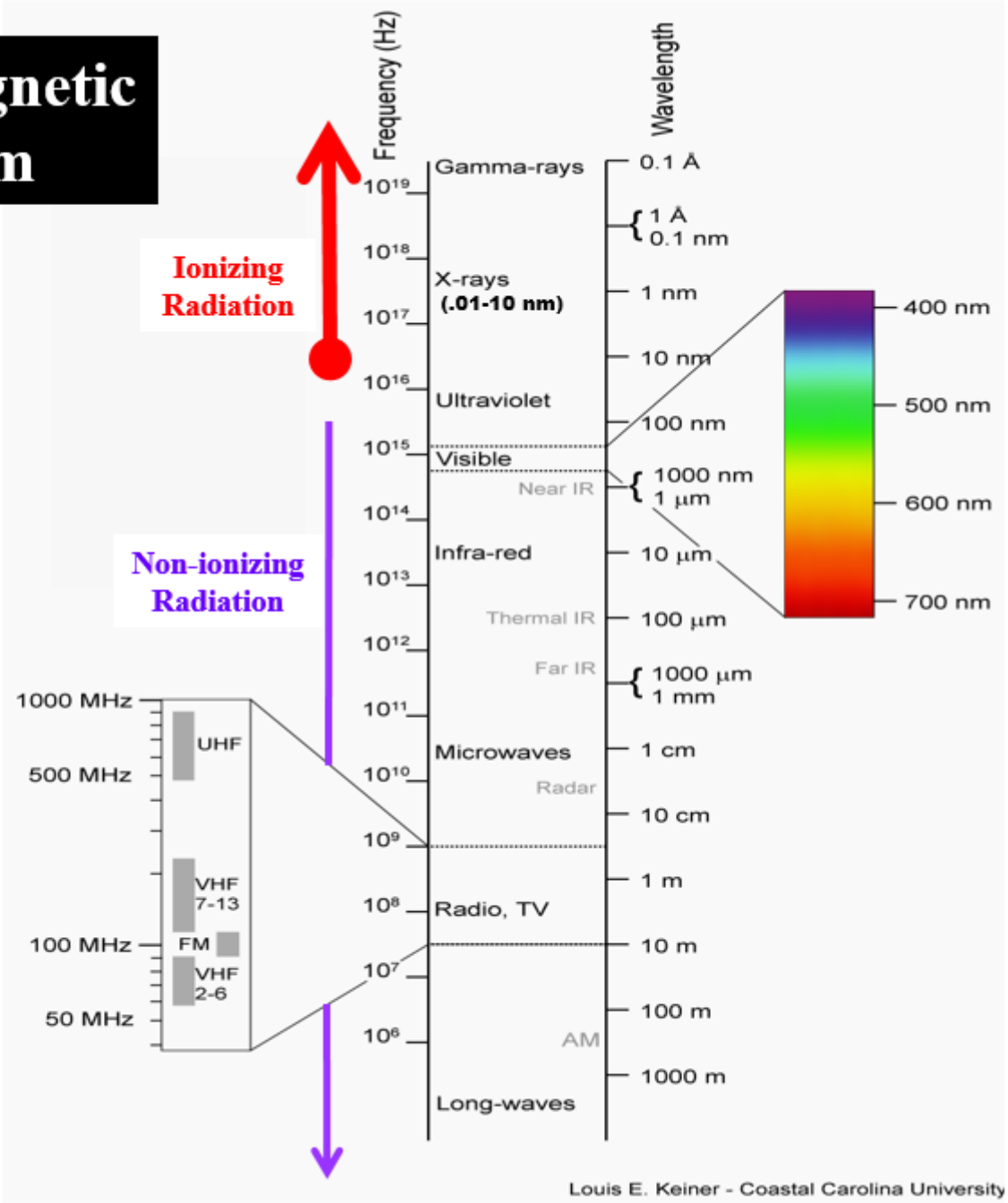
M.S. (1986) **Master of Science** (Radiological Sciences), University of Washington, Seattle, WA; Masters thesis: *"Microdosimetry near the Trajectory of High-Energy Heavy Ions"*

B.A. (1973) **Bachelor of Arts** (Biology, Physics), Whitman College, Walla Walla, WA

Outline

- What is ionizing radiation?
- What is a low dose radiobiology?
- Low dose research results
- A recent paper of interest
- The Future…?

Electro-Magnetic Spectrum



Sources of Exposure

- **Natural sources of exposure**
  - External
  - Internal
- **Manmade sources of exposure**
  - Patient exposures
  - Consumer exposures
  - Public exposures to various activities
  - Occupational exposures

Reference: **NCRP REPORT No. 160 (2009) "*Ionizing Radiation Exposure of the Population of the United States*"**

Natural Sources

- **Median average** background exposure in the U.S. is **3.1 mSv/year** (310 mrem/year) = 100%

- **External exposures:**
  - Naturally-occurring radioactive elements in **earth's crust** [**^{238}U** and **^{232}Th** series, **^{40}K**] (0.22 mSv/year = 7%)
  - Cosmic rays from **space** (0.34 mSv/year = 11%)

- **Internal exposures:**
  - Radioactive elements taken into our bodies through **food** and **water** [^{40}K, ^{14}C, ^{226}Ra] (0.28 mSv/year = 9%)
  - Breathed in from the **air** [^{222}Rn "radon", ^{220}Rn "thoron"] (2.26 mSv/year = 73%)

(NCRP Report 160, 2009)

Manmade Sources (1)

- **Patient exposure**
  - Medical therapy
  - Medical Diagnostics
  - Dental exams

Median average, all of the U.S. 3.0 mSv/yr

- **Occupational exposures**
  - Aviation (*calculated from flight segments*)
  - Medical (personnel monitoring)
  - Commercial nuclear power
  - Industry and commerce
  - Education and research
  - Government—DOE and military

Range of those exposed is from 1 – 3.1 mSv/yr

(NCRP Report 160, 2009)

Manmade Sources (2)

- **Public exposures to various activities**
  - Industrial - power generation, cleanup, etc.
  - Security inspections (airports, etc.)
  - Medical - contact with nuclear med patients
  - Educational, Research

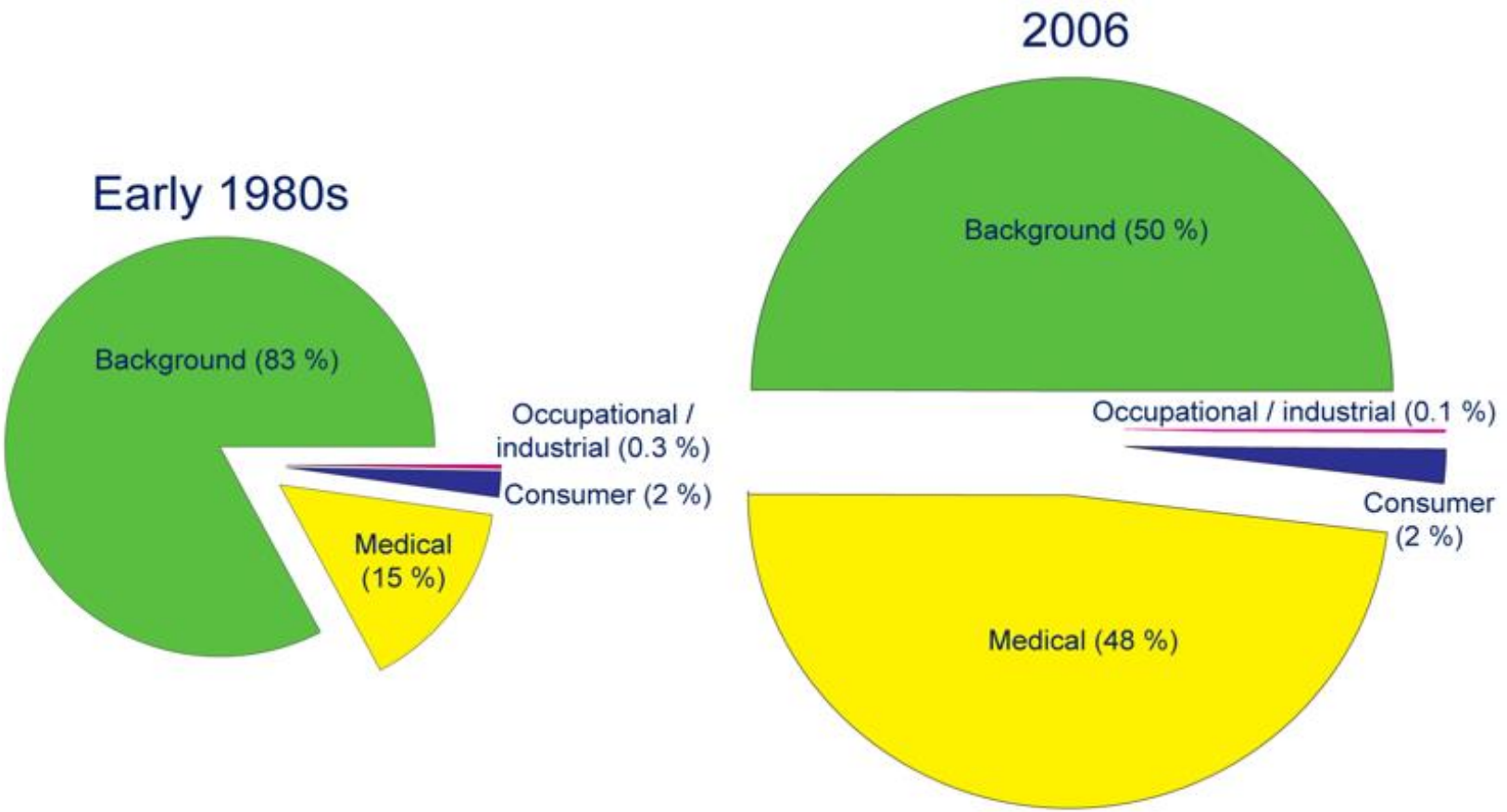
Range of those exposed is from 1 – 10 *μSv/yr* *(micro Sievert)*

- **Consumer exposure to products**
  - Building materials (NORM)
  - Cigarettes (NORM)
  - Mining and agriculture (NORM)
  - Fossil fuels (NORM)
  - Glass and ceramics (NORM)
  - Air travel (Cosmic/Solar)

Range of those exposed is from 1 – 300 *μSv/yr*

(NCRP Report 160, 2009)

NCRP Report No. 160, Ionizing Radiation Exposure of the Populations of the United States



	Early 1980s	2006
Collective effective dose (person-Sv)	835,000	1,870,000
Effective dose per individual in the U.S. population (mSv)	3.6	6.2

NCRP Report No. 160, Ionizing Radiation Exposure of the Populations of the United States

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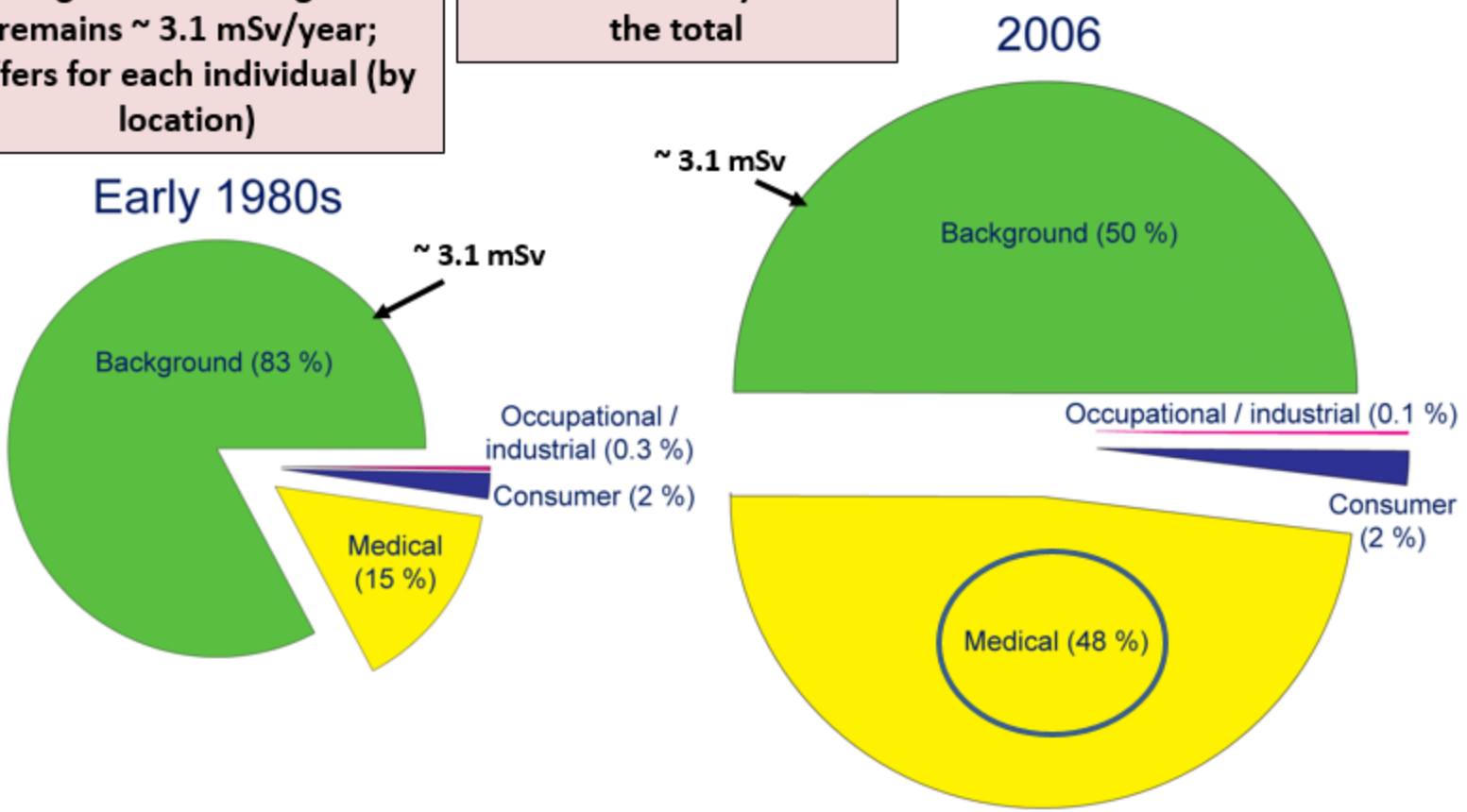
Average natural background remains ~ 3.1 mSv/year; differs for each individual (by location)

But it is now only 50% of the total



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Most U.S. citizens do not receive a medical dose in a given year-- ~ 84M treatments/diagnostics for a population of 300M (2006)

What is a Low Dose?

In general, <100 mSv is considered to be a low dose.

Airlie House Workshop, 1998

X- or Gamma- rays:

One photon track/cell ~ 2 mSv = 200 mrem

~ 2 mGy = 0.20 rads

1 MeV γ-ray; $(20\mu m)^3$ cell volume; = 0.14 rads

500 keV x-ray; $(20\mu m)^3$ 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.

Historic Animal Studies

- Historic mega-mouse and -dog studies were conducted from1970s – ’90s (49,000 mice, 17,000 beagle dogs)
- Historic (and newer) animal studies have shown:
  - A pronounced dose-rate effect for cancer
  - A low dose “sparing” effect
    - (Data and tissue archives re-examined)
- Animal studies help determine if cellular and molecular observations influence disease outcome
- Animal results still provides a link between cell and molecular mechanisms and human epidemiological data for risk assessment.

Molecular Techniques Enabled Study of Low Dose Effects

- **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**

- DOE was first research program to emphasize **whole tissue responses** using these technologies

What We Have Learned

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 apoptotic death

Cell/tissue growth and replacement

Immune system surveillance

Metabolic shift after low (but not high) dose exposure is protective — very new…

What We Have Learned

Old Assumptions		New Paradigms
Qualitatively similar radiation effects occur at high and low dose exposures	→	Qualitatively different processes are induced by high vs. low doses/dose-rates
All radiation effects contribute to the process of carcinogenesis	→	Many radiation effects do not contribute to the process of carcinogenesis
DNA damage is the only mechanism responsible for increasing cancer risk	→	In addition to DNA damage, cancer risk is highly dependent on the cell microenvironment

These assumptions have been prevalent since World War II

We now know much more about biology and radiobiology

Metabolic Shift and Adaptive Response

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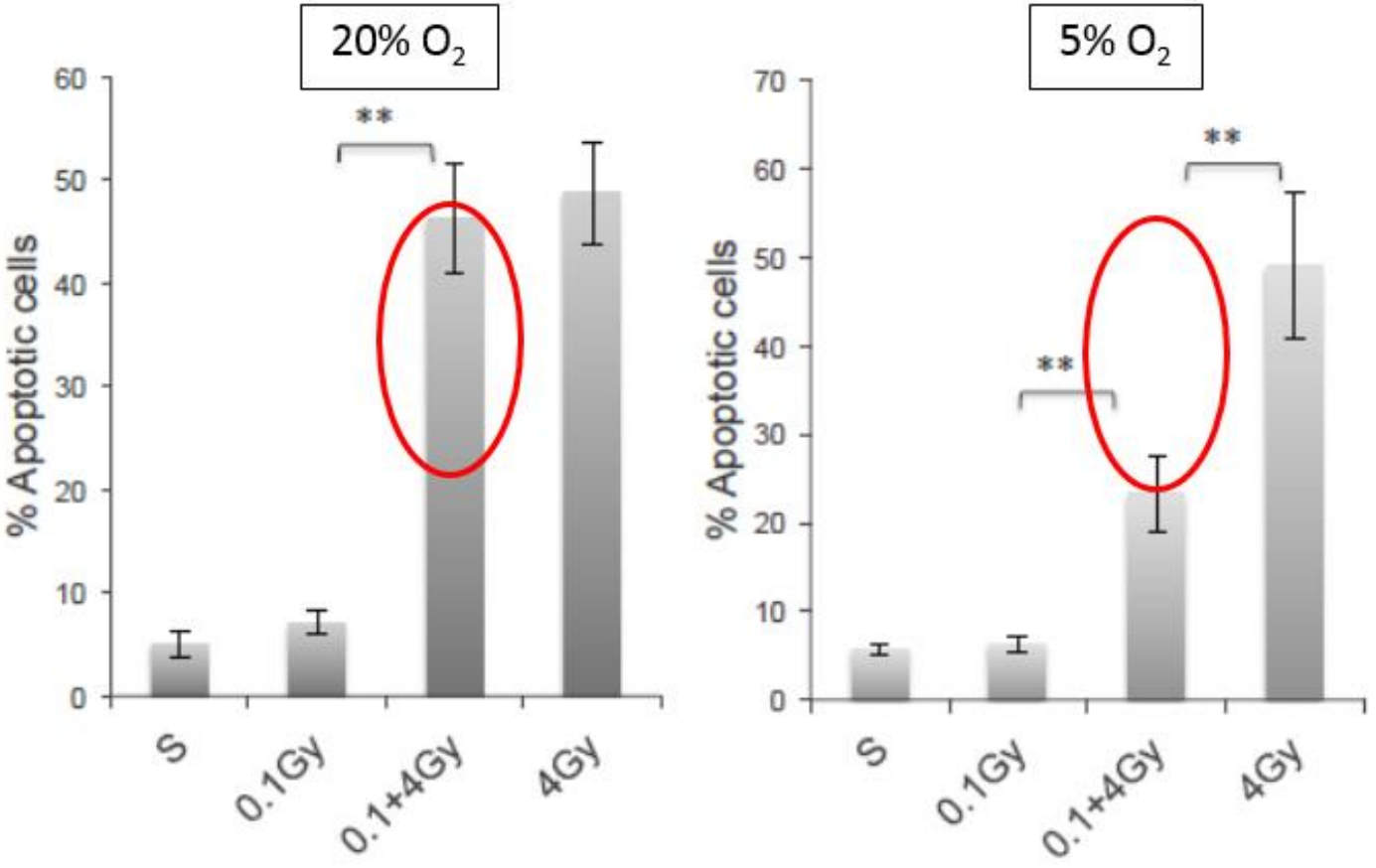
R Lall, *et al.*, "Low-dose radiation exposure induces a HIF-1-mediated adaptive and protective metabolic response", *Cell Death and Differentiation,* **2014**

This paper demonstrates systems biology applied to the study of adaptive response.

- 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.
  - **Human cell culture**
  - **Mouse model**

Metabolic Shift and Adaptive Response

Radio-adaptive response is extremely sensitive to Oxygen tension

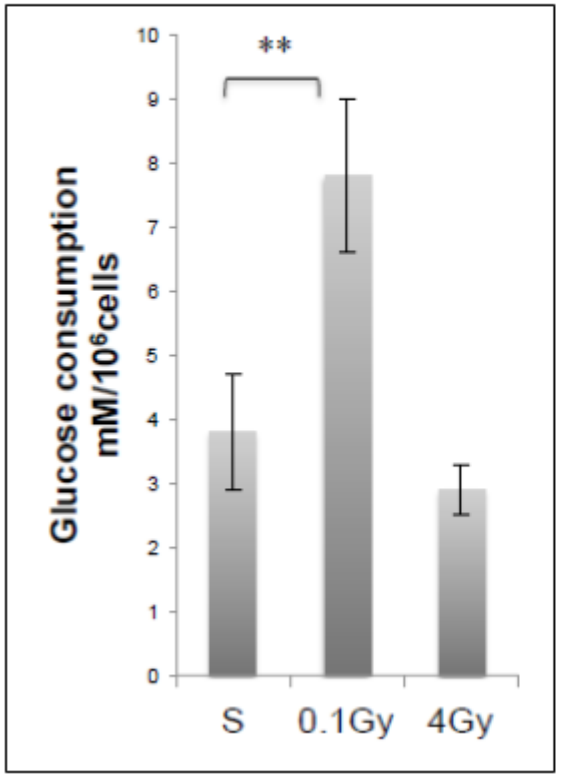


R Lall, *et al.*, 2014

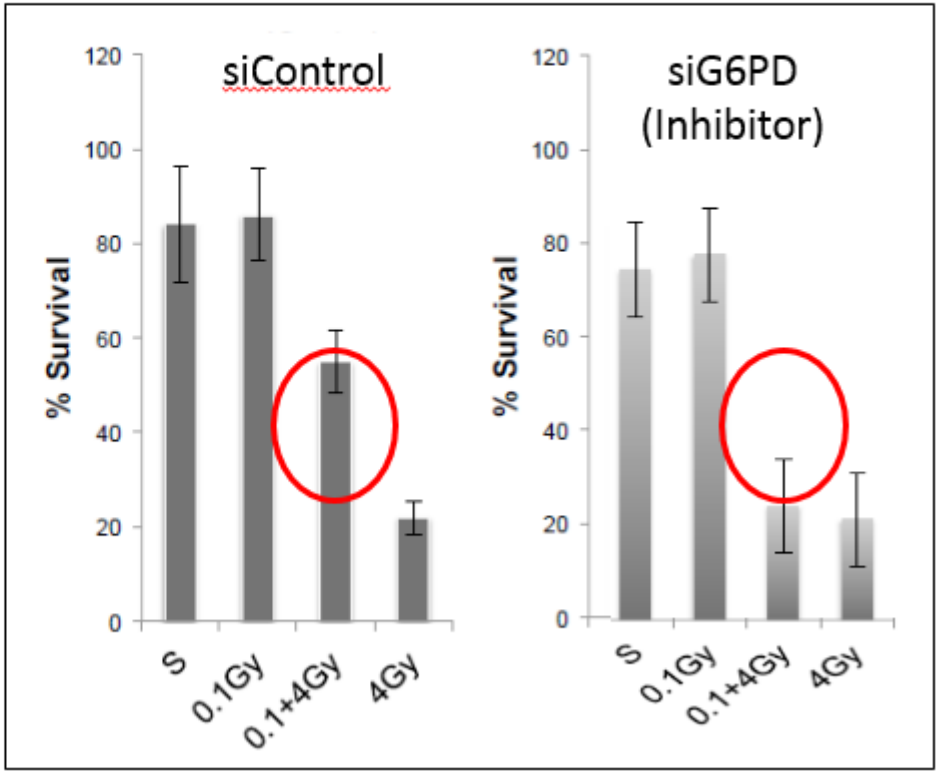
Metabolic Shift and Adaptive Response(Cont.)

Office of Environment, Health, Safety and Security

Low-dose exposure induces glycolysis



Glycolysis is essential for low-dose induced radiation resistance



R Lall, *et al.*, 2014

Metabolic Shift and Adaptive Response(Cont)

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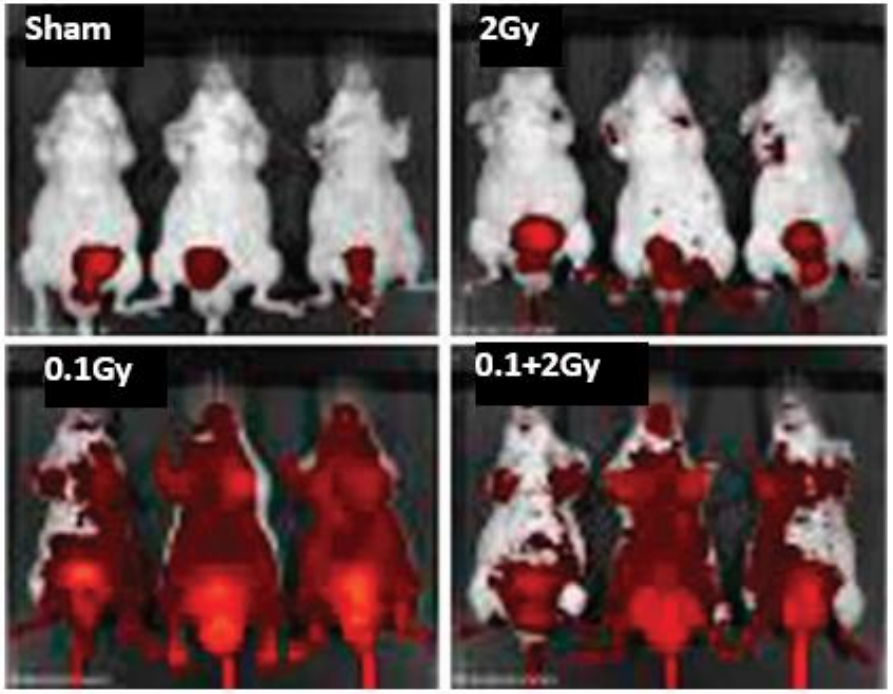
Live Imaging of Glucose Uptake

- 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.*, 2014

Metabolic Shift and Adaptive Response(Cont.)

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Conclusions from paper:

- Low dose exposure induces a metabolic reprogramming from oxidative phosphorylation to glycolysis
- Low dose induced glycolysis underpins the increased radio-resistance
- This metabolic response is exquisitely sensitive and can be readily induced *in vivo*
- A threshold dose between 0.15 - 0.2 Gy (15 to 20 rads) determines whether a protective or a damaging effect is produced in the biological models used here (human cell culture and mouse)

R Lall, *et al.*, 2014

The Future..?

- For single cells, it is the integral activity of biomolecules and organelles that count
- For multicellular organisms, it is the integral activity of cells, tissues, and organs that count
- A new definition for low dose threshold based on:
  - Systems biology
  - For multicellular organisms (humans)

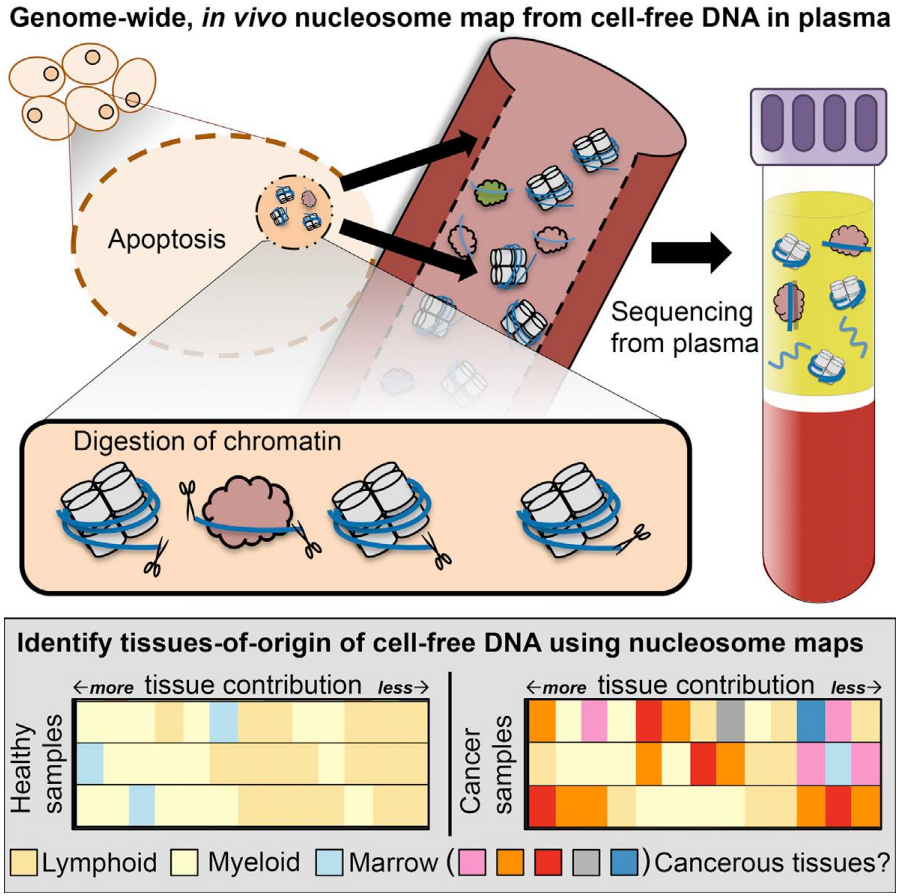
The Future definition..?

- **The threshold defined by that amount of radical species (ROS), that when added to the normal level of metabolically-generated ROS, is just able to overwhelm the native efficiency of cellular defenses and homeostatic mechanisms.**
- **The threshold defined by the number of fatally damaged cells within a tissue that, when added to the normal level of cellular turnover:**
  - Is just able to fatally compromise the integrity of that tissue (late effects), OR
  - Is just able to allow mutated or otherwise deregulated cells to survive within that tissue and proliferate.
- **The threshold defined by the number of fatally damaged tissues within an organism that, when added to the normal range of cell/tissue turnover, is just able to fatally compromise the health of the organism (human)...**

Cell-free DNA- a promising new direction

Cell-free DNA Comprises an *In Vivo* Nucleosome Footprint that Informs Its Tissues-Of-Origin

- Deep sequencing of circulating cell-free DNA
- Yields a dense, genome-wide map of nucleosome occupancy
- Enables identification of its cell-types of origin
- Potentially enabling the non-invasive monitoring of a much broader set of clinical conditions than currently possible
- **Human biological model for low dose studies..?**



Snyder et al., 2016, ***Cell*** 164, 57–68