Los Alamos NATIONAL LABORATORY

Characterization of Radiation Dose & Effects

Status and Thoughts about the Future

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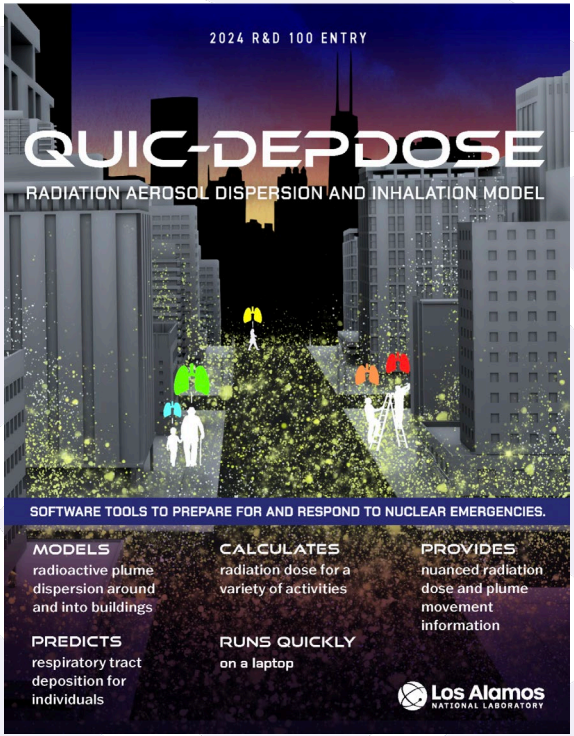
LANL statistics
$5.2B budget
40 square miles, ~50 technical areas
800+ bldgs., 8.4M sq ft.
13 nuclear facilities
17,500 workers
13,000 career employees
1,948 students, 502 postdocs
Average employee age: 41
67% male, 33% female, 51% minorities
39% were born in New Mexico

Multiple LANL missions depend on characterization of radiation dose and related effects

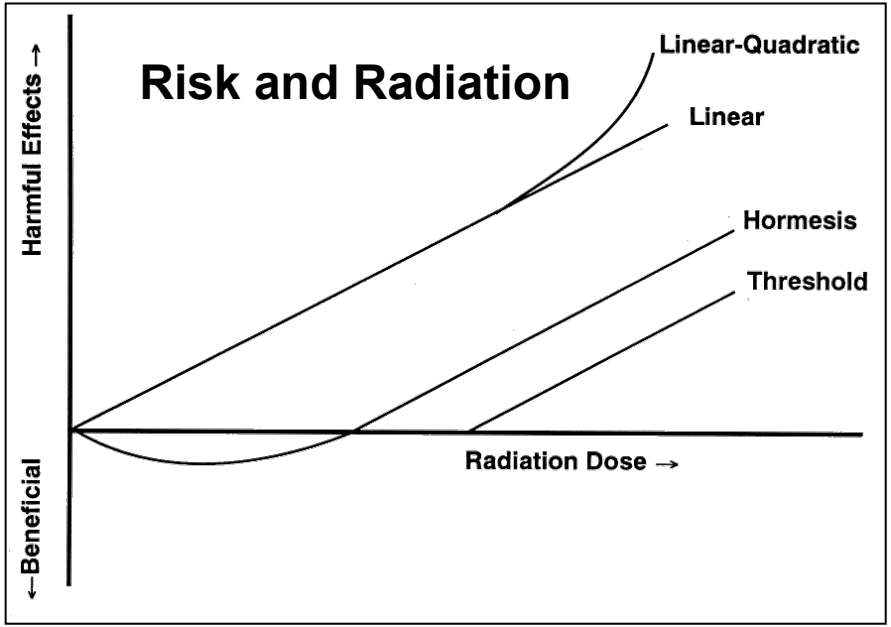
- National security mission areas
  - Weapons
  - Actinide R&D
  - Nuclear forensics
  - Event response & exposure risks assessment
  - Materials recovery & recycling
- Worker, public, & environment protection
- Medical isotopes
- Fundamental science



QUIC-DEPDOSE integrates plume and inhalation toxicology models to rapidly identify fallout exposures and risks

Building trust in an uncertain world

- More science is needed to understand absorbed dose response
  - Low dose (<100 mGy*)
  - Therapeutics
- Which model of dose (animal, plant) response to radiation is relevant in
  - The aftermath of a nuclear attack?
  - A sustained low-dose environmental or occupational exposure?
  - A medical therapeutic?

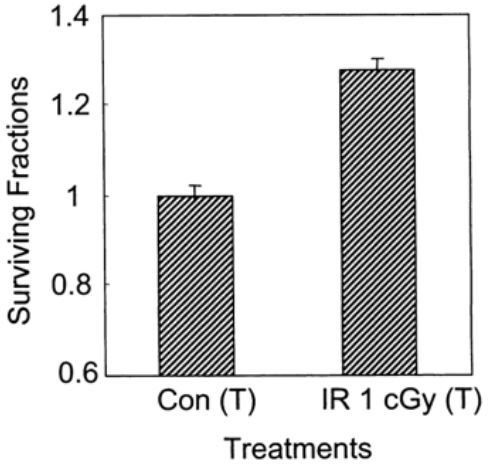


*UN Scientific Committee on the Effects of Atomic Radiation <100mGy, Gray=Joule/kg

Low Dose Radiation (LDR) – prior LANL research

- DOE-BER supported unique low-dose and worker exposure R&D in the 1990s
  - Linear No-Threshold (LNT) model was prevalent assumption
  - LANL focused on molecular/cellular level responses: Radioresistance mechanisms, pathway perturbations, carcinogenic potential
- Well conceived by DOE and executed by LANL and others
  - Did not address broad health risks or environmental impacts
  - Dependent on technology at the time
- BER ended LDR investments when focus transitioned to bioenergy and environmental missions

Radioadaptive bystander effect

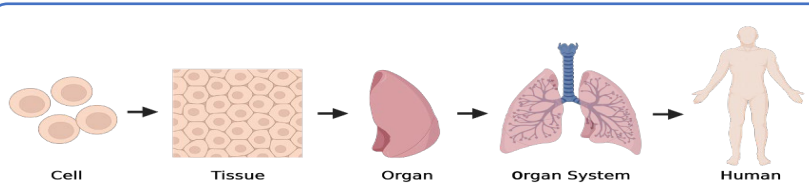


Treatment of unirradiated cells with supernatants from cells that were irradiated with 1 cGy of a particles [IR 1 cGy (T)] increases their ability to form colonies

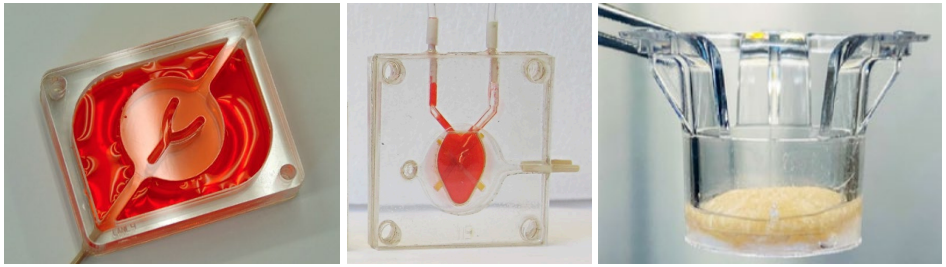
Iyer & Lehnert, Rad Res. 157 (2002)3-7.

Current LANL radiation research efforts increased attention to higher dose and acute effects

- Advanced approaches have opened up the aperture to studies at varied dose regimes and understanding effects on the environment
- IARPA TEI-REX program advances sensitivity of biomarker identification in a broad dose regime
  - Focus on transition ready methodologies and protocols and integrated models
- LDRD project applying human organoid models expands exposure routes
  - Integrated dose evaluation, modeling and toxicology enables triage approaches



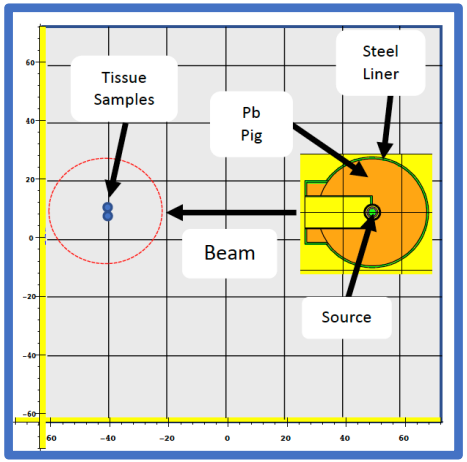
Complex human microphysiological systems



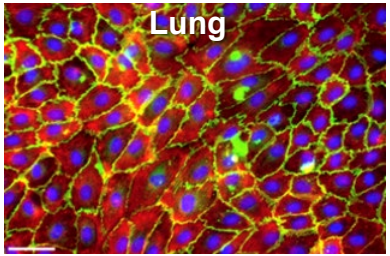
LANL human organoids: Lung, Heart, Skin (L-to-R)

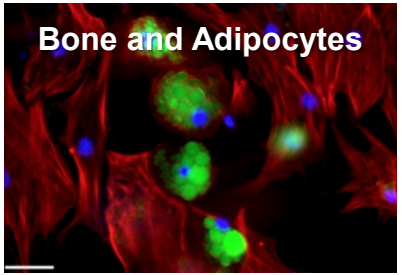
Combining research tools in novel ways enables new low-dose radiation research

Base MNCP Geometry

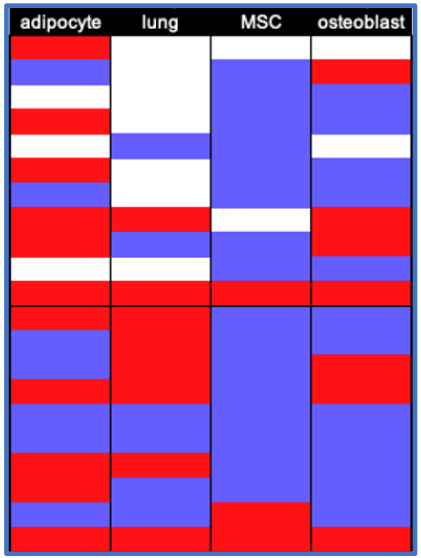


Experimental Geometry



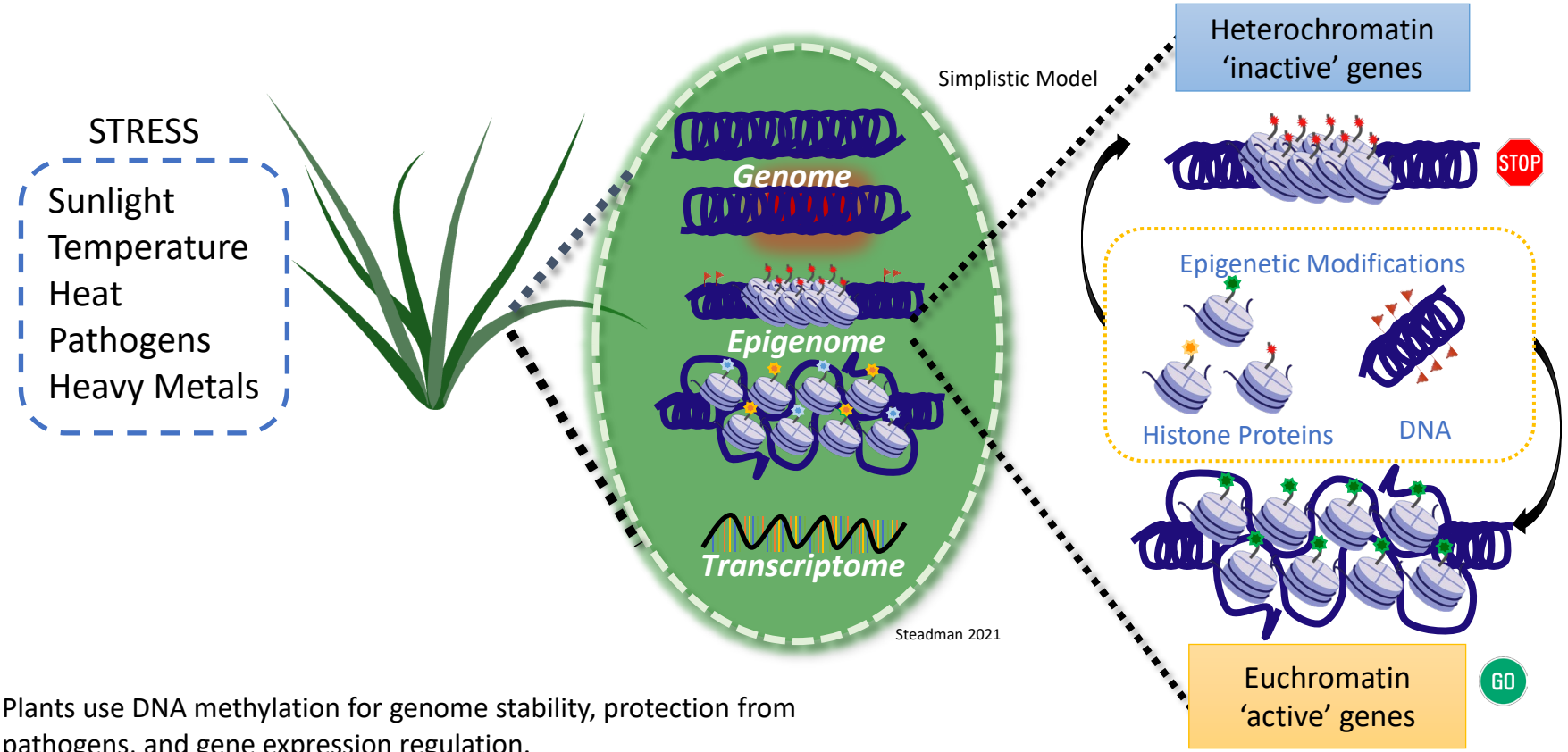


Human tissue development



Transcriptomics

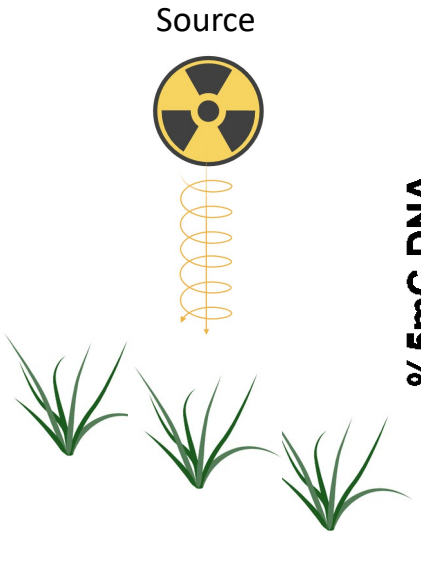
Epigenetic modifications alter accessibility of genes - regulating physiology and phenotype

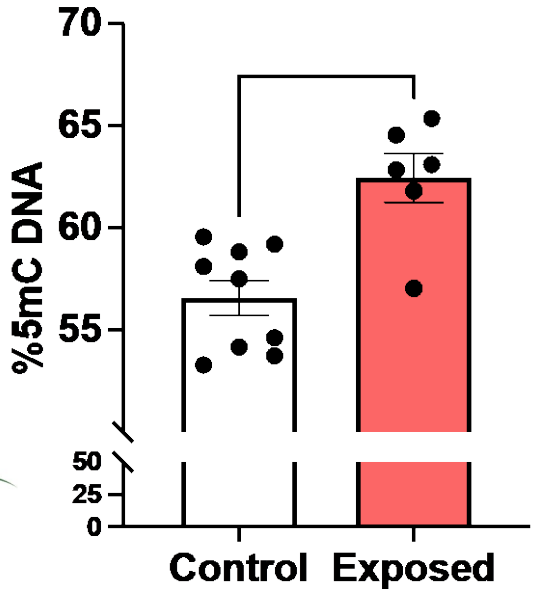


Plants use DNA methylation for genome stability, protection from pathogens, and gene expression regulation.

5-methyl cytosine in grass is impacted by radiation

- Other reports (Chernobyl) of radiation impacts on epigenetics
- Potential biosignature
- Preliminary study to determine how radiation effects plant DNA methylation
- Experimental design: 3 plants (Johnson grass) per condition (control versus exposed); 20 grey exposure (high acute)
- gDNA extracted from leaf samples using bead method leaf samples
- Analysis using ELISA method





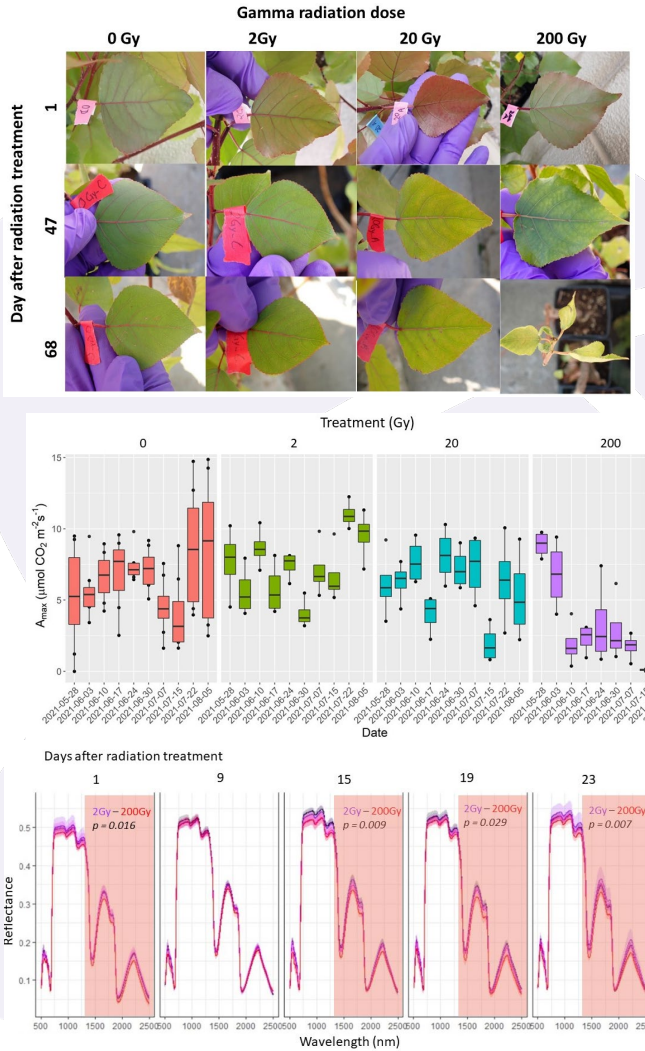
- %5mC methylation increased in exposed plants (p = .0012)
- **True epigenetic response or degradation of plant DNA?**
- Further gene-specific sequencing studies needed to elucidate function and potential for signature development

Steadman 2022, unpublished data

Images created with Biorender, Steadman 2024

Study 1: Gamma radiation effects on poplar plant function

- Five replicates per treatment
  - Exposed to gamma radiation from Sandia accelerator
  - Doses: 0 (control), 2, 20, 200 Gy given for 5 hours in one day.
  - Measurements: Photosynthesis, stomatal conductance, chlorophyll fluorescence and leaf hyperspectral reflectance were measured right after the radiation treatments followed by weekly measurements for three months.
- Results
  - Gamma radiation caused changes in leaf color, photosynthesis rate and chlorophyll fluorescence at different times after exposure depending on dose.
  - The highest dose (200 Gy) killed the plants in 3 months. The plants under lower doses (2 and 20 Gy) revived after 10 weeks.
  - **<u>Differences in leaf hyperspectral reflectance at wavelengths 1400-2500nm started showing right after the treatment and consistently after day 15.</u>**



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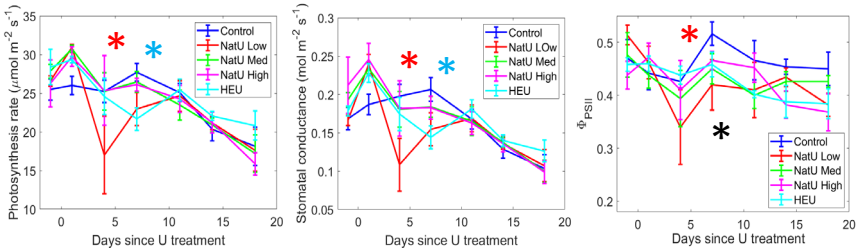
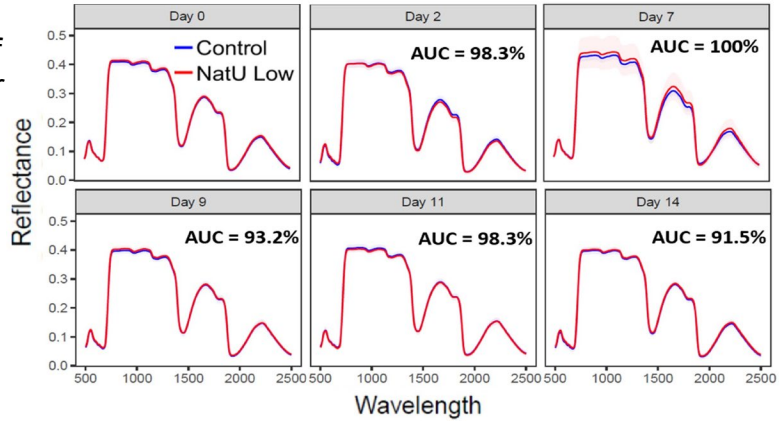
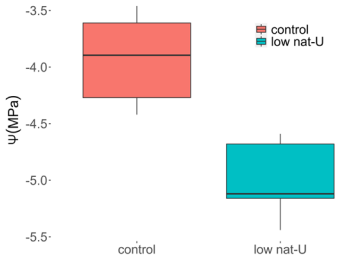
Study 2: Uranium exposure effects on maize plant function

- Five replicates per treatment
  - Exposed to natural (U) and highly enriched uranium (HEU)
  - Doses: 0 (control), 0.01 (low), 0.05 (med) and 0.1 (high) g of U and 0.05g of HEU in single dose mixed into irrigation water
  - Measurements: Photosynthesis, stomatal conductance, chlorophyll fluorescence and leaf hyperspectral reflectance were measured right after the radiation treatments followed by weekly measurements for 15 days
- Results
  - **<u>Exposure to trace doses of U and HEU cause a stress reaction in plants similar to drought.</u>**
  - The lowest dose of natural U and HEU reduced photosynthesis, stomatal conductance and chlorophyll fluorescence four and 6 days after exposure, respectively
  - Plants exposed to U could be distinguished from controls using leaf hyperspectral reflectance two days after exposure
  - Exposure to U reduced plant drought tolerance

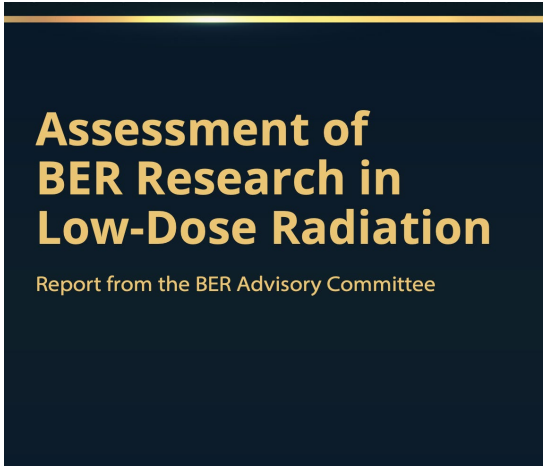






Renewed Interest in Low Dose Radiation (LDR) Effects

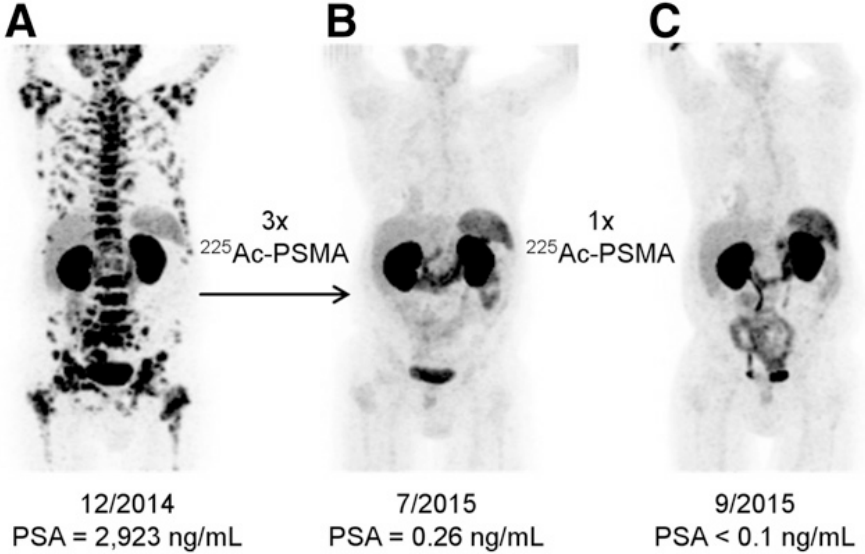
- Understanding impacts of unconventional human-activity induced sources of low dose radiation is gaining interest as also are effects beyond carcinogenesis
- SC-BER advisory committee (BERAC) recently released some key findings that encourage the use of DOE capabilities and instrumentation for LDR dose control and calibration in experiments that could enable physics–biology correlations and accurate description of the radiation dose and rate in biological systems
- The report points to the potential of leveraging DOE facilities and experience in rad research
- A recent Funding Opportunity Announcement by BER focuses on using a joint experimental/computational approach to study effects of LDR



May 2024 BERAC report in response to a charge from the Director of the Office of Science

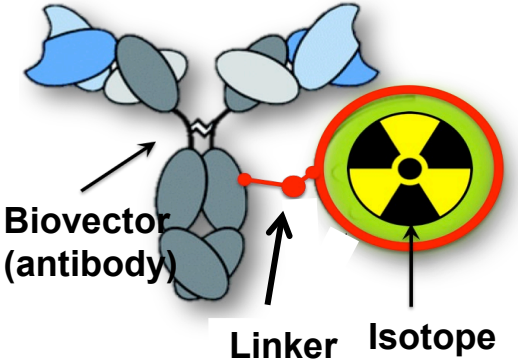
Medical Therapies: Actinium-225

- DOE Isotope program, with LANL, Oak Ridge, and Brookhaven National Laboratories are currently meeting the national demand of ^{225}Ac in support of human clinical trials.
- This isotope is a promising alpha therapy agent for the treatment of many kinds of cancer. The ability to target it to cancerous cells using human immunochemical techniques is particularly appealing
- We hope this isotope follows in the lead of ^{223}Ra (Xofigo) and ^{177}Lu (Pluvicto) as an FDA approved Targeted Alpha Therapy drug



Treatment of metastasized prostate cancer with ^{225}Ac

C. Kratochwil, University Hospital Heidelberg – *J. Nuc. Med.*, v57, 2016, p1941



LANL is the nation's Plutonium Center of Excellence: Pu intake is a substantial health risk to our workers

- Background
  - Pu at LANL often in insoluble forms (e.g., oxides, ceramics)
  - Inhalation can lead to substantial doses
  - Chelating agents cannot effectively immobilize insoluble Pu
  - Pulmonary lavage is effective but too risky and harsh
- Hypothesis: FDA-approved medications can enhance mechanical clearance from the respiratory tract [Surfactants (BLES), Mucolytics, Statins (Lovastatin)]
  - Animal models using radio-labeled aerosol
    (Note: animals will not need to be euthanized at experiment conclusion)
  - Collaboration with Colorado State University, Health Canada, and Institute for Radiation Protection & Nuclear Safety (IFSN-France)

Investigating possible psychological/cognitive side effects associated with plutonium chelating agents

- DTPA is current standard of care
  - Pu, Cm, and Am intakes are treated with DTPA and surgical excision
  - Conventional wisdom states that DTPA is benign
    - Treatment recommendations are extremely aggressive
  - Recent evidence calls the benign assumption into question
- Understanding risks is needed to make optimal treatment decisions
  Collaboration with Armed Forces Radiobiology Research Institute (AFRRI)
  - Impact on cognitive function, psychological health is important
  - Animal model study (mouse/rat) of DTPA, HOPO (in human trials), and saline control
  - Behavioral testing post injection (1 day; 1, 4, 12, 24 weeks)

Our proposed research has the potential to rapidly translate to human populations

AI may be a competitive advantage when the “control” has potentially multiple competing mechanisms

- Biomarker discovery is greatly enabled
  - Omic tools
  - Models
    - Computational, organoid/microsystem, environmental, animal
- Discovering a biomarker that can be induced is just the beginning
  - Characterizing the background in classical detection theory is essential
    - H0 covariance matrix
    - Nonlinear relations
  - AI tools have been applied in similar low signal/noise applications without explicit noise models