Low Dose Radiation Research Program

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Challenges in defining susceptibility mechanisms that predict low-dose health and safety risks

What are the major health and safety issues of low dose and low dose-rate radiation?

- Cancer risk
- Neurological risks (cognition, behavior and performance)
- Immune function
- Microbiome impacts
- Cellular senescence/inflammation/aging
- Individual variation

What is the status of current low dose radiation risk research in the US?

- Focused on epidemiological research (e.g. atomic bomb survivors, radiation cohorts, Million Person Study)
- Limited basic research funded primarily by NASA, with higher dose work funded by NIAID, DOD, other NIH

What are the long term strategic and essential components of a low dose research program?

- Biological model systems with low-dose sensitivity and quantitative read-outs of health-related outcomes.
- Molecular signatures at low dose and low dose-rates
- Mathematical models to enable translation to human risk and validation of the human risks

A systems biology approach to identify adverse outcome pathways for low dose radiation response

BioSciences

A genetic population resource, the Collaborative Cross murine model, was first used in our DOE Low Dose Radiation Program in 2014

After the Program ended, continued funding was obtained from internal (LDRD) and external sources (NIAID, NIEHS, DOD and ONR)

Analytical tools were developed to enable translation from mouse to human

- Database of blood profiles (hematologic toxicity) for 30 strains of mice (>1500 mice) after 100 cGy X-ray (and for >10 strains at 10 cGy)
- Genetic linkage data for spontaneous tumor susceptibility, the gut microbiome, memory, anxiety, motor performance, body weight and radiation sensitivity.
- Computational approaches were developed including machine learning tools that predict radiation sensitivity and the role of specific microbes on immune parameters and behavior.

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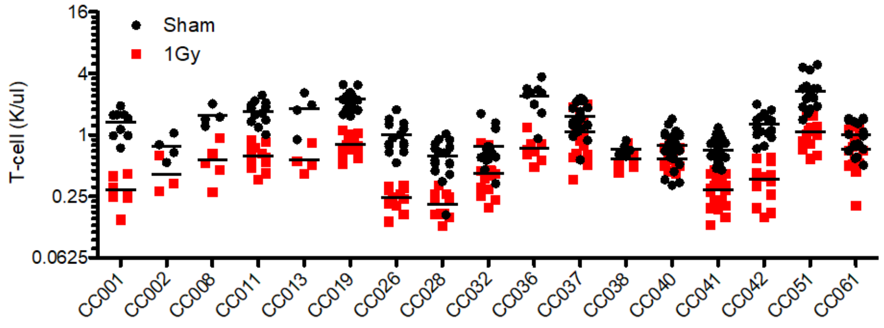
Collaborative Cross

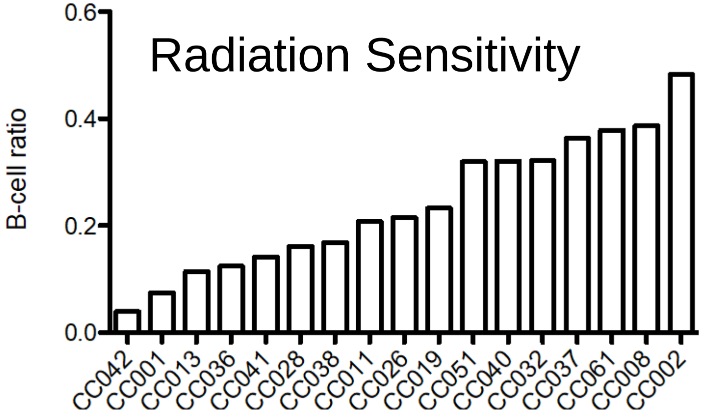
A mouse resource that mimics the variable genetic backgrounds found in the human population.

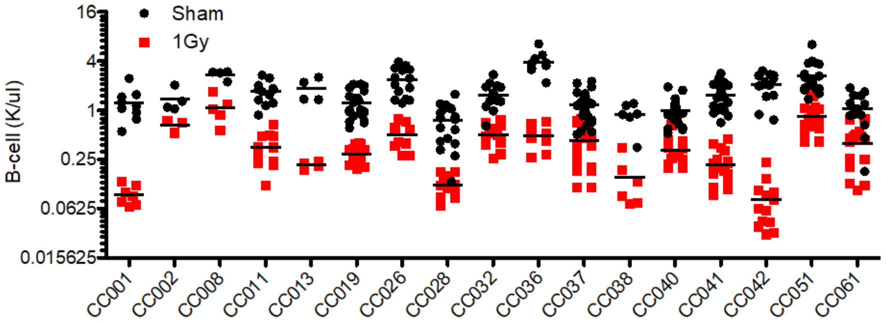
The Collaborative Cross Mouse Population-Based Resource

- **rotarod performance & Obesity (body weight)** Mao et al, ***Sci Rep*** (2015).
- **Gut microbiome composition & metabolome** Snijders et al, ***Nat Microbiol*** (2017).
- **Spontaneous cancer susceptibility** Wang et al, ***Gut*** (2019)
- **Microbiome & memory** Mao et al, ***Microbiome*** (2020)
- **Anxiety** Jin et al, ***Sci Rep*** (2021)
- **AOM-induced toxicity** Zhong et al, ***Arch Toxicol*** (2021)
- **AOM-induced colon tumor** In preparation, 2021
- **AOM-induced liver tumor** In preparation, 2021
- **Thirdhand smoking and behavior** He et al, ***Sci Rep*** (2021).
- **Cancer susceptibility to thirdhand smoking**
- **Immune cell composition**
- **Radiation sensitivity in immunity**
- **Plasma secretome**
- **Body temperature**

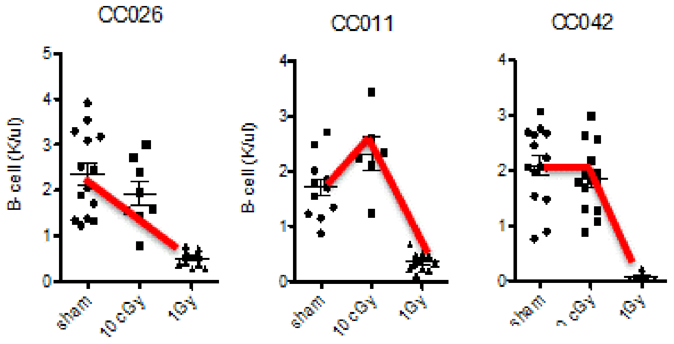


10 cGy

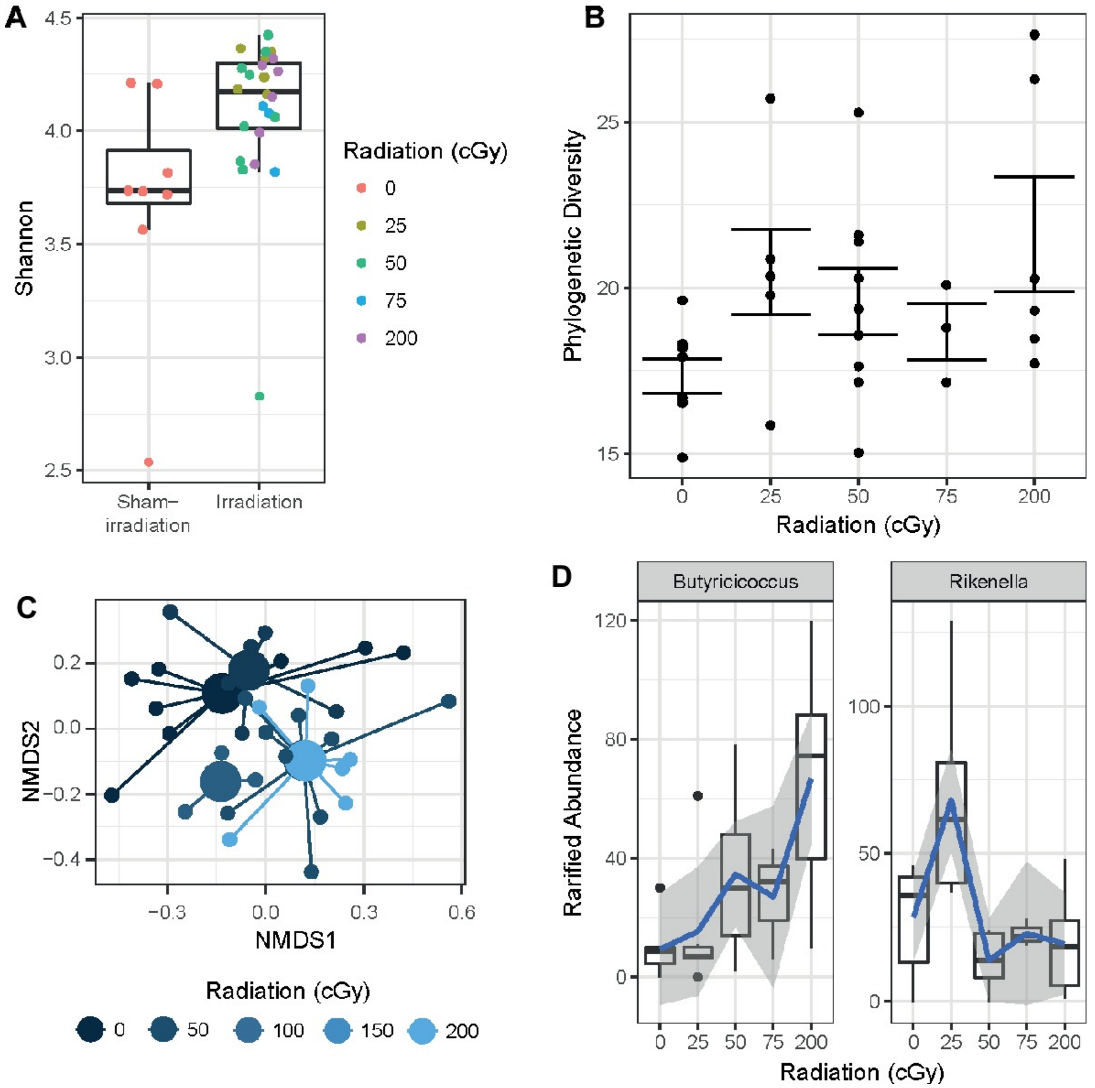




Immune response to radiation exposure



Combined exposure to sparsely and densely ionizing radiation alters the composition of the gut microbiome



Next steps:

Define how gut microbiome changes direct radiation health outcomes – e.g., behavioral and cognitive effects, tumor susceptibility, inflammatory responses

Apply mathematical models to link low dose radiation-driven microbiome changes to polygenic traits in the host and to specific health outcomes

Validation using gnotobiotic approaches and human data sets

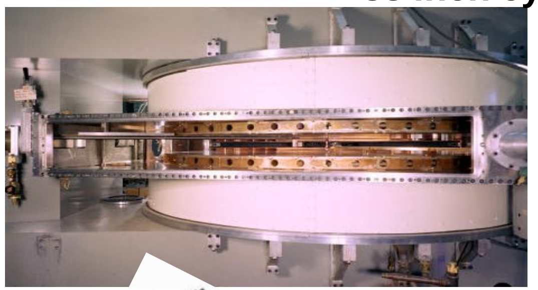
LBNL/DOE capabilities that can be leveraged for low dose and low dose-rate radiation studies

BioSciences

Gnotobiotic animal facility

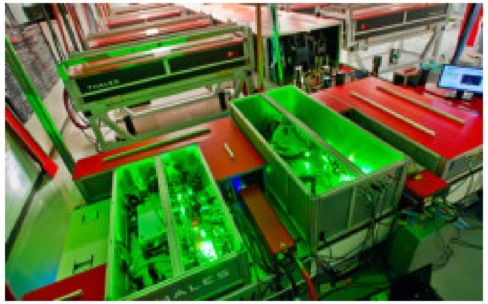
BASE BERKELEY ACCELERATOR SPACE EFFECTS

Protons
Heavy ions
Neutrons
88 inch cyclotron



BELLA

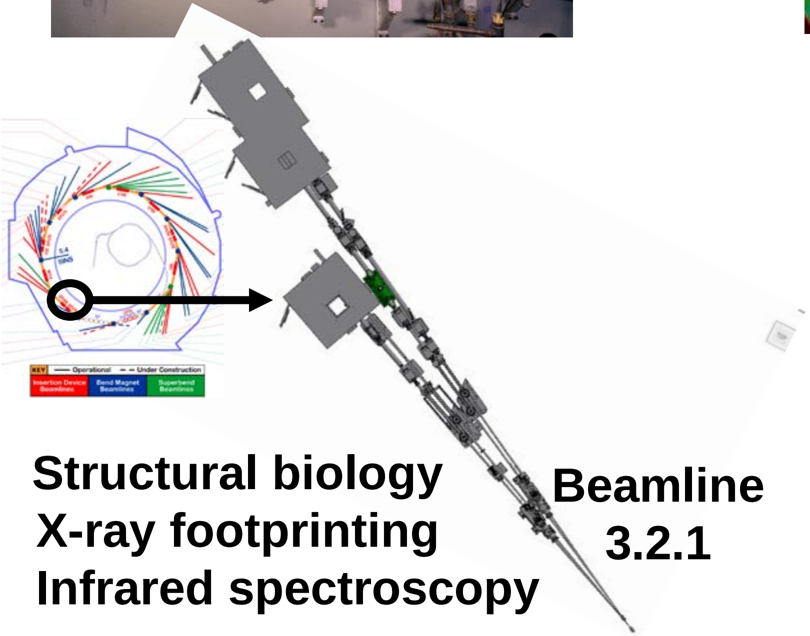
Protons
Electrons



Molecular Foundry

JGI JOINT GENOME INSTITUTE DEPARTMENT OF ENERGY

ALS ADVANCED LIGHT SOURCE



- Structural biology
- X-ray footprinting
- Infrared spectroscopy

Beamline 3.2.1

BSISB Berkeley Synchrotron Infrared Structural Biology Program ALS INFRARED BEAMLINE 5.4

NERSC

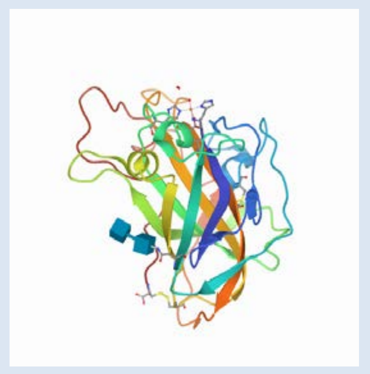
AI teams & supercomputing

PNNL

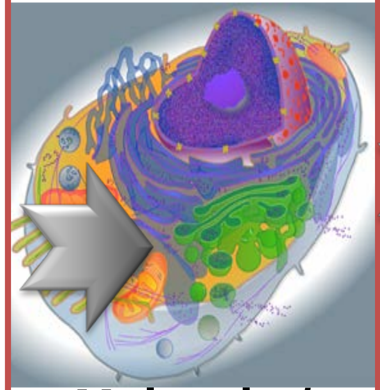
EMSL

Multi-Scale, Multi-Modal Analytical Capabilities at LBNL and PNNL Drive New Insights

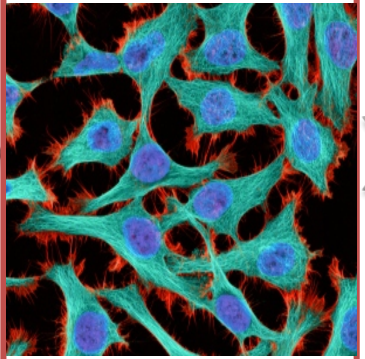
BioSciences



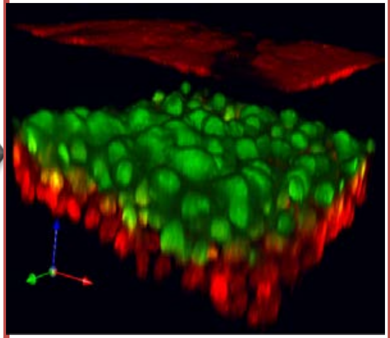
Structural biology



Molecular/ Cellular



Communities



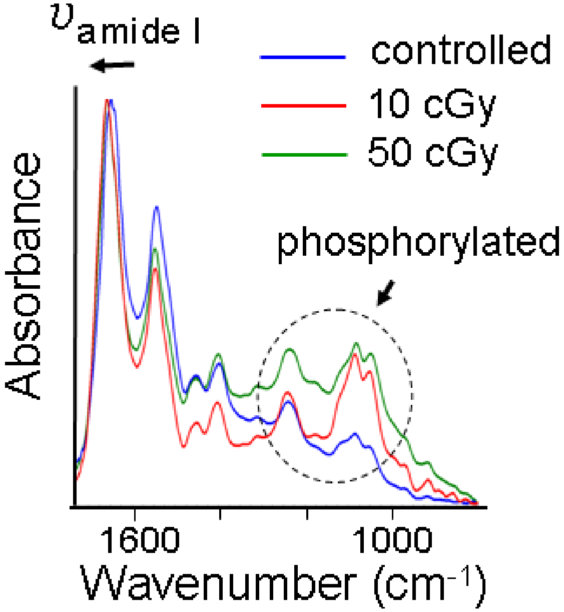
Tissues

- Cryo-EM and NMR protein structure determination
- Characterization of posttranslational modifications
- Native protein proteomics

- Super resolution microscopy
- fliFISH – single cell resolution transcript analysis
- Tissue tomography
- NanoPOTs for single and small cell number multi-omics
- Mass spectrometry imaging

- Tomography
- Laser capture microdissection
- Proteomics, metabolomics, lipidomics, glycomics

Synchrotron-Based Fourier Transform Infrared (SR-FTIR) Spectromicroscopy Beamlines 1.4/5.4

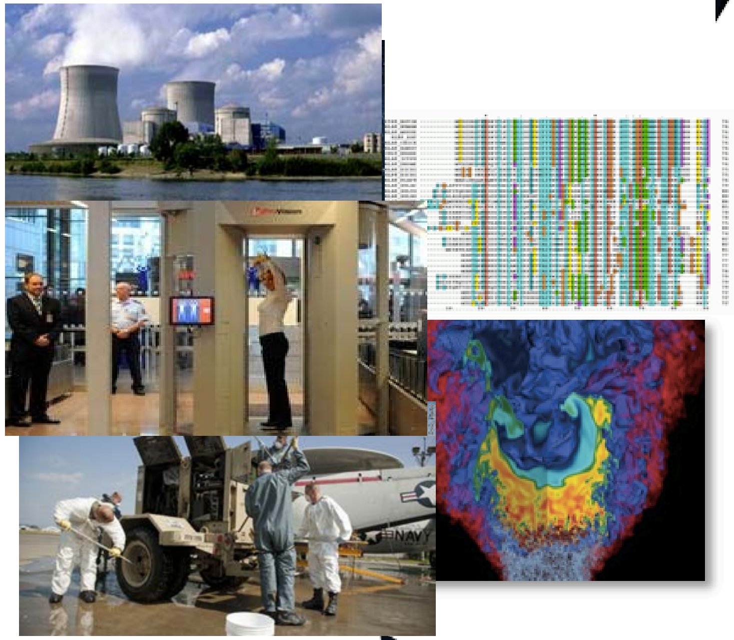


AI for low dose radiation risk estimation

BioSciences

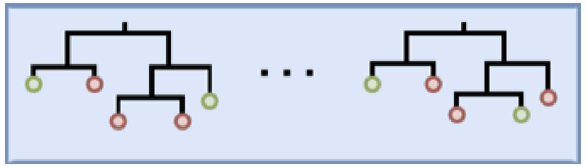
Data Sources

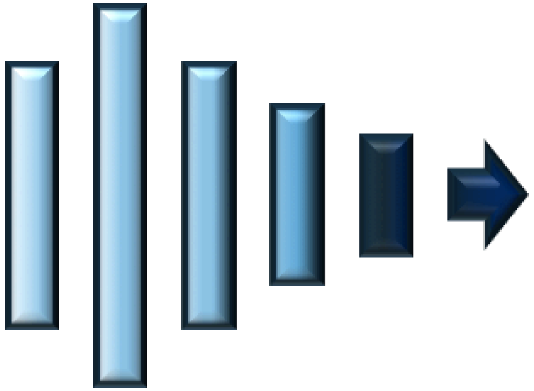
Detectors or physics-based simulations



Learning Methods

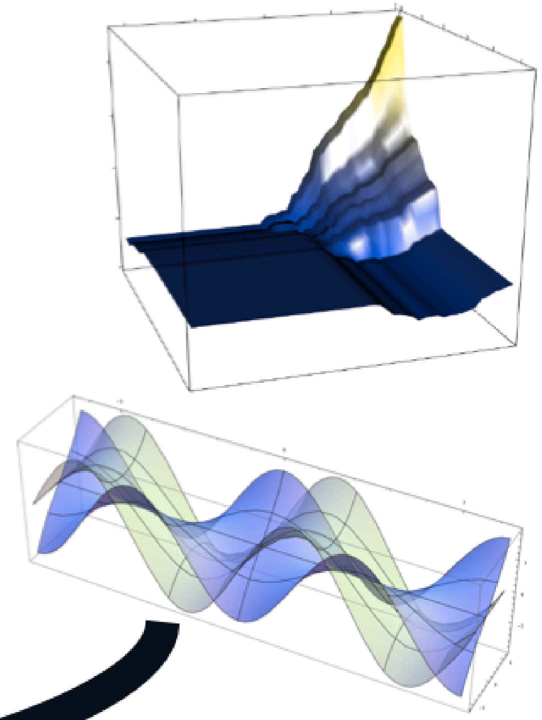
Ensembles or Deep Learning





Extraction Techniques

Dynamic response surfaces or reduced order surrogate models



Models used to design future studies or parameter sweeps

Critical scientific objectives concerning low dose radiation effects

- Define novel polygenic and physiological modifiers of low-dose risk of specific adverse health outcomes (cancer, neurological, cognitive and behavioral outcomes, immune response, cellular senescence/inflammation/aging).
- Define the role of the gut microbiome in mediating low-dose health risks.
- Identify novel biomarkers of susceptibility for low dose health risks based on biochemical modifications for specific cell types, tissues and individuals.
- Determine the role of dose-rate on low dose risk of specific adverse health outcomes.
- Apply advanced single cell and tissue imaging technologies to identify critical sub-cellular mechanisms of adverse health risks.
- Apply machine learning and computational modelling to predict adverse health risks in the context of modifying genetic and physiologic factors.