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Systems Biology Approaches to Decipher Low Dose Radiation Health Effects

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Developing a Long-Term Strategy for Low-Dose Radiation Research in the U.S.

Key Challenges and Opportunities for Radiation Research

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Challenges:

- How do genetic and epigenetic individual variations in human populations affect linearity and disease risks?
- What is the role of variations in microbiome composition, metabolites, tissue microenvironment, and immune system in disease risk?
- How do these individual factors interact to promote or reduce disease risks in response to radiation exposure?
  - Requires advanced computational analyses and integration
- Are risks linear or non-linear with respect to dose, and to what extent does this depend on individual variations?

Opportunities:

- Design strategies for disease prevention and risk management based on individual predispositions and systemic responses to radiation
- Manipulate reciprocal interactions between microbes and host to produce benefits (e.g. resistance)
- Inform national regulatory policies to balance energy needs while ensuring the health of humans and the biosphere

Individual variation is critical for determining disease risk in response to radiation exposure

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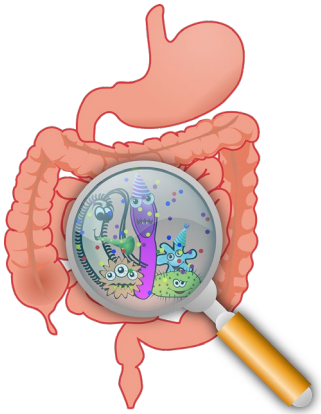
Genetic variations

> 100 million SNPs between individuals

Radiation

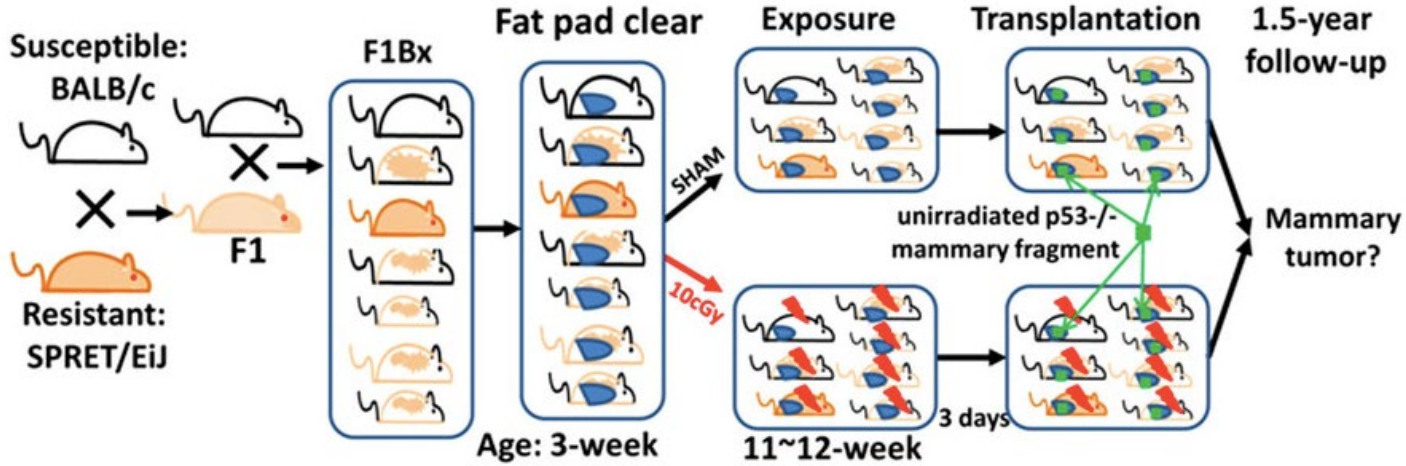
Gut Microbiome?



Radiation Response

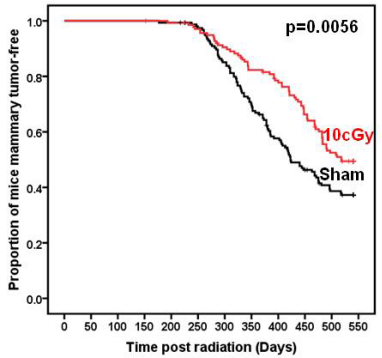
Tissue injury, Immune response, Neurodevelopment, Cancer, etc

Low-dose radiation mediated alterations of the tissue microenvironment controls mammary tumor susceptibility



A systems genetic approach to identify susceptible genes

Low-dose radiation of genetically diverse hosts *reduced* the mammary tumor incidence



15 Genetic loci strongly influence mammary cancer latency through mammary tissue microenvironment after exposure to LDIR

(Zhang et al., Sci Rep 2015)

Collaborative Cross mice recapitulate the genetic and phenotypic diversity of the human population

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Collaborative Cross mice

Population-based mouse models such as the Collaborative Cross are used to understand human individual variation in response to environmental exposures.

Huge variation in phenotypes across CC mice

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- **Behavior (rotarod performance)**
- **Obesity (body weight)**

Mao et al, Sci Rep, 5:16247 (2015).

- **Gut microbiome composition**
- **Gut metabolome**

Snijders et al, Nat Microbiol, 2:16221 (2017).

- **Spontaneous cancer susceptibility** Wang et al, Gut (2019)
- **Microbiome and memory** Mao et al, Microbiome (2020)
- **Microbiome and anxiety** Jin et al, Sci Rep (2021)
- **Azoxymethane sensitivity** Zhong et al, Arch Toxicol (2021)
- **Thirdhand Smoke on anxiety and memory** He et al, Sci Rep (2021)
- **Immune cell composition**
- **Radiation sensitivity**

In preparation, 2022

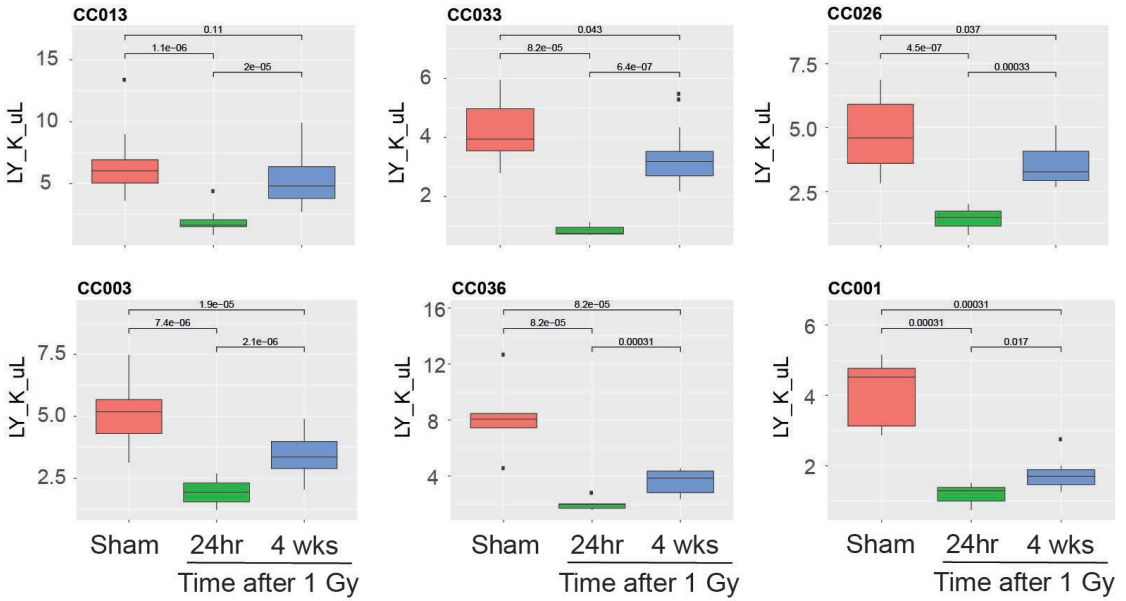
Early and late hematologic response to ionizing radiation in CC mice

Collaborative Cross (30 strains)

1 Gy X-ray
10 cGy X-ray

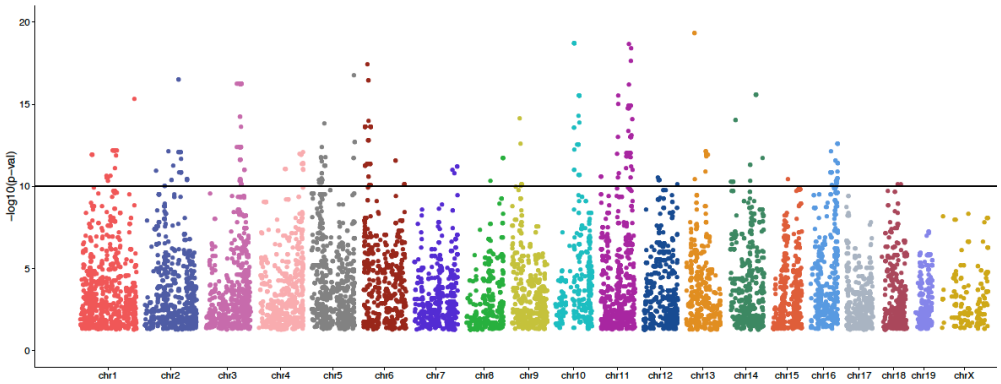
Acute immune response
24 hrs after radiation exposure

Persistent immune response
4 wks after radiation exposure



19 parameter complete blood count including B/CD4+T/ CD8+T

Currently approximately 1700 mice enrolled in study



Human homologs constitute putative biomarkers for radiation sensitivity

Individual sensitivity to radiation exposure in CC mice

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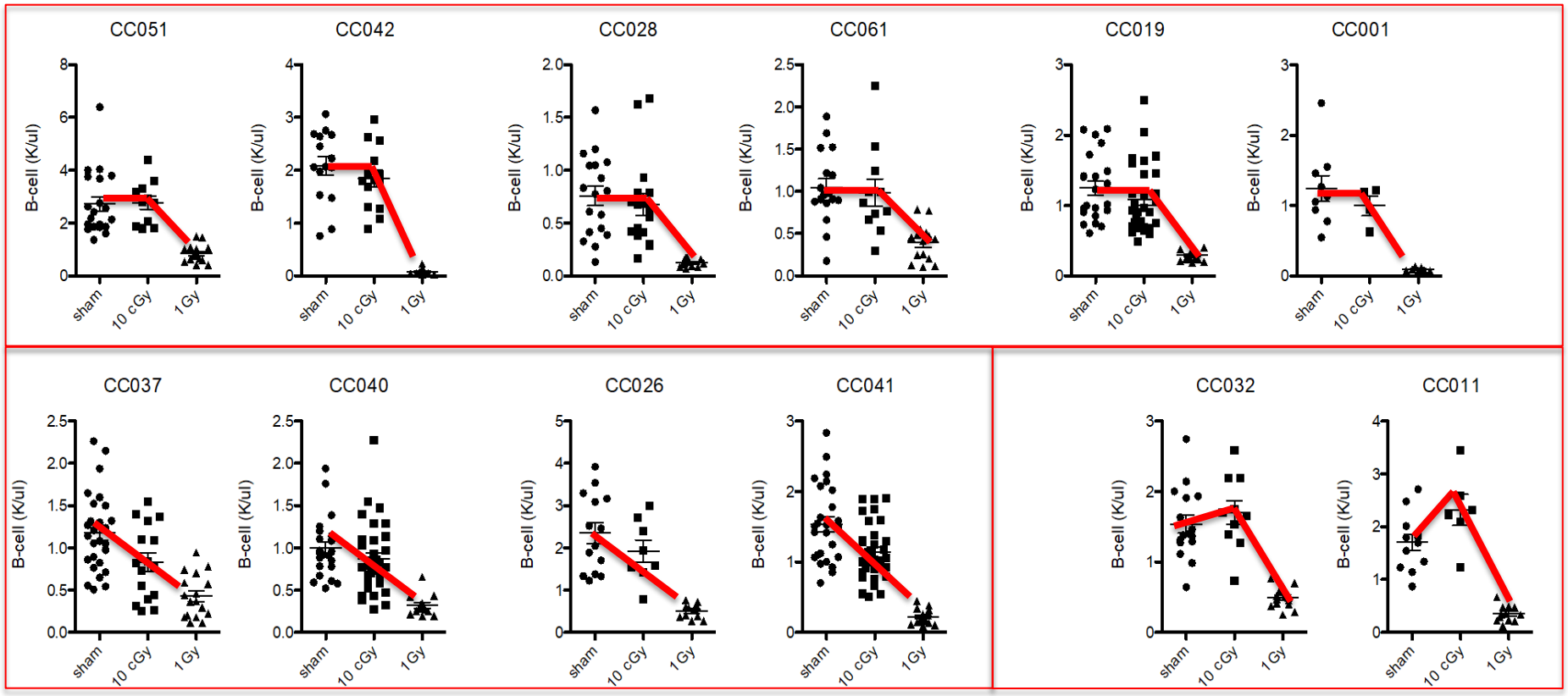

Radiation dose response relationship in immune counts depends on genetic background

Future research strategy: genetically diverse models to predict low-dose radiation health risks

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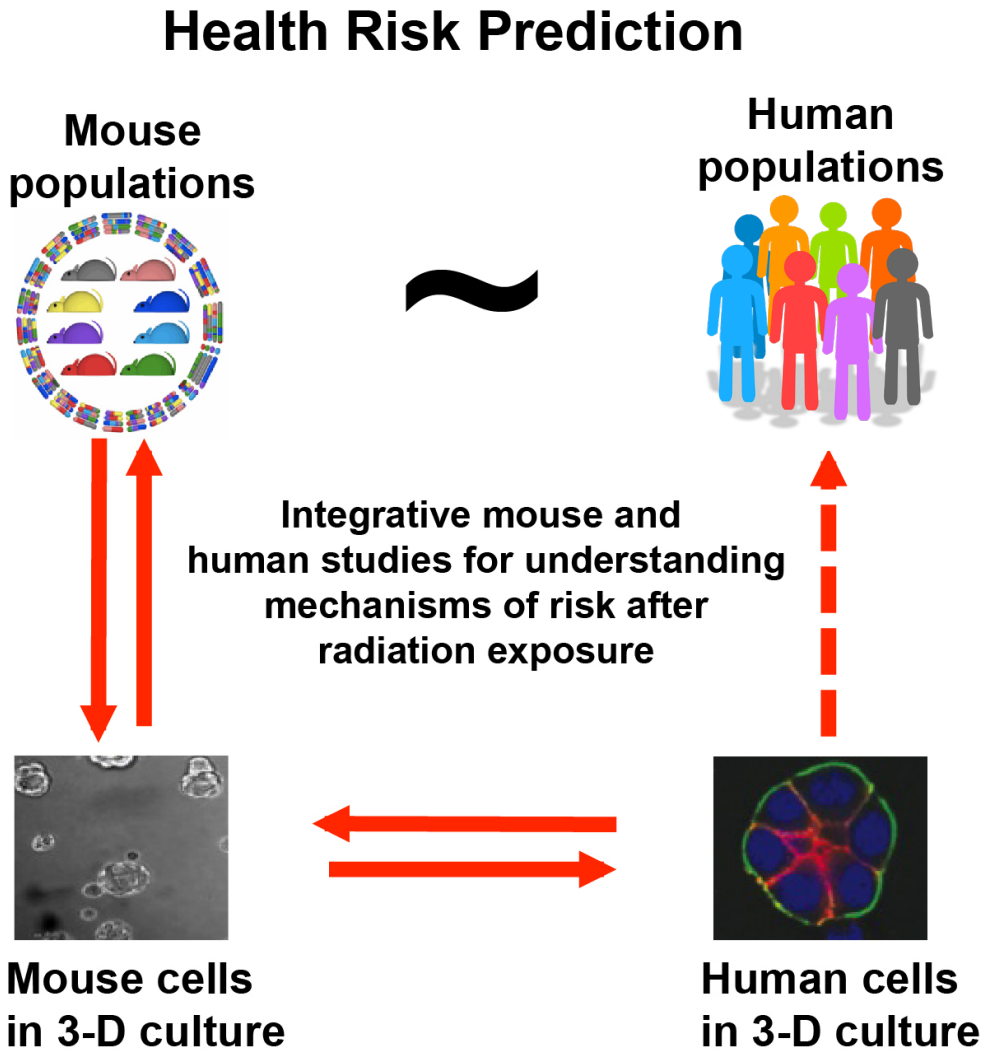

The 'parallelogram strategy'- Integrative Mouse and Human Systems Biology.

Experimental systems used to assess health impacts of radiation exposure and develop new approaches to mitigate tissue injuries arising from exposure to ionizing radiation taking into account INDIVIDUAL VARIABILITY in genes, microbiomes, environment and lifestyles

AI and Machine Learning to translate risk from Mouse to Human

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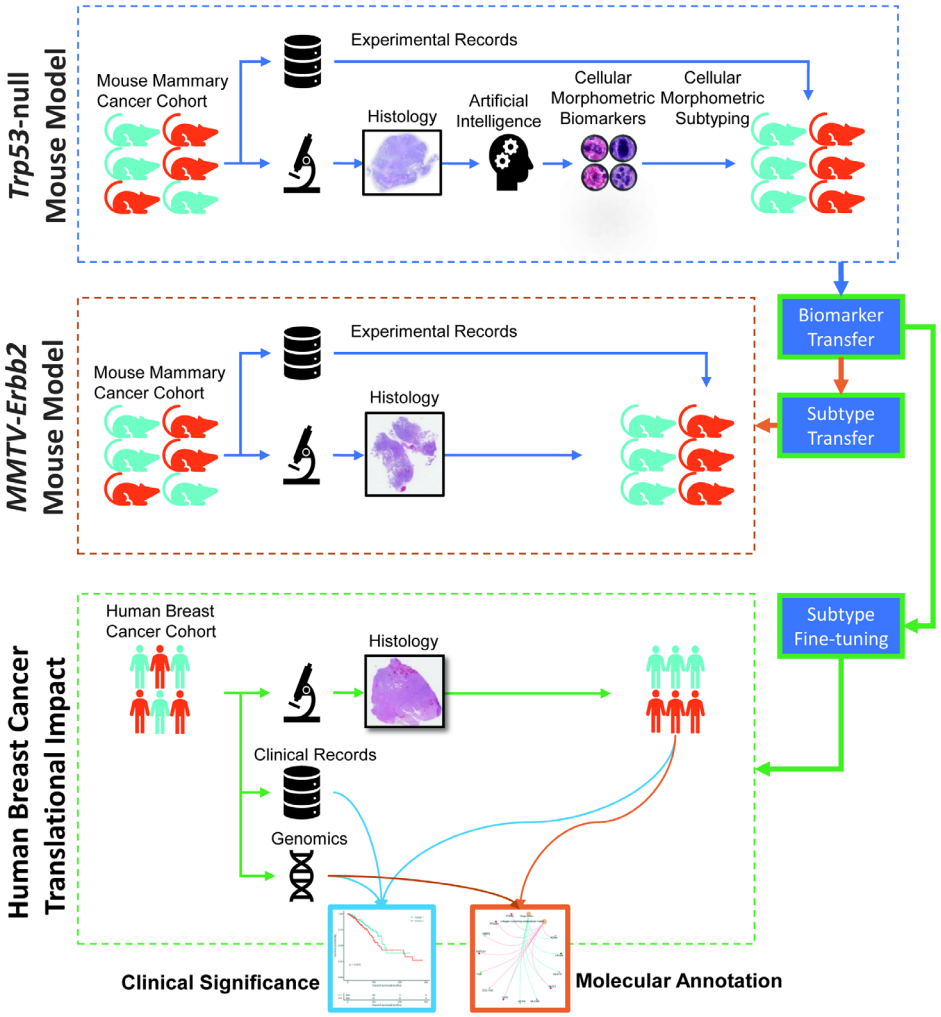

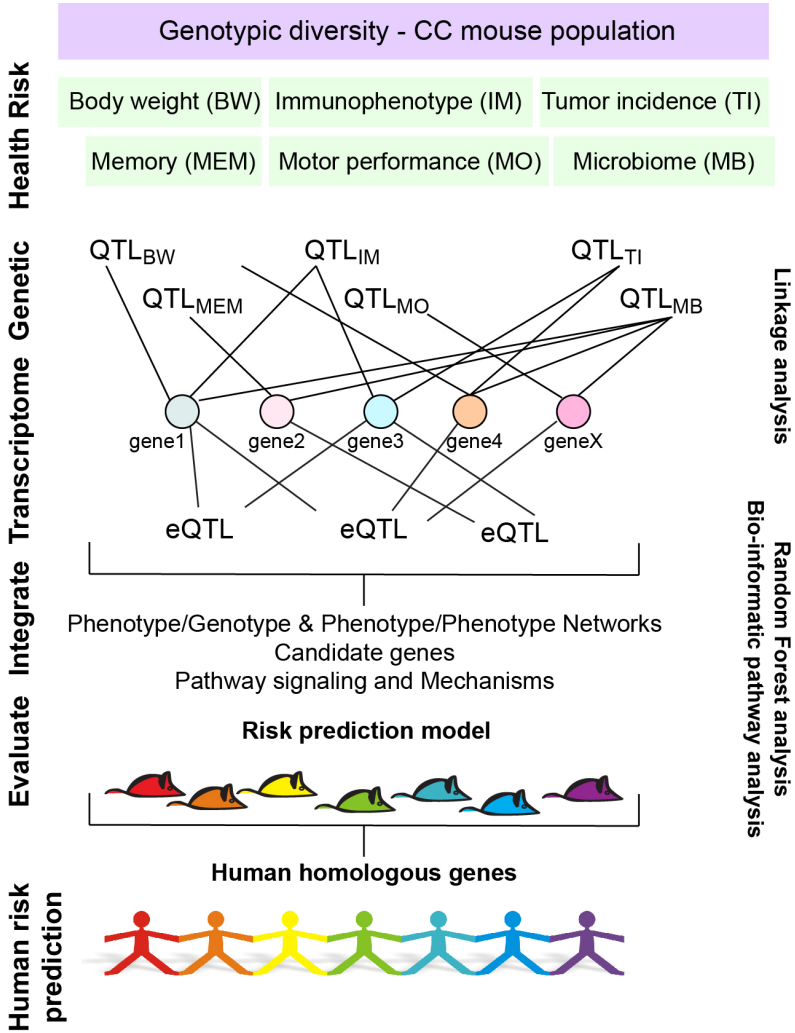

Chang et al, Frontiers in Oncology, 2022

Interest in low-dose radiation effects goes beyond health impact into detection

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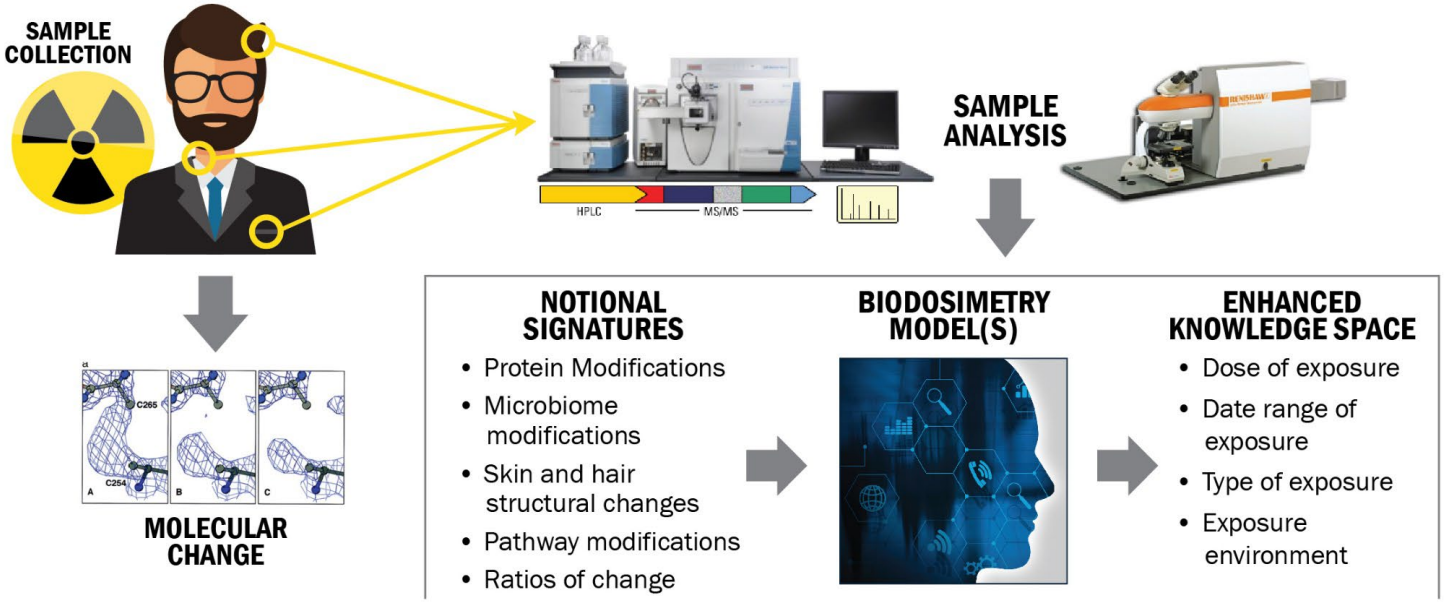
The IARPA TEI-REX low-dose radiation program takes advantage of the unique strengths of National Laboratories, Academic Institutions and Industry Partners to address difficult challenges and push the boundaries of science

TEI REX
Advancing Biodosimetry



Development of transition-ready methodologies and protocols for discovery and characterization of biomarker signatures associated with low dose ionizing radiation exposure.

Proposed impact and payoff

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- Understand the acute impacts of low-dose radiation exposure on human fitness taking into account genetic variation:
  - Identify **biological indicators of radiation exposure** (radiation biomarkers) that assess levels and types of radiation exposure.
  - Identify targets for development of **radiation medical countermeasures.**

- Provide the evidence needed to predict disease risks after radiation exposure incorporating **individual variability** in genes, environment, and lifestyle for each person.

- Define the **mechanism** by which radiation exposure affects health risk using multi-scale and multi-omics systems biology approaches across different model systems.

- Impacts in both countermeasures, therapies, prevention, and nuclear material handling (e.g., reprocessing and storage)

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