Low Dose Radiation Research in DOE

Nuclear and Radiation Studies Board

January 12, 2023

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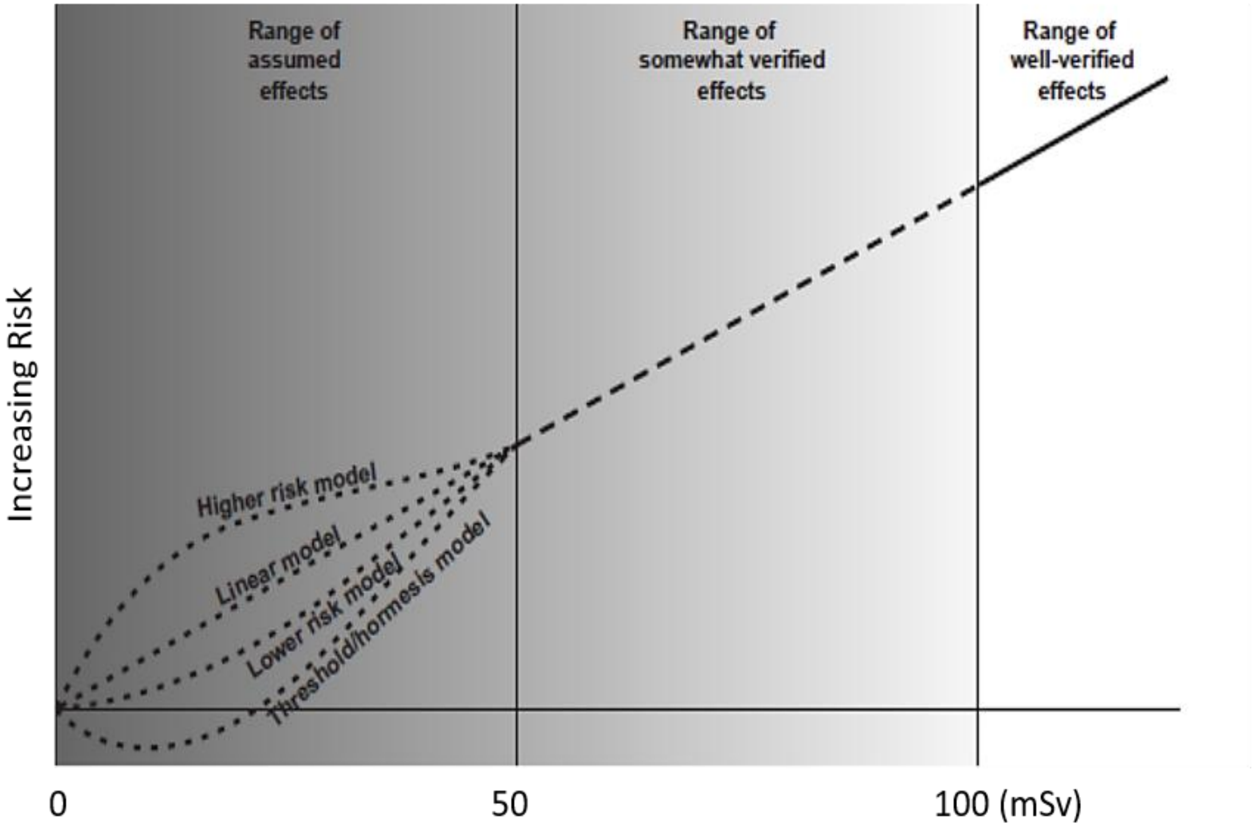
Background - Low Dose Radiation Research

- Low dose radiation defined as < 100mSv
- Radiation research at higher doses indicates a linear relationship between the risk of adverse health effects and radiation dose
- At doses below 100mSv the data is ambiguous
- Current radiation safety protections extrapolate risk linearly with dose, hence the Linear No-Threshold (LNT) hypothesis
- The actual shape of the dose-response curve remains hotly debated to this day and unresolved due to the difficulty of problem

Health Risk Models for Low Dose Radiation



Illustrative diagram of cancer risk models for low dose radiation, including the LNT dose-response (non-threshold)

- **Radiation is a known carcinogen**
- **The primary health risk of radiation exposure is cancer**

What are the Major Sources of Low Dose Radiation Exposure?

- Natural annual background radiation dose is about 3mSv
- Average annual dose in the U.S. is about 6mSv
- Medical diagnostics span a range of exposure levels from very low to significant
- For reference, lethal doses of radiation are in the range of 5.5 -7.5 Sv

An increasing and major source of radiation exposure to the general public is through medical diagnostics and imaging

Exposure route	Dose (mSv)
Airport X-ray scanner	0.00007
Rounds trip flight LA- NYC	≈ 0.037
Dental (x-ray)	0.005*
EPA dose limit – public drinking water	0.04
EPA dose limit – from release in air	0.1
Chest x-ray	0.1*
Mammography	0.4*
DOE, NRC dose limit for the public (ICRP, NCRP)	1
Natural Background, USA (includes radon)	≈ 3.1
Head Computed Tomography (CT) scan (x-ray)	2*
Chest CT scan (x-ray)	7*
Abdominal & Pelvis CT (x-ray)	10*
DHS Emergency guideline for relocation	20
DOE, NRC dose limit for workers	50
International Space Station (ISS) mission typical daily exposure	≈ 0.5-1.2 mSv d-1
Acute exposure detectable in blood	>400
Life Span Study (A-bomb survivors)	0 – 4000
Human LD_{50} acute exposure (no medical intervention)	3500 – 5000
Whole body, acute; circulating blood cell death; moderate GI damage (death probably 2-3wks)	5500 – 7500

Radiation doses and dose limits for various environments and diagnostic procedures

Challenges to Resolving Potential Health Threats of Low Dose Radiation Exposure

- Low dose radiation is a weak carcinogen (high doses are very carcinogenic)
- Cancer has many other known causes (smoking, sedentary life-style, environmental factors, etc.)
- Cancer is a common affliction (40% adults will have some form of cancer over their lifetime)

Attempts to clearly define the contribution of low dose radiation to cancer initiation in humans has been actively researched for past the ~40+ years

- Epidemiological studies at low doses have been inconclusive and non-causative
- Research on surrogate models do not necessarily translate well to humans
- Current radiation protection regulations are based largely on the Life Span Study (LSS) of atomic bomb survivor; one of the most detailed and complete health study of irradiated human beings
- For broader impact on cancer health effects, a revised low dose radiation research effort would need to produce results that add to, explain and extend results of the LSS

DOE's Previous Low Dose Radiation Research Program

- Managed in DOE-BER for 18 years
- Extension of DOE's historical radiobiology efforts extending back decades
  - Focused on doses below 100mSv
- Research performed in university and DOE laboratory-led projects
- A focus of technology development (ex. microbeam technology)
- Some fundamental discoveries:
  - New insights to the "hit model", bystander effect, ROS species, adaptive response
- Ended in 2016 as the DOE-BER portfolio shifted towards bioenergy and environment

- ***Some good insights into the effects of low dose radiation on cellular function***
- ***Little impact on radiation protection regulations or ameliorating public fear of radiation/nuclear power***

What is DOE Doing Now in Low Dose Radiation Research

Congress has appropriated funding to restart low dose radiation research in DOE in FY20, ($5M), FY21 ($5M) and FY22 ($8M) and for FY23 up to $20M

Since FY20 DOE has initiated a different, but complementary approach to low dose radiation research

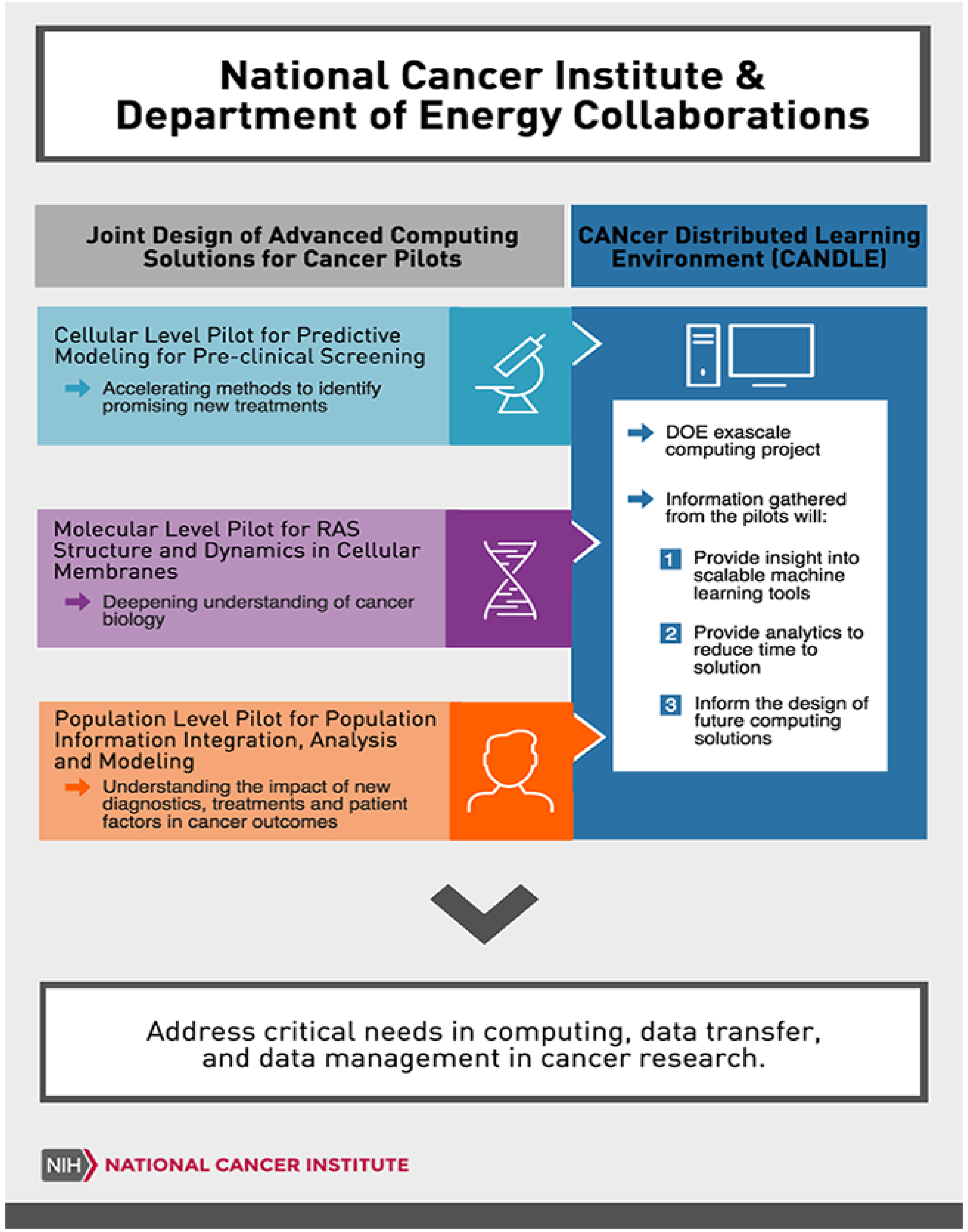
- Genomics-centric focus starting with development of a computationally-driven approach
  - Leveraging the JDACS4C partnership with NCI
  - Focus on human genomic/'omic information from datasets and published literature
- Seeking patterns of harmful/harmless mutations related to radiation exposure
  - Link with NCI datasets (Cancer genome atlas, others)
  - Link with NCBI datasets (GEO, etc.)
  - International datasets (UKBiobank, RERF, etc.)
  - Link with radiooncology and radiation epidemiology efforts
- Use the data to build physical models of risks posed by radiation-induced mutations across a range of dosages
  - Seek to reproduce cancer incidences with dose in LSS data and other data sets of radiation and cancer (other DOE legacy epidemiological datasets)
  - Develop more "causal" links between genomics and radiation exposure and cancer

Bringing Artificial Intelligence and Machine Learning Techniques to Low Dose Radiation Research

- Supplement existing/ongoing joint computational efforts between DOE and NCI for cancer research under the Joint Design of Advanced Computing Solutions for Cancer (JDACS4C) program

- Project led by Argonne National Laboratory in collaboration with: Brookhaven National Laboratory and Oak Ridge National Laboratory

Couples DOE's computational capabilities with NCI's vast datasets and cancer research data



[Joint Design of Advanced Computing Solutions for Cancer (JDACS4C) | CBIIT]

The RadBIO-AI Project is a Supplement to CANDLE

CANcer Distributive Learning Environment (CANDLE)

- An open source, collaboratively developed software platform that provides deep learning methodologies for accelerating cancer research
- One of the DOE-NCI JDACS4C projects
  - Identification of key molecular interactions, based on molecular dynamic simulations of proteins, specifically RAS
  - Predictions of tumor response to drug treatments, based on molecular features of tumor cells and drug descriptors
  - Better characterization of cancer patient trajectories and outcomes using a growing compendium of clinical information

ECP EXASCALE COMPUTING PROJECT

One of DOE's Exascale Computing Projects

Using AI and ML concepts to as tools link molecular scale interactions with cancer drug treatments/responses to patient outcomes

Extending this effort to the low dose radiation research

RadBIO-AI Project

Campaign 1 *is aimed at the questions related to discovering signatures of radiation damage, characterizing these signatures, and producing a set of predictive models that can be used to detect these signatures in a sample*

- Train models on patterns of gene expression data that can be linked to:
  - radiation exposure
  - dose rate
- Patterns of genomic variation that may be indicative of radiation exposure, e.g., changes in:
  - single nucleotide variation
  - multi-nucleotide variation
  - indels
  - other changes beyond random mutation
- Test the models against published datasets

- **Gene expression datasets from NCBI GEO**
- **Gene expression and variation data from Genomic Data Commons (GDC)**
- **SNP/genotyping datasets from UK Biobank**

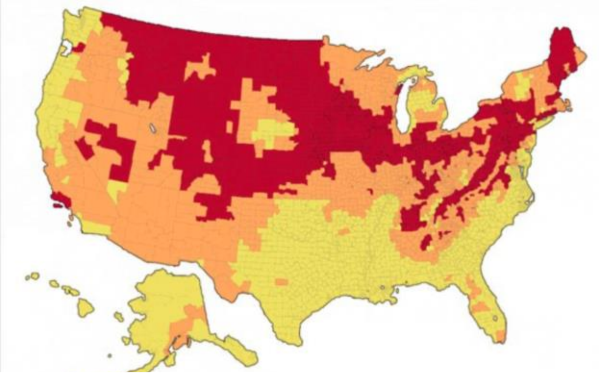
Davidson, P.R., Sherborne, A.L., Taylor, B. *et al.* **A pooled mutational analysis identifies ionizing radiation-associated mutational signatures conserved between mouse and human malignancies.** *Sci Rep* **7,** 7645 (2017). https://doi.org/10.1038/s41598-017-07888-0

Jain V, Das B. **Global transcriptome profile reveals abundance of DNA damage response and repair genes in individuals from high level natural radiation areas of Kerala coast.** PLoS One. 2017 Nov 21;12(11):e0187274. doi: 10.1371/journal.pone.0187274. PMID: 29161272; PMCID: PMC5697823.

LifeSpan Study (LSS) data from RERF

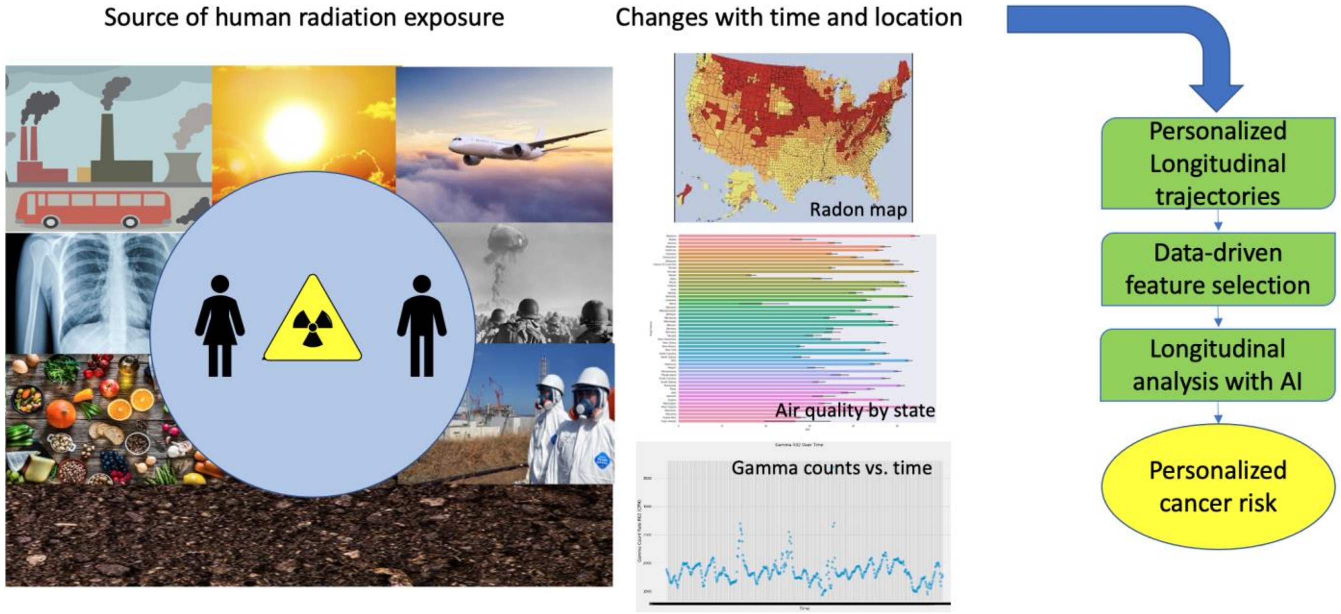
RadBIO-AI Project Cont'd

***Campaign 2** is aimed at building a framework for capturing longitudinal radiation exposure profiles and using these profiles to estimate cancer risk*



- Capture and model longitudinal environmental exposure
- Estimate how environmental factors change the risk of cancer throughout an individual's lifetime?
- Extract terms from medical records that indicate a patient was exposed to radiation

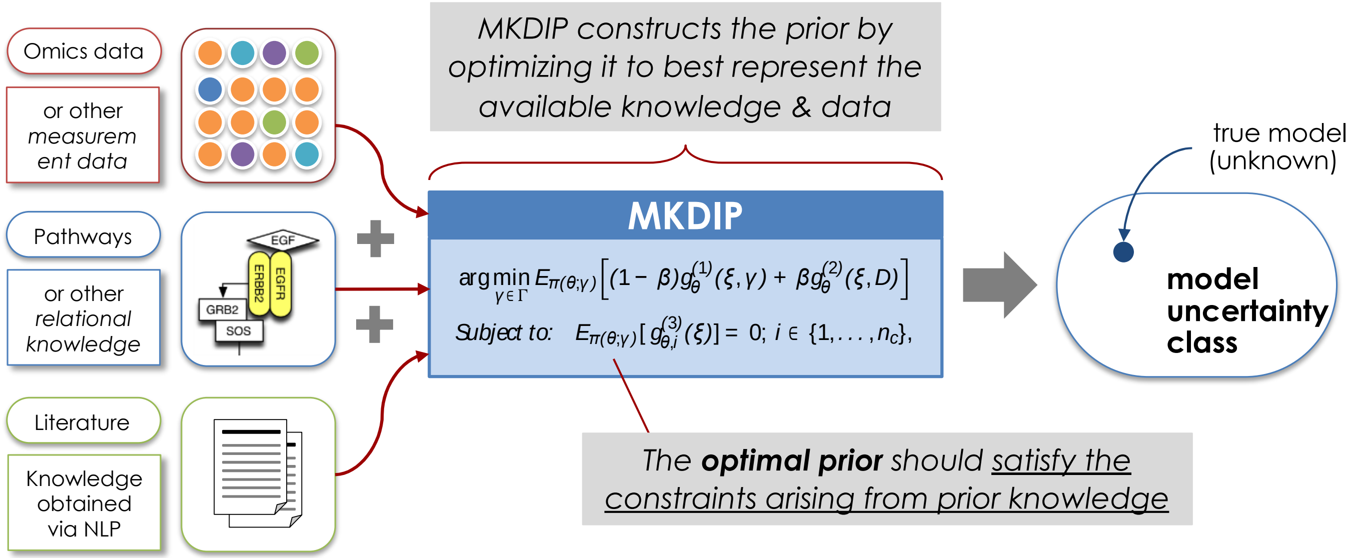
Dataset
Radnet (background gamma counts)
Radon zone (EPA)
Nuclear power plant
I-131 exposure (NCI)
Per capita air travel
Air quality
Cancer Incidence



RadBIO-AI Project Cont'd

Campaign 3 *is aimed at extracting associations from the scientific and biomedical literature that can be used to advance our understanding of low-dose radiation biology, create novel hypotheses for computational testing, and to create Bayesian priors that may improve the predictive capacity of our machine learning methods*

- Use machine learning/AI to extract from the biomedical literature the identification of radiation induced cellular pathway perturbations?
- Use the biomedical literature to generate priors that improve our machine learning methods?



Use Natural Language Processing (NLP) to search the literature, identify datasets, add the relevant datasets to the existing knowledgebase and improve predictions

Links back and informs Campaign 1

Potential Outcomes of AI/ML Approaches

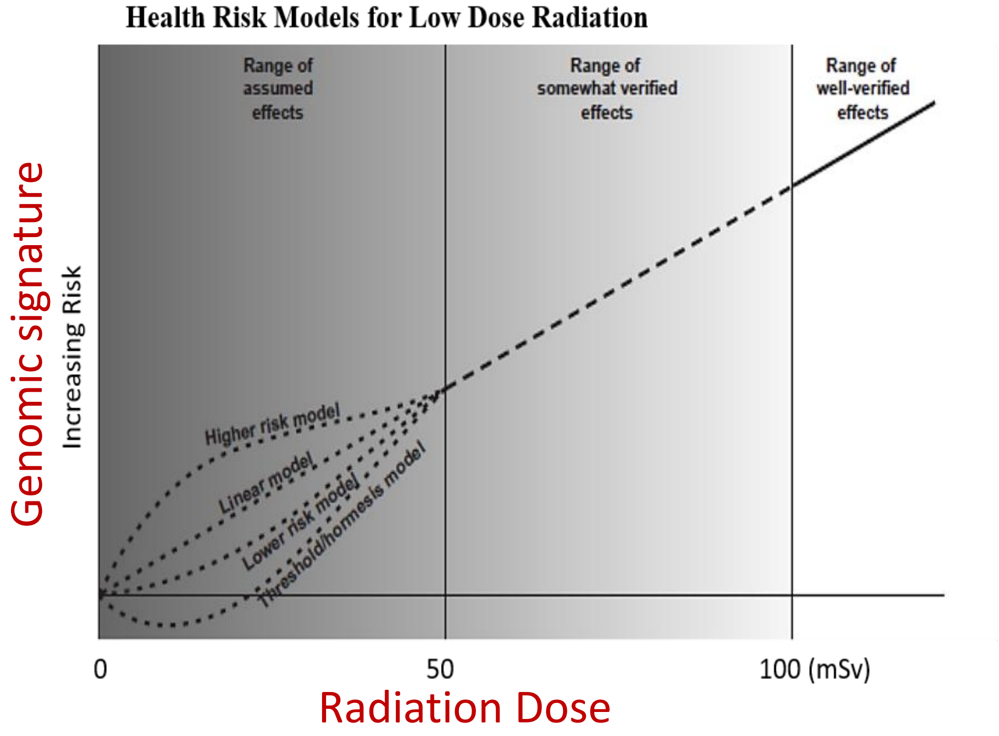
Leveraging AI/ML techniques and high-performance computing to:

- Integrate multiple complex genomic/omics datasets/records/cancer treatment information
- Analyze radiation exposure data (environmental, medical diagnostics, workplace, etc.)
- Examine the <u>totality</u> of the published research literature on cancer and radiation exposure studies
- Seek predictive patterns of genomic/omic changes due to radiation exposure linked to health impact

➡ ***Building a powerful capability to identify subtle patterns in massively complex and disparate data leading to testable hypotheses regarding cancer and low dose radiation exposure***

A Goal for these Computational Efforts

- Identify mutational patterns related to cancer incidence due to radiation exposure
  - Known mutations and identify unknown patterns.
- Seek to develop relationships between patterns of observed genomic mutations and radiation dose.
- Develop physical models that may help explain patterns of genomic mutations leading to cancer relative to expected random patterns of genomic mutation
  - Implications for identifying a "threshold" dose and even specific patterns that may be related to enhanced susceptibility
  - Implications to examine other health effects as well.



Improved genomic-focused understanding of cancer on which to re-examine the relationship between radiation dose and health risk

Potential Links with NCI Programs

Building a Robust AI/ML Capability for Low Dose Radiation Exposure

- Seeking to find patterns of genomic mutational signatures associated with radiation exposure leading to adverse health outcomes (e.g. cancer)
- Mutation patterns may be a way to “scale” estimates of risk to lower radiation doses.
  - Need access to large human genome datasets and associated health data to establish baseline level of natural variability
  - Compare with known cancer-related mutational signatures
  - Seek ways to understand mutational patterns of radiation exposure.
  - Need epidemiological data that includes genomic data
- Adapt physical models and simulation to mutational patterns to assess risk.

Potential Connections with NCI programs

- NCI datasets (NIAID, NHGRI)
- Epidemiology groups (radiation epidemiology)
- Radiation Oncology Branch
  - Mutational patterns of radiation exposure at varying doses

Complements Priority Low Dose Radiation Research Goals from a NASEM Strategic Plan

Priority Research Goal	Approach
E1 Develop and deploy analytical tools for radiation epidemiology.	Develop cohorts of sufficient size, with detailed health information and biosample collection and accurate dosimetry, to support epidemiological studies of radiation-induced health effects in medically, occupationally, and environmentally exposed U.S. populations.
E2 Improve estimation of risks for cancer and non-cancer health outcomes from low-dose and low-dose-rate external and internal radiation exposures.	More precisely define health outcomes to enable exclusion of diseases caused by other effects, identifying easily measured signatures that can serve as disease surrogates by improving dosimetry and identifying and compensating for confounding and modifying factors.
E3 Determine factors that modify the low-dose and lowdose-rate radiation-related adverse health effects.	Assess the impact of genetic makeup, epigenomic status, DNA repair efficacy, comorbidities, exposure history to radiation and other agents, lifestyle and psychosocial factors, and immune status on radiation induced adverse health outcomes.
B1 Develop appropriate model systems for study of lowdose and low-dose-rate radiation-induced health effects.	Identify laboratory model systems in which molecular, cellular, and pathological features of radiation-induced health effects are similar to humans.
B2 Develop biomarkers for radiation-induced adverse health outcomes.	Identify radiation-induced changes in cellular and molecular features that causally link to adverse health effects in appropriate model systems.
B3 Define health-effect dose-response relationships below 10 mGy and below 5 mGy/h.	Establish radiation dose-response curves for molecular and cellular endpoints and for associated early- and late-stage diseases at doses below 10 mGy and dose rates below 5 mGy/h.
B4 Identify factors that modify or confound estimation of risks for radiation-induced adverse health outcomes.	Assess the impact of genetic makeup, epigenomic status, DNA repair efficacy, comorbidities, exposure history to radiation and other agents, lifestyle factors, and immune status on low-dose and low-dose-rate radiation-induced adverse health effects and associated cellular and molecular response endpoints.
I1 Tools for sensitive detection and precise characterization of aberrant cell and tissue states.	Identify, develop, and deploy bulk and single-cell -omics*a* and image measurement and computational analysis workflows to quantify disease-linked cellular and molecular signatures that are sufficiently sensitive, reliable, and low cost for wide-scale application.
I2 Harmonized databases to support biological and epidemiological studies.	Develop accessible databases that document exposure levels, rates, types, and durations as well as cell, molecular, and health outcomes for human populations and experimental models.
I3 Dosimetry for low-dose and low-dose-rate exposures.	Elucidate biological localization of internalized radionuclides; directly measure radiation-induced damage and associated response mechanisms; develop high-fidelity anatomically and physiologically based dosimetry; develop and apply modern statistical and computational methods for dose reconstruction.
I4 Facilities for low-dose and low-dose-rate exposures	Ensure access to low-dose and low-dose-rate exposure facilities, including those allowing internal exposure in model systems by a variety of routes (e.g., inhalation, ingestion) or invest in new facilities.

Outlook for AI/ML Computational Capabilities

Computational Efforts are a Start to Revamping Low Dose Radiation Research in DOE

- To date, it has not been possible to establish the broad-scale program envisioned in the NASEM strategic plan report, given the resources provided
- The AI/ML efforts being undertaken by DOE are not the sole solution to low dose research
    - It is a different approach – takes advantage of rapidly advancing AI/ML techniques for research
    - Applies world-class leading-edge capabilities to a challenging problem
    - Could help guide future epidemiological and experimental efforts in a broader portfolio
    - Not a short-term issue – requires early investment to establish the capability
- It is opportunity for DOE to apply unique signature capabilities to a challenging problem
    - Continues and broadens an established collaboration with NCI
    - Seeks additional connections with other elements within NCI and broader NIH programs

AI/ML computational capabilities hold potential to be incredibly valuable resources for low dose research

Efforts in FY 2023

Funding in FY 2023

- BER's appropriation guidance for low dose radiation research in FY 2023 is "up to" $20M.
- Overall BER's budget is extremely tight
- It is likely that BER will be able to maintain at least an $8M effort given the significant guidance.

DOE's Office of Environment, Health, Safety and Security (EHSS)

- Coordinate access to legacy epidemiology datasets with the RAD-Bio AI project
- Coordinate on research needs within the EHSS portfolio
- Gain assistance from EHSS staff with backgrounds in radiation biology

Thank you

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