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Developing a Long-Term Strategy for Low-Dose Radiation Research in the United States

PUBLIC MEETING #5 (Virtual)
November 16-17, 2021, All times are ET

DRAFT PUBLIC AGENDA

ZOOM CONNECTION

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Also in the agenda:

Pointers to Speakers (See individual agenda items.)
Reading Material
Speaker Biographies
Statement of Task

Nuclear and Radiation Studies Board
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DAY 1: November 16

11:00 AM – 11:10 AM **Welcome and Open Public Session**
Joe Gray, Committee Chair

11:10 AM – 11:30 PM **Setting the Stage: New Directions for Low-Dose Radiation Research (15-20 min)**
Jonine Bernstein, Memorial Sloan Kettering

- The committee is interested in your views and perspectives on its statement of task.
- What are your views on research priorities for low dose radiation research?
- How can epidemiology contribute to further understanding risks?
- What are some limitations and how can these be overcome?

11:30 PM – 11:45 PM **Q+A with the Committee and Staff**
Moderated by Joe Gray, Committee Chair

11:45 AM – 12:25 PM **Genetics, epigenetics, and the Microbiome (15-20 min each)**
Dale Ramsden, UNC-Chapel Hill

- Molecular approaches to improve understanding of DNA repair following low dose radiation exposures.
- Gaps and opportunities
- Views on research priorities

Chris Mason, Weill Cornell Medicine

- Epigenetic changes and their applications to radiation epidemiology (with examples)
- Clonal hematopoiesis and space radiation.
- Techniques used to identify functional elements of the microbiome.
- Application of these techniques following radiation exposures (with examples)
- Opportunities and challenges for epigenetics and microbiome research in low dose radiation exposures.
- Views on research priorities.

12:25 PM – 12:50 PM **Q+A with the Committee and Staff**
Moderated by Joe Gray, Committee Chair

12:50 PM – 1:10 PM **BREAK**

1:10 PM – 1:30 PM **In Utero Exposure (15-20 min)**
Richard Wakeford, University of Manchester

- Overview of studies of in utero exposure to radiation with emphasis on low doses.
- Opportunities and challenges.
- Views on research priorities

1:30 PM – 1:40 PM **Q+A with the Committee and Staff**
Moderated by Joe Gray, Committee Chair

1:40 PM – 2:20 PM **The Future of Low-Dose Radiation Risk Modeling (15-20 min each)**

Dale Preston*, *Hirosoft International

- Dose-response challenges at low doses.
- Limitations of low-dose epidemiological studies (with examples)
- Opportunities for low-dose epidemiological studies (with examples)
- Effect modification, uncertainties, and dose error: issues and opportunities to overcome these in low dose studies
- Views on research priorities

Igor Shuryak*, *Columbia University

- Modeling radiation effects including radiation carcinogenesis, normal tissue complications, radioresistance and non-targeted effect (with examples)
- Incorporation of uncertainties
- Opportunities and challenges of modeling radiation effects at low doses. Please discuss cancer and non-cancer effects.
- Views on research priorities.

2:20 PM – 2:40 PM **Q+A with the Committee and Staff**

Moderated by Joe Gray, Committee Chair

2:40 PM – 3:20 PM **The Future of Low-Dose Radiation Dosimetry (15-20 min each)**

Wes Bolch*, *University of Florida

- Advancements in dosimetry to support radiation epidemiology (with examples)
- Opportunities and challenges of using these advancements in low dose radiation research including for evaluating and addressing uncertainties.
- Views on research priorities

Note: please focus the presentation on new technologies. Dr. Choonsik (NCI) will focus on applications.

Choonsik Lee*, *National Cancer Institute

- Methods and tools to estimate radiation dose in low dose radiation studies of medical, occupational, and environmental exposures (with examples)
- Limitations of epidemiological studies (with examples)
- Opportunities for epidemiological studies (with examples) including for evaluating and addressing uncertainties.
- Views on research priorities

Note: please focus the presentation on applications. Dr. Bolch (U. Florida) will focus on technologies.

3:20 PM – 3:35 PM **Q+A with the Committee and Staff**

Moderated by Joe Gray, Committee Chair

3:35 – 3:45 PM **BREAK**

3:45 PM – 4:45 PM **Modern Tools in Neuroscience and Tumor Immunogenicity Research (15-20 min each)**

Ruben Gur*, *University of Pennsylvania

- Tools for functional neuroimaging.
- Application of these tools following radiation exposures (with examples).
- Opportunities and challenges to use these techniques in low dose radiation exposures.
- Views on research priorities.

Daniel Marks*, *Oregon Health & Science University

- Tools and methods to study brain-disease interactions.
- The role of stress on how brain influences health and function of peripheral tissues.
- Opportunities and challenges to use these techniques in low dose radiation exposures.

Sandra Demaria*, *Weill Cornell

- Methods to study immune response and its role in cancer development and treatment.
- Applications of these methods to low-dose radiation exposure.
- Opportunities and challenges to improve understanding of the immune response at low doses.
- Views on research priorities.

4:45 PM – 5:05 PM **Q+A with the Committee and Staff**

Moderated by Joe Gray, Committee Chair

5:05 PM – 5:25 PM **Social Disparities and Environmental Exposures (15-20 min)**

Johnnye Lewis*, *University of New Mexico

- Work to understand exposures (radiation or other) in Native communities and interactions with traditional lifestyles, culture, and health.
- Perceptions of exposures in Native communities
- Opportunities and challenges in relation to low dose radiation exposures.
- Views on research priorities

5:25 PM- 5:35 PM **Q+A with the Committee and Staff**

Moderated by Joe Gray, Committee Chair

5:35 PM – 6:20 PM **Low-Dose Radiation Research in Japan (12-15 min each)**

Tatsuhiko Imaoka*, *Quantum and Radiological Science and Technology (QST), Japan

Shizuko Kakinuma*, *QST

Yoshiya Shimada*, *Institute for Environmental Sciences

- Please provide an overview of the type of low-dose radiation research carried out in your organizations with emphasis on cutting-edge technologies.
- Please describe the radiation facilities housed in your organizations that are used for low-dose and low-dose rate experiments. Are these facilities accessible to other research groups within or outside of Japan?

- Who are the primary funding sources of your low-dose research?
- How do you communicate research findings with expert and non-expert groups?
- Is low-dose research coordinated with other organizations within Japan or elsewhere? If yes, how is this coordination achieved.

6:20 PM – 6:30 PM **Q+A with the Committee and Staff**
Moderated by Joe Gray, Committee Chair

6:30 PM **Adjourn Day 1**

DAY 2: November 17

11:00 AM – 11:05 AM **Welcome and Open Public Session**
Joe Gray, Committee Chair

11:05 AM – 12:05 PM **Advances in Understanding Cancer Evolution and Cellular Response to Radiation (15-20 min each)**
***Stephen Chanock*, National Cancer Institute**
- Modern techniques for characterization of cancer susceptibility regions in the human genome.
- Use of these techniques in radiation epidemiology studies (with examples)
- Opportunities and challenges of using these techniques in low dose radiation research.
- Views on research priorities

***Phil Jones*, Sanger Institute**
- Modern techniques for mapping cells carrying mutations in normal tissues.
- Applicability of these techniques in radiation epidemiology studies
- Opportunities and challenges of using these techniques in low dose radiation research.
- Views on research priorities

***Serge Candéias*, CEA, France**
- Methods to study immune response at low doses of radiation (with examples)
- Opportunities and challenges to improve understanding of the immune response at low doses.
- Views on research priorities.

12:05 PM – 12:25 PM **Q+A with the Committee and Staff**
Moderated by Joe Gray, Committee Chair

12:25 PM – 1:25 PM **What can the Low-Dose Radiation Program Learn from Other Programs? (15-20 min each)**
***Ed Harlow*, Harvard Medical School**

- Scope and origin of NCI's Provocative Questions
- Process for identifying and selecting provocative questions and for issuing requests for applications
- Link between provocative questions and NCI's overall research priorities
- Effectiveness and impact of the effort in terms of funding of the identified research priorities and answering the scientific questions

Mike Snyder, Stanford

- Scope of HTAN and HuBMAP, driver(s) for the initiatives, rationale for organization
- Process for organizing research goals and creating a strategy to achieve those goals
- Infrastructure (facilities and experts) to support these efforts
- Metrics to assess progress and impact
- Coordination and cooperation across participating organizations
- Lessons to be learned for low-dose research

Cheryl Walker, Baylor College of Medicine

- Scope of the TaRGET II Consortium, driver(s) for the initiative, rationale for organization
- Process for organizing research goals and creating a strategy to achieve those goals
- Infrastructure (facilities and experts) to support the consortium
- Metrics to assess progress and impact
- Coordination and cooperation across participating organizations
- Lessons to be learned for low-dose research

1:25 PM - 1:45 PM	**Q+A with the Committee and Staff** *Moderated by Joe Gray, Committee Chair*
1:45 PM – 2:10 PM	**Opportunity for Public Comment**
2:10 PM	**Adjourn Open Session**
~2:30 – 6:00 PM	**Closed Session for Committee and Staff**

Reading Material

Candéias

- Baselet, B., O. Azimzadeh, N. Erbeldinger, M. V. Bakshi, T. Dettmering, A. Janssen, S. Ktitareva, D. J. Lowe, A. Michaux, R. Quintens, K. Raj, M. Durante, C. Fournier, M. A. Benotmane, S. Baatout, P. Sonveaux, S. Tapio, and A. Aerts. 2017. Differential Impact of Single-Dose Fe Ion and X-Ray Irradiation on Endothelial Cell Transcriptomic and Proteomic Responses. Front Pharmacol 8: 570.

- Donaubauer, A. J., I. Becker, P. F. Ruhle, R. Fietkau, U. S. Gaipl, and B. Frey. 2020. Analysis of the immune status from peripheral whole blood with a single-tube multicolor flow cytometry assay. Methods Enzymol 632: 389-415.
- Feehan, K. T., and D. W. Gilroy. 2019. Is Resolution the End of Inflammation? Trends Mol Med 25: 198-214.
- Lumniczky, K., N. Impens, G. Armengol, S. Candeias, A. G. Georgakilas, S. Hornhardt, O. A. Martin, F. Rodel, and D. Schaue. 2021. Low dose ionizing radiation effects on the immune system. Environ Int 149: 106212.
- UNSCEAR 2020 Report, Annex C “Biological mechanisms relevant for the inference of cancer risks from low-dose and low dose rate radiation”. To be published in 2021.

Demaria

- Radiation therapy and anti-tumor immunity: exposing immunogenic mutations to the immune system https://pubmed.ncbi.nlm.nih.gov/31221199/
- Emerging biomarkers for the combination of radiotherapy and immune checkpoint blockers. https://pubmed.ncbi.nlm.nih.gov/29258856/
- Low dose ionizing radiation effects on the immune system. https://pubmed.ncbi.nlm.nih.gov/33293042/
- Aggressive mammary cancers lacking lymphocytic infiltration arise in irradiated mice and can be prevented by dietary intervention. https://pubmed.ncbi.nlm.nih.gov/31831632/
- It's not 'just a tube of blood': principles of protocol development, sample collection, staffing and budget considerations for blood-based biomarkers in immunotherapy studies. https://pubmed.ncbi.nlm.nih.gov/34321277/

Imaoka, Kakinuma, and Shimada

1. Experimental studies on the biological effects of chronic low dose-rate radiation exposure in mice: overview of the studies at the Institute for Environmental Sciences.
   Braga-Tanaka I 3rd, Tanaka S, Kohda A, Takai D, Nakamura S, Ono T, Tanaka K, Komura JI.
   Int J Radiat Biol. 2018 May;94(5):423-433. doi: 10.1080/09553002.2018.1451048. Epub 2018 Apr 3.
   PMID: 29533133 Review.
2. Prominent Dose-Rate Effect and Its Age Dependence of Rat Mammary Carcinogenesis Induced by Continuous Gamma-Ray Exposure.
   Imaoka T, Nishimura M, Daino K, Hosoki A, Takabatake M, Nishimura Y, Kokubo T, Morioka T, Doi K, Shimada Y, Kakinuma S.
   Radiat Res. 2019 Mar;191(3):245-254. doi: 10.1667/RR15094.1. Epub 2018 Dec 13.
   PMID: 30543491
3. Establishing the Japan-Store house of animal radiobiology experiments (J-SHARE), a large-scale necropsy and histopathology archive providing international access to important radiobiology data.
   Morioka T, Blyth BJ, Imaoka T, Nishimura M, Takeshita H, Shimomura T, Ohtake J, Ishida A, Schofield P, Grosche B, Kulka U, Shimada Y, Yamada Y, Kakinuma S.
   Int J Radiat Biol. 2019 Oct;95(10):1372-1377. doi: 10.1080/09553002.2019.1625458. Epub 2019 Jun 26.
   PMID: 31145030 Review.
4. Funding for radiation research: past, present and future.
   Cho K, Imaoka T, Klokov D, Paunesku T, Salomaa S, Birschwilks M, Bouffler S, Brooks AL, Hei TK, Iwasaki T, Ono T, Sakai K, Wojcik A, Woloschak GE, Yamada Y, Hamada N.

Int J Radiat Biol. 2019 Jul;95(7):816-840. doi: 10.1080/09553002.2018.1558303. Epub 2019 Feb 15.
PMID: 30601684 **Free PMC article.** Review.

5. Differential effect of parity on rat mammary carcinogenesis after pre- or post-pubertal exposure to radiation.
Takabatake M, Daino K, Imaoka T, Blyth BJ, Kokubo T, Nishimura Y, Showler K, Hosoki A, Moriyama H, Nishimura M, Kakinuma S, Fukushi M, Shimada Y.
Sci Rep. 2018 Sep 25;8(1):14325. doi: 10.1038/s41598-018-32406-1.
PMID: 30254198 **Free PMC article.**
6. Exome of Radiation-induced Rat Mammary Carcinoma Shows Copy-number Losses and Mutations in Human-relevant Cancer Genes.
Moriyama H, Daino K, Ishikawa A, Imaoka T, Nishimura M, Nishimura Y, Takabatake M, Morioka T, Inoue K, Fukushi M, Shimada Y, Kakinuma S.
Anticancer Res. 2021 Jan;41(1):55-70. doi: 10.21873/anticanres.14751.
PMID: 33419799
7. Radiation-associated loss of heterozygosity at the Znfn1a1 (Ikaros) locus on chromosome 11 in murine thymic lymphomas.
Shimada Y, Nishimura M, Kakinuma S, Okumoto M, Shiroishi T, Clifton KH, Wakana S.
Radiat Res. 2000 Sep;154(3):293-300. doi: 10.1667/0033-7587(2000)154[0293:raloha]2.0.co;2.
PMID: 10956435
8. Spectrum of Znfn1a1 (Ikaros) inactivation and its association with loss of heterozygosity in radiogenic T-cell lymphomas in susceptible B6C3F1 mice.
Kakinuma S, Nishimura M, Sasanuma S, Mita K, Suzuki G, Katsura Y, Sado T, Shimada Y.
Radiat Res. 2002 Mar;157(3):331-40. doi: 10.1667/0033-7587(2002)157[0331:soziia]2.0.co;2.
PMID: 11839096
9. Genomic and gene expression signatures of radiation in medulloblastomas after low-dose irradiation in Ptch1 heterozygous mice.
Ishida Y, Takabatake T, Kakinuma S, Doi K, Yamauchi K, Kaminishi M, Kito S, Ohta Y, Amasaki Y, Moritake H, Kokubo T, Nishimura M, Nishikawa T, Hino O, Shimada Y.
Carcinogenesis. 2010 Sep;31(9):1694-701. doi: 10.1093/carcin/bgq145. Epub 2010 Jul 8.
PMID: 20616149
10. Sensitive Detection of Radiation-Induced Medulloblastomas after Acute or Protracted Gamma-Ray Exposures in Ptch1 Heterozygous Mice Using a Radiation-Specific Molecular Signature.
Tsuruoka C, Blyth BJ, Morioka T, Kaminishi M, Shinagawa M, Shimada Y, Kakinuma S.
Radiat Res. 2016 Oct;186(4):407-414. doi: 10.1667/RR14499.1. Epub 2016 Sep 30.
PMID: 27690174
11. High Relative Biological Effectiveness of 2 MeV Fast Neutrons for Induction of Medulloblastoma in Ptch1+/- Mice with Radiation-specific Deletion on Chromosome 13.
Tsuruoka C, Kaminishi M, Shinagawa M, Shang Y, Amasaki Y, Shimada Y, Kakinuma S.
Radiat Res. 2021 Aug 1;196(2):225-234. doi: 10.1667/RADE-20-00025.1.
PMID: 34046685
12. Interstitial chromosomal deletion of the tuberous sclerosis complex 2 locus is a signature for radiation-associated renal tumors in Eker rats.
Inoue T, Kokubo T, Daino K, Yanagihara H, Watanabe F, Tsuruoka C, Amasaki Y, Morioka T, Homma-Takeda S, Kobayashi T, Hino O, Shimada Y, Kakinuma S.
Cancer Sci. 2020 Mar;111(3):840-848. doi: 10.1111/cas.14307. Epub 2020 Feb 3.
PMID: 31925975 **Free PMC article.**

Lewis

- Lewis et al., 2017. Mining and Environmental Health Disparities in Native American Communities. Curr Envir Health Rpt, 4:130–141, DOI 10.1007/s40572-017-0140-5

Mason

- Clonal Hematopoiesis Before, During, and After Human Spaceflight https://www.cell.com/cell-reports/fulltext/S2211-1247(20)31447-9
- Telomere Length Dynamics and DNA Damage Responses Associated with Long-Duration Spaceflight https://www.cell.com/cell-reports/fulltext/S2211-1247(20)31446-7
- Haplotype diversity and sequence heterogeneity of human telomeres https://genome.cshlp.org/content/31/7/1269
- The NASA Twins Study: A multidimensional analysis of a year-long human spaceflight https://www.science.org/doi/10.1126/science.aau8650
- Shotgun transcriptome, spatial omics, and isothermal profiling of SARS-CoV-2 infection reveals unique host responses, viral diversification, and drug interactions https://www.nature.com/articles/s41467-021-21361-7

Speaker Biographies

Dr. **Jonine Bernstein** is an Attending Epidemiologist at Memorial Sloan Kettering Cancer Center and co-Leader of the institution-wide Population Sciences Research Program. She received a Ph.D. in Epidemiology from Yale University, an M.S. in Applied Biometry from the University of Southern California and an A.B. in Urban Environmental Health (Independent Concentration) from Brown University. Dr. Bernstein's research focuses on genetic and molecular epidemiology, particularly in the etiology of breast cancer and gliomas and the late effects of treatment. She is also spear-heading projects developing and validating biomarkers of breast cancer and cognitive impairment. Dr. Bernstein is the PI of the international population-based 25-center Women's Environmental Cancer Radiation and Epidemiologic (WECARE) Study which was specifically designed to examine the interaction of radiation exposure and genetic predisposition in breast cancer, especially radiation-associated contralateral breast cancer. On-going WECARE Studies include examining the role of mutations in candidate genes (e.g., ATM, BRCA1, BRCA2, Palb2, Chek2) and pathways (e.g., DNA repair, immune response) as well as tumor molecular markers and risk of developing contralateral breast cancer. Dr. Bernstein serves as a member of the U.S. EPA Radiation Advisory Committee and as a Scientific Advisory Board Member for the Radiation Effects Research Foundation (in Hiroshima). At the National Committee Radiation Protection and Measurement, she is a current Council Member, co-Chair of the Program Area Committee-1 and a former member of the Board of Directors. Dr. Bernstein is Past President of the American College of Epidemiology and a past member of the Board of Scientific Counselors Clinical Sciences &Epidemiology at NCI. She is an elected member of the American Epidemiological Society.

Wesley E. Bolch is Associate Dean for Academic Affairs in the College of Engineering at the University of Florida. Dr. Bolch is a professor of biomedical engineering and medical physics in the J. Crayton Pruitt Family Department of Biomedical Engineering. He has served as chair of the College Tenure and Promotion Committee for the past several years and thus is very experienced in the T&P process. In addition to his work on the College T&P Committee, he serves as Director of ALRADS – the Advanced Laboratory for Radiation Dosimetry Studies at

UF. Dr. Bolch earned his BSE degree in environmental engineering in 1984, his ME and Ph.D. degrees in radiological physics in 1986 and 1998, respectively, from the University of Florida. Dr. Bolch has managed a broad research program including (1) NIH and DOE funded projects to construct high-resolution models of the skeleton to support dose-response studies in radionuclide therapy and radiation epidemiology, (2) NIH funded projects to develop scalable NURBS-based and voxel-based computational phantoms of adult and pediatric patients and associated software for organ dose assessment in nuclear medicine, computed tomography, interventional fluoroscopy, and radiotherapy, (3) private company funded projects to develop stereotactic kilovoltage x-ray treatments for age-related macular degeneration and glaucoma, and (4) CDC funded projects in stochastic modeling of worker inhalation and gamma-ray exposures following radiological accidents and potential terrorist events. He is the recipient of the 2014 Distinguish Scientific Achievement Award by the Health Physics Society acknowledging outstanding contributions to the science and technology of radiation safety. Internal radiation dosimetry, radiation damage to DNA, NMR microscopy of bone, organ dose assessment in diagnostic radiology, radiation bioeffects.

Serge M. Candéias, PhD, HDR, obtained his PhD in Molecular and Cellular Biology specialized in Immunology at the University of Strasbourg (France) in 1991 for his work on the molecular analysis of the antigenic T cell receptor gene repertoire during T lymphocyte differentiation. He pursued this work as a post-doc at the National Jewish Hospital (Denver, CO, USA, 1991-1995), and then as a scientist in the Laboratory of Immunoregulation at the National Cancer Institute (Frederick, MD, USA, 1995-1996) where he began to study the effects of ionizing radiation on T lymphocyte development. In 1996, he joined the French Alternative Energies and Atomic Energy Commission (CEA, FR) where his work currently addresses the relationship between the immune system and the radiation response, in vivo and in vitro. He obtained his Habilitation (HDR) from the University of Grenoble in 2005. His work on the influence of radiation exposure on T lymphocyte homeostasis in mice was funded in part in the Euratom/FP7 NoE DoReMi. He was also in charge of DoReMi's Dissemination activities, including websites management. S. Candéias then coordinated the VIBRATO task, addressing the modulation of immune parameters in prostate cancer patients during and after RT in Euratom/FP7 project OPERRA. He co-organized two EU-sponsored workshops on the effects of radiation exposure on the immune system. He served as a Lead Writer for immunology in the UNSCEAR expert group conducting a review of biological mechanisms relevant for the inference of cancer risks from low-dose and low-dose-rate radiation, and is currently a member of the SRA working group of the Multidisciplinary European Low Dose Initiative (MELODI, http://www.melodi-online.eu) platform.

Dr. **Stephen Chanock** is the Director of the Division of Cancer Epidemiology and Genetics (DCEG) in the US National Cancer Institute, appointed in 2013. He received his M.D. from Harvard Medical School in 1983 and completed clinical training in pediatrics, pediatric infectious diseases, and pediatric hematology/oncology and research training in molecular genetics at Boston Children's Hospital and the Dana-Farber Cancer Institute, Boston. Previously, he was a tenured investigator in the Genomic Variation Section of the Pediatric Oncology Branch in the NCI Center for Cancer Research. In 2001, he was appointed as Chief of the Cancer Genomics Research Laboratory (formerly Core Genotyping Facility), and in 2007 as Chief of the Laboratory of Translational Genomics, both within the DCEG. Dr. Chanock co-led the Cancer Genetic Markers of Susceptibility project. From 2012 to 2013, he also served as Acting Co-Director of the NCI Center for Cancer Genomics. He is a leading expert in cancer genomics with a focus on the discovery and characterization of cancer susceptibility regions in the human genome. He has led many international consortia that have discovered susceptibility alleles and characterized genetic mosaicism/clonal hematopoiesis. He has led a series studies investigating the integration of somatic and germline genetics into epidemiological studies of radiation

exposure and non-smoking lung cancer. He has received numerous awards for his scientific contributions and serves on a number international and national scientific advisory boards.

Sandra Demaria, M.D., is Professor of Radiation Oncology and Pathology and Laboratory Medicine at Weill Cornell Medicine. She obtained her M.D. from the University of Turin, and then moved to New York City for her post-doctoral training in immunology as a Damon Runyon-Walter Winchell Cancer Research Fund awardee, followed by a residency in anatomic pathology at NYU School of Medicine. Dr. Demaria is internationally known for her pioneering studies demonstrating the synergy of radiation with immunotherapy. She was the first to show that focal radiation therapy can be used to overcome the resistance of poorly immunogenic tumors to immune checkpoint inhibitors, a finding later translated in clinical trials. Her lab has a central interest in addressing the molecular mechanisms that regulate ionizing radiation's ability to generate an in situ tumor vaccine in both preclinical models as well as cancer patients. Seminal findings from her lab include the demonstration that radiation upregulates the expression of chemokines that attract effector T cells to the tumor, activates canonical pathways of viral defense that elicit the production of interferons, and enhances the production and presentation by cancer cells of mutational neoantigens recognized by T cells. In addition, she has tested in preclinical models several immune modulators for the ability to induce therapeutically effective anti-tumor immune responses when used with radiation, providing the rationale for clinical testing of these combinations. She has published > 150 peer reviewed papers in leading journals including Nature Medicine, Nature Communications, Journal of Clinical Investigations, Cancer Research and others. She is currently the Chair of the AACR Cancer Immunology Working Group and has previously served in the board of the Society for the Immunotherapy of Cancer (SITC) and the Radiation Research Society (RRS). She has received several awards for her scientific contributions and has served/serves on the editorial board of several scientific journals, and several scientific advisory boards.

Dr. **Ruben Gur** received his B.A. in Psychology and Philosophy from the Hebrew University of Jerusalem, Israel, in 1970 and his M.A. and Ph.D. in Psychology (Clinical) from Michigan State University in 1971 and 1973, respectively. He did Postdoctoral training with E.R. Hilgard at Stanford University and came to Penn as Assistant Professor in 1974. His research has been in the study of brain and behavior in healthy people and patients with brain disorders, with a special emphasis on exploiting neuroimaging as experimental probes. As Professor in the Departments of Psychiatry, Radiology & Neurology, and Director of the Brain Behavior Laboratory and the Center for Neuroimaging in Psychiatry, he has developed tools for "deep phenotyping" of brain and behavioral parameters using computerized acquisition tools that can integrate clinical and neurocognitive measures with neuroimaging and genomic data within the framework of large multicenter studies. His work has documented sex differences, aging effects, and abnormalities in regional brain function associated with schizophrenia, affective disorders, stroke, epilepsy, movement disorders and dementia. His work has been supported by grants from the NIMH, NIH, NIA, NINDS, NSF, DOD, NASA, private foundations (Spencer, MacArthur, EJLB, Brain and Behavior Research Foundation) and industry (Pfizer, AstraZeneca, Lilly, Merck).

Dr. **Edward (Ed) E. Harlow, Jr.** Ph.D. is a distinguished molecular biologist and an internationally recognized leader in cancer biology, who is best known for his discoveries regarding the control of cell division and critical changes that allow cancer to develop. He currently splits his time between an appointment as Professor of Biological Chemistry and Molecular Pharmacology at Harvard Medical School and Senior Advisor to the Director, National Cancer Institute. He served as Chief Scientific Officer of Constellation Pharmaceuticals, Inc. from 2009 to 2011. From 1998 to 2009, he served as Professor and Chair of the Department of

Biological Chemistry and Molecular Pharmacology at Harvard Medical School and was Associate Director of the Dana-Farber/Harvard Cancer Center. From 1990 to 1998, he served as Scientific Director for the Massachusetts General Hospital Cancer Center and was Associate Director for Science Policy at the National Cancer Institute, where he helped direct U.S. cancer research planning. Prior to 1990, Dr. Harlow served on the faculty of Cold Spring Harbor Laboratory. Dr. Harlow has served on a number of influential advisory groups, including the Board of Life Sciences for the National Research Council, External Advisory Boards for UCSF, Stanford, UCLA, and NYU Cancer Centers and the Scientific Advisory Board for the Foundation for Advanced Cancer Studies. He has chaired or served on numerous biotechnology and pharmaceutical companies advisory boards, including Onyx, 3V Biosciences, Alnylam, and Pfizer Pharmaceuticals. Dr. Harlow has received numerous scientific honors, including election to the National Academy of Sciences in 1993 and the Institute of Medicine in 1999, appointment as Fellow of the American Academy of Arts and Sciences, and recipient of the American Cancer Society's highest award, the Medal of Honor. Dr. Harlow with Dr. David Lane are co-authors of one of the all time best-selling research manuals, Antibodies: A laboratory manual. Dr. Harlow received his B.S. and M.S. from the University of Oklahoma and his Ph.D. at the Imperial Cancer Research Fund in London in 1982.

Tatsuhiko Imaoka PhD completed his PhD at the University of Tokyo Graduate School of Science (zoology and biological sciences) in 2002. He studied mammary gland biology as a Visiting Scientist at the University of Cincinnati College of Medicine, USA (2000–2001). In 2002, he became a researcher at the National Institute of Radiological Sciences (NIRS), Japan, which was reorganized as the National Institutes for Quantum Science and Technology (QST) in 2016. He has been working on the magnitude and mechanism of radiation carcinogenesis in experimental animals, serving as a Researcher (2002–2008), Senior Researcher (2008–2011), and Team Leader (2011–2016) at NIRS and a Group Leader at the Department of Radiation Effects Research, QST (2016–). He also serves as a Group Leader (2019–) and a Senior Group Leader (2020–) at the Institute for Quantum Life Science, QST, and engaged in application of quantum sensing to cancer biology. He specializes in radiobiology, with his interests covering radiation carcinogenesis, stem cell biology, integration of radiation epidemiology and biology, and biological application of quantum technology. He is also a Visiting Professor at the Tokyo Metropolitan University (2017–), an Executive Director of the Japanese Radiation Research Society (2018–), and a Corresponding Member of the International Commission on Radiological Protection Task Group 111 (2019–).

Phil Jones is clinician scientist who researches how somatic mutations linked to cancer alter the behaviour of normal stem cells in normal skin and oesophagus in the earliest stages of cancer development. He is Professor of Cancer Development at the University of Cambridge UK and a Senior Group Leader at the Wellcome Sanger Institute UK and a Fellow of the UK Academy of Medical Sciences. His work encompasses mapping mutant clones in human tissues and modelling the effects of mutations in advanced cell cultures and mice. Integrating experiment with computational modelling has revealed how simple cell dynamics explain both normal and mutant cell behaviour. Using molecular and cellular assays to uncover the basis of mutant cell fitness has guided the development of interventions to halt the expansion or deplete oncogenic mutant clones from normal tissues, with the potential benefit of reducing cancer risk. Phil was a member of the Euratom funded RISK IR consortium investigating the effects of low dose ionizing radiation on stem cells. Phil's clinical practice is in skin cancer.

Shizuko Kakinuma PhD completed her master's degree at Kitasato University Graduate School of Pharmacy, Japan, in 1981. She worked at Roche Japan (1981–1982) and then moved to National Jewish Hospital Research Center, Colorado, USA (1982–1984). She worked at Kitasato Institute, Japan (1984–1990 and 1992–1997) and Bristol-Myers Squibb Institute

(1990–1992). In the meantime, she received her PhD (pharmacy) from Kitasato University in 1990. She moved to the National Institute of Radiological Sciences (NIRS), Japan, in 1999. She served as a Team Leader at NIRS (2006–2016) and now as the Director of the Department of Radiation Effects Research (2016–) and the Director of Diversity Promotion Office (2015–), National Institutes for Quantum Science and Technology (QST), Japan. She served as a member of the Investigation Committee on the Accident at the Fukushima Nuclear Power Stations (2011–2012), which was established by the Japanese government, and of the government's expert panel for the follow-up of governmental implementation of Committee recommendations (2012–2013). She serves an Executive Director of the Japanese Society for Biological Sciences in Space (2019–) and an Executive Director of Japanese Society for Quantum Medical Science (2021–). She specializes in radiobiology, with her interests covering radiation carcinogenesis, genomic alteration (including 'radiation signature') in tumors that develop after irradiation, and the effect of space radiation and exposure during radiotherapy. She led an International Space Station (ISS) experiment, "Lifetime Heritable Effect of Space Radiation on Mouse Embryos Preserved for a Long-term in ISS (EMBRYO RAD)". She has been teaching radiation biology at Japanese universities and also involved in activities of the Japanese Radiation Research Society to teach radiation risks for students at elementary and junior high schools as well as publicly conveying the health effects of radiation.

Dr. **Choonsik Lee** received a Ph.D. degree in health physics in 2002 from Hanyang University in South Korea. He subsequently joined the Innovative Technology Center for Radiation Safety in South Korea as a postdoctoral fellow and later completed extensive training in computational medical physics as a postdoctoral researcher at the University of Florida. Dr. Lee joined the Radiation Epidemiology Branch (REB) as a tenure-track investigator in 2009, and was awarded scientific tenure and promoted to senior investigator in 2016, and named Head of REB's Dosimetry Unit. Dr. Lee is a full member of two task groups of the International Commission on Radiological Protection (ICRP). In 2021, he was appointed to the ICRP Committee 2 (Doses from Radiation Exposure) and delivered the prestigious Dade Moeller Lectureship at the Health Physics Society annual meeting. He also serves on the editorial board of *Radiation Protection Dosimetry*.

Dr. **Johnnye Lewis** is a Research Professor and Director of the Community Environmental Health Program (CEHP) at the University of New Mexico Health Sciences Center College of Pharmacy. Her Ph.D. in Pharmacology from the University of Manitoba was followed by a postdoctoral fellowship in inhalation toxicology at the Department of Energy Inhalation Toxicology Research Institute in Albuquerque, NM, and private sector work as owner and CEO of Environmental Health Associates, an environmental health consulting firm providing risk modeling and assessment methodology development for Indigenous tribes, Los Alamos National Laboratory, and NRC. She moved to academia in 1996 and developed CEHP to merge her scientific research in toxicology with community concerns, creating partnerships among multidisciplinary researchers, communities, policy and decision-makers, and clinicians to develop creative and integrative transdisciplinary solutions to environmental contamination problems. Today Dr. Lewis leads multiple center-level programs including the Navajo Birth Cohort Study, Environmental influences on Child Health Outcomes (NIH-OD), the METALS Superfund Research Center (NIH-NIEHS), the Center for Native Environmental Health Equity Research (NIEHS/USEPA Phase 1, NIMHD Phase 2). CEHP's primary focus is on risk to Indigenous communities from chronic exposures to abandoned uranium mine waste from Cold War weapons development throughout the Western US. The Centers focus on environmental mobility and multigenerational toxicity, engaging teams of trained indigenous community researchers, indigenous language and culture specialists, artists, toxicologists, engineers, mineralogists, geochemists, geographers, statisticians and mathematicians, immunologists, ethnographers, and clinicians. The Centers work with communities to Integrate indigenous

knowledge, language, and art into design and implementation of clinical trials and novel risk reduction strategies to form a framework from which to build culturally acceptable solutions.

Dr. **Daniel Marks**' special interests are weight regulation in children, particularly involuntary weight loss or poor growth in chronic diseases (cachexia, failure to thrive). His clinical areas of interest are all aspects of pediatric endocrinology (including growth, puberty, thyroid, diabetes and adrenal disorders), pediatric obesity and failure to thrive. Dr. Marks received both his medical degree and Ph.D. in 1995 from the University of Washington in Seattle. Dr. Marks completed his residency at the University of Utah, SLC in 1998, followed by a fellowship in pediatric endocrinology at Oregon Health & Science University in 2001. Dr. Marks is currently the Senior Associate Dean for Research in the School of Medicine, Associate Director of the OHSU MD, Ph.D. program, Director of the Patient Resiliency Program for the Brenden-Colson Center for Pancreatic Care and the Director of the Papé Family Pediatric Research Institute at Oregon Health & Science University in Portland, OR. Dr. Marks also served as a Consulting Senior Scientific Advisor for the Bill & Melinda Gates Foundation.

Dr. **Christopher Mason** is a Professor of Genomics, Physiology, and Biophysics at Weill Cornell Medicine. He completed a dual B.S. in Genetics & Biochemistry at University of Wisconsin-Madison (2001), a Ph.D. in Genetics from Yale University (2006), Post-doctoral Fellowship in Clinical Genetics at Yale Medical School (2009) while also serving as the first Visiting Fellow of Genomics, Ethics, and Law at the Information Society Project at Yale Law School (2006-2009). In 2010, he became an Assistant Professor of Genomics, Physiology, and Biophysics at Weill Cornell Medicine, was then promoted to Associate Professor in 2015, made the Director of the WorldQuant Initiative for Quantitative Prediction in 2017, and promoted to Full Professor in 2021. He also holds appointments at Tri-Institutional Program on Computational Biology and Medicine (Cornell, Memorial Sloan-Kettering Cancer Center and Rockefeller University), the Sandra and Edward Meyer Cancer Center, the Feil Family Brain and Mind Research Institute, (BMRI), and is an affiliate fellow of the Information Society Project (ISP) at Yale Law School, affiliate faculty of the Consortium for Space Genetics at Harvard Medical School, and a Core Faculty Member of New York Genome Center (NYGC). He was named as one of the “Brilliant Ten” Scientists by Popular Science, featured as a TEDMED speaker, and called “The Genius of Genetics” by 92Y. He has >250 peer-reviewed papers and scholarly works that have been featured on the covers of *Nature*, *Science*, *Cell, Nature Biotechnology*, *Nature Microbiology*, and *Neuron*, as well as legal briefs cited by the U.S. District Court and U.S. Supreme Court. He is an inventor on four patents, co-founder of five biotechnology start-up companies, and serves as an advisor to 17 others as well as 3 non-profits.

Dale L. Preston, Ph.D., is a biostatistician with 40 years’ experience describing and quantifying the long-term health effects of radiation in humans. He played a central role in developing the modern methods and tools used to characterize radiation effects and has authored or co-authored more than 200 peer-reviewed scientific publications. Between 1981 and 2004, while living in Hiroshima, Dr. Preston worked on studies of Hiroshima and Nagasaki atomic-bomb survivors at the Radiation Effects Research Foundation and remains active in the Foundation’s research. Since 1987 he has been involved in studies of various Russian populations, initially Chernobyl victims, but primarily people exposed to radiation because of the operations of the Russian reactor and plutonium production complex (Mayak). Over several decades Dr. Preston worked with the Radiation Epidemiology Branch of the National Cancer Institute on a variety of projects. He has served as a consultant for the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), the US National Academy of Sciences Committee on the Biological Effects of Ionizing Radiation, and other groups around the world. Dr. Preston was a member of Committee 1 of the International Commission on Radiation Protection (ICRP) for

many years. Dr. Preston is a Fellow of both the American Statistical Association and the American Association for the Advancement of Science. In 2017 he received the Radiation Research Society's Failla award in recognition of a history of significant contributions to radiation research. In 2020 he received the Gold Medal for Radiation Protection from the ICRP and the Royal Swedish Academy of Sciences.

Dale Ramsden (PhD) has worked to characterize mechanisms of DNA metabolism in mammalian systems for more than 30 years. He has concentrated on two processes essential to human health - V(D)J Recombination and double strand break repair - and has a sustained track record making seminal observations in both research areas. With regard to technical training, he applies standard and cutting-edge tools in molecular and cellular biology, biochemistry, and more recently somatic cell genetics. His group benefits from a rare local concentration of groups with more general interest in genome replication, repair, and recombination. To develop deep understanding, from molecular mechanism to biological role, he employs these approaches in collaboration with colleagues with expertise in structural biology, biophysics, cancer biology, genomics, and model organism (drosophila, mouse) genetics. He maintain a focus on the role of DNA polymerases in repair of chromosome breaks by end joining pathways.

Yoshiya Shimada PhD completed his PhD at the University of Tokyo Graduate School of Science (Zoological Sciences) in 1985, with a study on the effect of radiation on gametogenesis of the medaka fish. After his postdoctoral research at Japan Science and Technology Agency (1985–1987) and Tokyo Metropolitan Institute of Gerontology (1987–1989), he moved to the National Institute of Radiological Sciences (NIRS), Japan in 1989. At NIRS, he dedicated himself in the study of age dependence of the risk and mechanism of radiation tumorigenesis, leading the Low Dose Radiation Effects Research Project (2004–2006), Experimental Radiobiology for Children's Health Project (2006–2011), and Radiobiology for Children's Health Program (2011–2016). When NIRS was reorganized as National Institutes for Quantum Science and Technology (QST), he served as one of the first Executive Directors (2016–2019). He then moved to the Institute for Environmental Sciences, Japan, as the President (2019–) and is directing the research projects on biological effects of low dose rate radiation and radioecology. He was the Vice President of the International Association for Radiation Research (IARR, 2015–2019), and now is the President of IARR (2019–), President of Japanese Radiation Research Society (2018–), Auditor of the Quantum Life Science Society (2019–) and a member of ICRP Committee 1 (2021–).

Igor Shuryak is an Assistant Professor in the Center for Radiological Research, Department of Radiation Oncology at Columbia University Irving Medical Center. His research interests focus on mechanistic mathematical modeling of the effects of ionizing radiation on living organisms. They include modeling radiation-induced carcinogenesis at both low and high doses (e.g., second cancers induced by radiotherapy for primary malignancies), cancer therapy (e.g., tumor control and normal tissue complications), nontargeted ("bystander") effects of radiation (e.g., for densely-ionizing radiation exposures such as those occurring on manned space missions), and mechanisms of resistance to ionizing radiation in human and nonhuman cells.

Michael Snyder is the Stanford Ascherman Professor and Chair of Genetics and the Director of the Center of Genomics and Personalized Medicine. Dr. Snyder received his Ph.D. training at the California Institute of Technology and carried out postdoctoral training at Stanford University. He is a leader in the field of functional genomics and multiomics, and one of the major participants of the ENCODE project. His laboratory study was the first to perform a large-scale functional genomics project in any organism, and has developed many technologies in genomics and proteomics. These including the development of proteome chips, high resolution

tiling arrays for the entire human genome, methods for global mapping of transcription factor (TF) binding sites (ChIP-chip now replaced by ChIP-seq), paired end sequencing for mapping of structural variation in eukaryotes, de novo genome sequencing of genomes using high throughput technologies and RNA-Seq. These technologies have been used for characterizing genomes, proteomes and regulatory networks. Seminal findings from the Snyder laboratory include the discovery that much more of the human genome is transcribed and contains regulatory information than was previously appreciated (e.g. lncRNAs and TF binding sites), and a high diversity of transcription factor binding occurs both between and within species. He launched the field of personalized medicine by combining different state-of–the-art "omics" technologies to perform the first longitudinal detailed integrative personal omics profile (iPOP) of a person, and his laboratory pioneered the use of wearables technologies (smart watches and continuous glucose monitoring) for precision health. He is a cofounder of many biotechnology companies, including Personalis, SensOmics, Qbio, January, Protos, Oralome, Mirvie and Filtricine.

Richard Wakeford is Honorary Professor at the Centre for Occupational and Environmental Health at The University of Manchester, United Kingdom, where he specializes in radiation epidemiology. He graduated with a BSc in Physics, and then received a PhD in High Energy Physics, from the University of Liverpool before joining British Nuclear Fuels Ltd (BNFL) in 1977. He worked for BNFL for nearly 30 y, most of the time advising on the risks to health from exposure to radiation, before taking early retirement in 2006 and joining the academic staff of The University of Manchester. In 1994 he received the Founder's Prize of the U.K. Society for Radiological Protection for "contributions of distinction to radiological protection." Dr. Wakeford has worked on many research projects involving exposure to radiation and has published and lectured extensively in the field of radiation epidemiology and risk assessment. He has been Editor-in-Chief of Journal of Radiological Protection since 1997 and is a member of the Editorial Board of British Journal of Cancer. He has been a member of a number of U.K., European Union, and international expert groups, including Committee 1 of the International Commission on Radiological Protection, the United Nations Scientific Committee on the Effects of Atomic Radiation, and the U.K. Committee on Medical Aspects of Radiation in the Environment. Following the 2011 Fukushima nuclear accident, he was a member of the U.K. Government's Scientific Advice Group for Emergencies and the World Health Organization's Health Risk Assessment Expert Working Group on the Fukushima accident. Dr. Wakeford was a member of the NCRP Scientific Committee that produced NCRP Commentary No. 27 on the LNT model and radiation protection.

Dr. **Cheryl Lyn Walker** holds the Alkek Presidential Chair in Environmental Health and is the founder and Director of the Center for Precision Environmental Health at Baylor College of Medicine in Houston, TX. She also directs the NIEHS P30 Gulf Coast Center for Precision Environmental Health (https://gc-cpeh.org). Dr. Walker has >200 publications in the scientific literature and is an elected member of the National Academy of Medicine. Her research on gene:environment interactions and environmental epigenomics has led to new insights into how early-life exposures reprogram the developing epigenome to alter disease susceptibility across the life-course. She has been recognized with the Roy O. Greep Laureate Award from the Endocrine Society, Leading Edge in Basic Science Award from the Society of Toxicology (SOT), and the Distinguished Scientist Award from the American College of Toxicology. In addition to her research accomplishments, she has held significant professional administrative and leadership positions including President of SOT, President of Women in Cancer Research for the American Association for Cancer Research (AACR), and was the founding Chair of the Systemic Injury from Environmental Exposures (SIEE) Study Section for the Center for Scientific Review of the NIH. Dr. Walker has also served on the Boards of Scientific Advisors and Scientific Councilors of the National Cancer Institute and National Toxicology Program.

Statement of Task

The National Academies of Sciences, Engineering, and Medicine will perform a study and provide a report with findings and recommendations on the current status and development of a long-term strategy for low-dose radiation research in the United States. Specifically, the objectives of the study will be to:

1. Define the health and safety issues that need to be guided by an improved understanding of low dose and low dose rate radiation health effects.
2. Identify current scientific challenges for understanding low dose and low dose rate radiation health effects.
3. Assess the status of current low dose radiation research in the United States and internationally.
4. Recommend a long-term strategic and prioritized research agenda to
    - address scientific research goals for overcoming the identified scientific challenges in coordination with other research efforts
    - support education and outreach activities to disseminate information and promote public understanding of low-dose radiation.
5. Define the essential components of the research program that would address this research agenda within the universities and National Laboratories.
6. Address coordination between federal agencies (including the National Institutes of Health, the National Science Foundation, National Aeronautics and Space Administration, and different DOE offices) and with international efforts to achieve objectives.
7. Identify and, to the extent possible, quantify, potential monetary and health-related impacts to Federal agencies, the general public, industry, research communities, and other users of information produced by such research program.

The National Academies will prepare a report with findings and recommendations that addresses the objectives above.