The National Academies of
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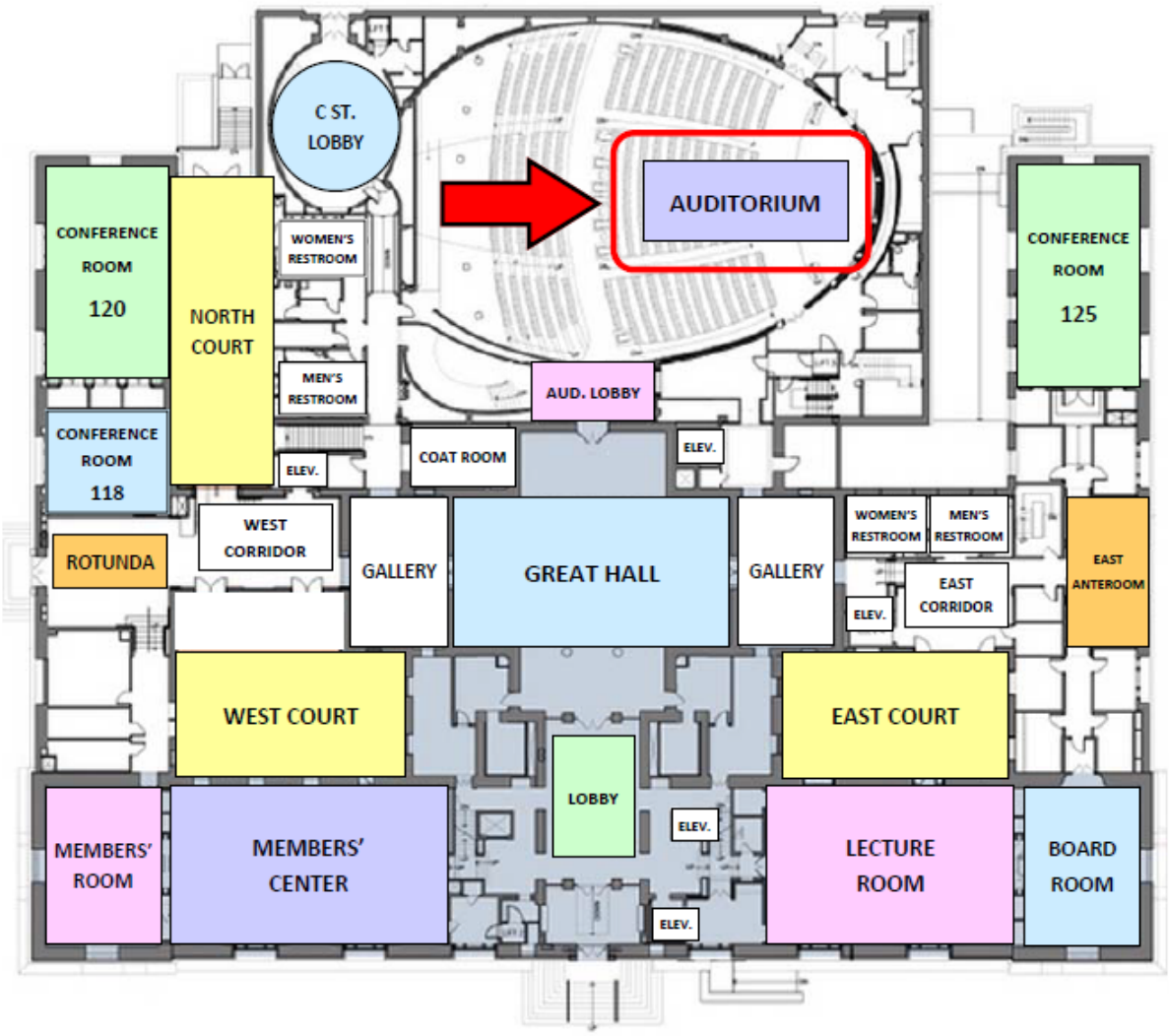
The Future of Low-Dose Radiation Research in the United States

May 8-9, 2019

The National Academy of Sciences Historic Building
Fred Kavli Auditorium
2101 Constitution Ave NW
Washington, DC 20418

Floor Plan—First Floor

C STREET NW



CONSTITUTION AVENUE NW

Agenda

DAY 1: May 8, 2019

8:30 AM	**PLENARY SESSION: Setting the Stage** *Moderated by Joe Gray, Oregon Health & Science University (OHSU)* **Call to Order and Welcome (20')** *Joe Gray, OHSU* **Remembering Gilbert Beebe (10')** *Dale Preston, Hirosoft International* **Low Dose Radiation and Societal Decisions (15')** *David Brenner, Columbia University* **Status of Low-Dose Research in the United States (15')** *John Neumann, Government Accountability Office* **Global Low-Dose Research Coordination (20')** *Ted Lazo, Organisation for Economic Co-operation and Development- Nuclear Energy Agency*
10:00 AM	**Question and Discussion on Plenary Session**
10:20 AM	**BREAK**  coffee available at Great Hall

10:35 AM	**SESSION 1: Low-Dose Radiation Programs** *Moderated by Michaela Kreuzer, Federal Office For Radiation Protection, Germany* **History of the U.S. Department of Energy Low Dose Radiation Research Program (20')** *Tony Brooks, Washington State University Tri-Cities* **The Multidisciplinary European Low Dose Initiative (20')** *Michaela Kreuzer, Federal Office For Radiation Protection, Germany* **The Low-Dose Radiation Research Program in Japan (20')** *Ignacia Braga-Tanaka III, Institute for Environmental Sciences, Japan* **Low-Dose Radiation Research in Canada (20')** *Dmitry Klokov, Canadian Nuclear Laboratories*
12:00 PM	**Questions and Discussion on Session 1**
12:30 PM	**LUNCH** Committee members, speakers, and session moderators please proceed to West Court for buffet lunch. All other participants can purchase lunch at lower level refectory.

1:45 PM

SESSION 2: Perspectives on Need for Low-Dose Research Program

Panel Group A: Government agency perspectives
Moderated by Jim Brink, Harvard Medical School

- *Isaf Al-Nabulsi, Department of Energy*
- *Mike Boyd, Environmental Protection Agency*
- *Armin Ansari, Centers for Disease Control and Prevention*
- *John Gilstad, Armed Forces Radiobiology Research Institute*
- *Mike Noska, Food and Drug Administration*
- *Jeri Anderson, National Institute for Occupational Safety and Health*
- *Steve Blattnig, National Aeronautics and Space Administration*
- *Terry Brock, Nuclear Regulatory Commission*
- *Andy Scott, Department of Homeland Security*
- *Jenny Goodman, Conference of Radiation Control Program Directors*

2:50 PM **Panel Discussion for Session 2, Part A**

3:20 PM

BREAK

 coffee available at Great Hall

3:40 PM	**Panel Group B: Other Stakeholders** *Moderated by Jim Brink, Harvard Medical School* • *Kathy Held, National Council on Radiation Protection and Measurements* • *Nolan Hertel, Health Physics Society* • *Alan Waltar, American Nuclear Society* • *Donald Cool, Electric Power Research Institute* • *Kimberly Applegate, Committee 3 of the International Commission on Radiological Protection* • *Brian Marples, American Society for Radiation Oncology* • *Larry Dauer, American Association of Physicists in Medicine* • *Mike Lawing, Powerful Patient Inc.*
4:30 PM	**Panel Discussion for Session 2, Part B**
5:00 PM	**Closing Remarks for Day 1** **Adjourn Day 1**

DAY 2: May 9, 2019

8:30 AM	**Call to Order and Welcome (5')** *Joe Gray, Oregon Health & Science University*
8:35 AM	**SESSION 3: Current Directions for Low-Dose Radiation Research** **Part A: Contributions from Epidemiological Studies** *Moderated by Gayle Woloschak, Northwestern University* **Current Research Activities at the Radiation Effects Research Foundation (20')** *Bob Ullrich, Radiation Effects Research Foundation* **Occupational Studies (20')** *David Richardson, University of North Carolina* **Environmental Exposure Studies (20')** *Dale Preston, Hirosoft International* **Medical Exposure Studies (20')** *Amy Berrington de González, National Cancer Institute*
10:05 AM	**Questions and Discussion for Session 3 Part A**
10:30 AM	**BREAK**  coffee available at East Court

10:50 AM	**Part B: Contributions from Radiation Biology** *Moderated by David Richardson, University of North Carolina* **Low Dose and Low Dose Rate Responses in Animals (15')** *Gayle Woloschak, Northwestern University* **Molecular Injury Responses Triggered by Low Dose Radiation and Implications for Long-Term Effects in Normal Tissues (15')** *Al Fornace, Georgetown University* **Epigenetic Alterations from Low-Dose Radiation (15')** *Randy Jirtle, North Carolina State University*
11:40 AM	**Questions and Discussion for Session 3 Part B**
12:05 PM	**LUNCH** Committee members, speakers, and session moderators please proceed to West Court for buffet lunch. All other participants can purchase lunch at lower level refectory.
1:15 PM	**SESSION 4: New Directions in Low-Dose Radiation Research** *Moderated by Alexandra Miller, AFRRI* **Biomarkers for Molecular Epidemiological Studies (20')** *Janet Hall, French National Institute of Health and Medical Research* **Technological Advancements (30')** • *Joe Gray, OHSU* • *Sadik Esener, OHSU* **Single Cell Genomics (15')** *Charles Gawad, St. Jude Children's Research Hospital* **Immune Response (15')** *Silvia C. Formenti, Weill Cornell Medicine*

2:45 PM	**BREAK**  coffee available at East Court
3:00 PM	**Session 4 (cont.)** **Systems Biology (15')** *Francis Cucinotta, University of Nevada, Las Vegas* **Microbiome (15')** *Eleanor Blakely, Lawrence Berkeley National Laboratory*
3:35 PM	**Questions and Discussion for Session 4**
4:00 PM	**SESSION 5: Models for Coordinated Research** *Moderated by Joe Gray, OHSU* **Lessons learned from Coordinated Research on the Health Effects of Air Pollution (20')** *Dan Greenbaum, Health Effects Institute* **Lessons Learned from Large-Scale Biology Initiatives (20')** *Anna Barker, Arizona State University*
4:50 PM	**Discussion on Session 5 and Relevance to Future Low-Dose Radiation Research Program**
5:25 PM	**Closing Remarks** *Joe Gray, OHSU*
5:30 PM	**Adjourn**

Biographies

Ralph Andersen *(committee member)* was the senior director of radiation safety & environmental protection at the Nuclear Energy Institute (NEI) in Washington, DC. He represented the nuclear energy industry to the Congress, the Administration, federal agencies, and other national and international organizations on management and environmental protection. Prior to joining NEI in 1992, Mr. Andersen worked for 20 years in radiation protection in the areas of nuclear energy, research, education, and medicine. During that time, he has held such positions as radiation protection manager at the Fermi 2 nuclear power plant, director of safety assessment and environmental protection for the Detroit Edison Company, radiation safety officer and lecturer in the Department of Physics and Astrophysics at the university of Colorado, and principal researcher and associate radiation safety officer at the University of Maryland Medical Center. Mr. Andersen is a certified as a health physicist by the American Board of Health Physics and is a U.S. delegate to the International Radiation Protection Association (IRPA). He received his B.A. degree from the University of Maryland and has completed graduate studies in the Department of Radiation Biology and Radiology at Colorado State University.

Dr. **Jeri Anderson** *(panelist)* is a Health Physicist at the National Institute for Occupational Safety and Health (NIOSH) in Cincinnati, Ohio, a position she has held since June 2004. She is primarily responsible for performing retrospective radiation exposure assessment in support of epidemiological studies of workers occupationally exposed to radiation and radioactive materials. She also provides technical support to workplaces with radiological concerns and during radiological/nuclear emergency response and preparation activities.

Armin Ansari *(panelist)* is the Radiological Assessment Team Lead at the Centers for Disease Control and Prevention (CDC). He received his B.S. and PhD degrees in radiation biophysics from the University of Kansas and completed his postdoctoral research in radiation mutagenesis at Oak Ridge and Los Alamos National Laboratories. His focus since joining CDC in 2002 has been on public health preparedness and response planning for nuclear and radiological emergencies and he has led the development of key national guidance documents as well as numerous training programs directed at public health professionals. He is a fellow and past president of the Health Physics Society and is certified in comprehensive practice by the American Board of Health Physics. He is also an elected member of the National Council on Radiation Protection and Measurements, and serves as member of the United States delegation to the United Nations Scientific Committee on the Effects of Atomic Radiation.

Kimberly Applegate *(panelist)* is a professor of radiology and pediatrics, at the University of Kentucky in Lexington. Dr. Applegate is the Chair of Committee 3 of the International Council for Radiation Protection (ICRP), focusing on radiation protection in medicine. Dr. Applegate is a leader in radiology— Dr. Applegate's policy and research work, including 200 publications, has resulted in an improved understanding of the structure, process, and outcomes of how pediatric imaging is practiced, including the *volume* of ionizing imaging in children, the *variation* in

radiation dose in pediatric CT, and the *standardization* of practice for both children and adults. She has worked collaboratively around the world across medical specialties and geographic boundaries to improve access to best practices. On the Steering Committee of the *Image Gently Alliance* from its start in 2007 to the present, she is dedicated to its mission to improve safe and effective imaging care of children worldwide. Kimberly has received a number of awards that include the American Association for Women in Radiology's Marie Sklowdoska Curie Award for her unique roles in leadership and outstanding contributions to the advancement of women in the Radiology Professions.

As co-director of Complex Adaptive Systems –Biomedicine at Arizona State University, Dr. **Anna Barker** *(presenter)* designs and implements new research knowledge networks, projects and models to address major problems in biomedical research and biomedicine. She currently focuses on complex systems science as applied to the discovery and systems development of biomarkers, next-generation clinical trials and the applications of artificial intelligence and advanced analytics for biomarker discovery. Prior to ASU, she served as the Deputy Director and Deputy Director for Strategic Scientific Initiatives for the National Cancer Institute (NCI)/National Institutes of Health (NIH) where she developed and led trans-disciplinary programs such as the Nanotechnology Alliance for Cancer, The Cancer Genome Atlas (TCGA); Clinical Proteomics Technologies Initiatives and the Physical Sciences – Oncology Centers. She was founding co-chair of the NCI-FDA Interagency Task Force (IOTF), founding co-chair of the Cancer Steering Committee of the FNIH Biomarkers Consortium (FNIH-BC), and was responsible for the NCI's international cancer research programs. She was a senior executive at Battelle Memorial Institute for 18 years where as a Senior Vice and Group President she pioneered key initiatives in cancer research and biomedicine. Dr. Barker was also co-founder and CEO of a public biotechnology company focused on novel strategies to control reactive oxygen damage in inflammatory diseases and cancer. She serves on a number of boards of for profit and non-profit organizations, as chair of national committees and in strategic advisory roles. Current examples include: Member, Board of Trustees, Sanford Burnham Prebys Institute; Friends of Cancer Research Board of Directors; Senior Fellow, Milken Institute, Faster Cures; Board Member, Quantum Leap Health Collaborative (ISPY 2 trials network); Chair, Data Standards Committee and Advisor, Biden Cancer Initiative; Chair, AACR Scientist Survivor Program; MIT New Digs and LEAP Initiative, Program Advisor; Member, and member of the Caris Scientific Advisory Board. Dr. Barker has received a number of awards for her cancer research, policy and advocacy efforts. Recent awards include; the 2009 AACR Margaret Foti Award for Leadership and Extraordinary Achievements in Cancer Research; 2014 Distinguished Alumni Award, College of Arts and Sciences, The Ohio State University; and the 2018 AACR Distinguished Award, Exceptional Leadership in Cancer Science Policy and Advocacy. She received her M.A. and Ph.D. at the Ohio State University, where she trained in immunology and microbiology.

Dr. **Amy Berrington** *(presenter)* is the Branch Chief and senior investigator in the Radiation Epidemiology Branch. She is an internationally recognized expert in the potential cancer risks from medical radiation exposures. Dr. Berrington is co-PI of the UK Pediatric CT scans cohort, which was the first epidemiological study to suggest a direct link between CT scans and subsequent cancer risk. She also leads studies on the risk of second cancer after proton therapy and other emerging radiotherapy techniques. Dr. Berrington is currently a member of the NAS Nuclear and Radiation Studies Board and has participated in many national and international radiation committees. She is an elected member of the American Epidemiological Society and served on the editorial board for the American Journal of Epidemiology. Before joining the NCI in 2008 she held faculty positions at Oxford and Johns Hopkins University.

Eleanor A. Blakely *(presenter)* is a graduate of the University of San Diego, San Diego, CA (B.A. Biology with Chemistry minor), and the University of Illinois, Urbana-Champaign, IL (M.S. Biophysics and Ph.D. Physiology) as a U.S. Atomic Energy Commission Special Fellow in Radiation Science and Protection. She has spent her entire professional career at the Lawrence Berkeley National Laboratory (LBNL) where she is a Senior Staff Biophysicist with more than 44 years of professional experience in molecular, cellular and animal radiobiological research directed at studying the basic mechanisms of radiation responses, with an emphasis on charged particle radiation effects. She also holds a Faculty Affiliate Appointment in the Department of Radiological Health Sciences at Colorado State University, Fort Collins, Colorado and is a Clinical Professor of Radiation Medicine (nontenured) at Loma Linda University, School of Medicine, Loma Linda, California. Her professional activities have included service on advisory panels for several hospitals, universities, the National Academy of Sciences (NAS), and numerous federal agencies including the U.S. Department of Energy, the National Institutes of Health (NIH), and the National Aeronautics and Space Administration (NASA) and the Department of Defense (DOD). In June, 2015 she retired after 40 years at LBNL, but was rehired by LBNL in October 2015, and continues to work part-time. In 2015 she received the Berkeley Laboratory Director's Award for Exceptional Achievement: the Berkeley Lab Citation Award. Dr. Blakely is a Fellow of the American Association for the Advancement of Science (AAAS), a recipient of the Distinguished Service Award of the Radiation Research Society, and a Distinguished Emeritus Member of the National Council on Radiation Protection and Measurements (NCRP).

Dr. **Steve Blattnig** *(panelist)* has been working on many aspects of space radiation research for the last 20 years. He graduated from UW-Milwaukee with a Ph.D. in Physics, and his graduate work comprised the development of a pion and muon radiation transport code, including the associated particle production cross section modeling. In January 2003 he began work as a physicist at the NASA Langley Research Center (LaRC). His major areas of research have included the development of space radiation transport methodologies, nuclear and particle physics modeling and their application to mission analysis and vehicle design, and the development of radiation shielding materials. He has also been integral to the development of validation methodologies and on the use of model results in decision making. He is one of the primary authors of the NASA Standard for Models and Simulations, NASA-STD-7009. More recently, his focus has been on the development of probabilistic risk methodology and radiation biology modeling for effects including cancer, cardiovascular disease, and acute radiation syndrome. He was the project manager for the space radiation transport and measurement project and was the PI of the space radiation risk assessment project.

Mike Boyd *(panelist)* is the Director of the Center for Science and Technology in the U.S. Environmental Protection Agency's Office of Radiation and Indoor Air/Radiation Protection Division. The Center is responsible for the development of radiation dose and risk assessment guidance and for providing technical support for radiation protection policy issues. Mr. Boyd is also the co-chair of the Federal Guidance Subcommittee of the Interagency Steering Committee on Radiation Standards. He is a member of the NCRP's PAC 5 and was recently elected to the NCRP Board of Directors. He is a member of the International Commission on Radiological Protection (ICRP) Committee 4 and chairs ICRP Task Group 98 on Application of the Commission's Recommendations to exposures resulting from contaminated sites from past industrial, military and nuclear activities. Since 2015, he has chaired the Organisation for Economic Cooperation and Development/Nuclear Energy Agency's Committee on Radiological Protection and Public Health. Mr. Boyd is an active member of the Health Physics Society and is a delegate to the International Radiation Protection Association where he is currently a member of its International Congress Program Committee for IRPA 15, which will be held in

Seoul, Korea in May 2020. He has a BS in Biology and MS in Public Health from the University of North Carolina at Chapel Hill.

David Brenner *(presenter)* is the Director of the Columbia University Center for Radiological Research, which is the oldest and largest radiation biology center in the US. He is also P.I. of the Center for High-Throughput Minimally-Invasive Radiation Biodosimetry, a multi-institute consortium to develop high-throughput biodosimetry technology to rapidly test individual radiation exposure after a radiological incident. He is also Director of the Columbia Radiological Research Accelerator Facility (RARAF), which is a national facility dedicated to probing the mechanisms of radiation induced cancer. Brenner's research focuses on mechanistic models for the effects of ionizing radiation on living systems. He divides his research time between the effects of high doses of ionizing radiation (relating to radiation therapy) and the effects of low doses of radiation (relating to radiological, environmental, and occupational exposures). At low doses, he was the first to quantify the potential risks associated with the rapidly increasing usage of CT scans in the US. At high doses, his proposal to use large-fraction radiotherapy for prostate cancer (hypofractionation) is increasingly being used in the clinic. Dr. Brenner has published more than 350 peer-reviewed papers; in addition, he is the author of two books on radiation for the lay person: "*Making the Radiation Therapy Decision"* and "*Radon, Risk and Remedy"*. He is a recipient of the Failla gold medal, the annual award given by the Radiation Research Society for contributions to radiation research.

James A. Brink, MD, *(committee member and session moderator)* is chief of radiology at the Massachusetts General Hospital (MGH) and the Juan M. Taveras Professor of Radiology at the Harvard Medical School. Dr. Brink has expertise and broad experience in medical imaging, including utilization and management of imaging resources and monitoring and control of medical radiation exposure. Before joining MGH, Dr. Brink was an associate professor at the Mallinckrodt Institute of Radiology at Washington University School of Medicine and professor and chair of the Yale Department of Diagnostic Radiology. He is a fellow of the Society for Computed Body Tomography/Magnetic Resonance, past-president of the American Roentgen Ray Society, fellow and chair (effective May 17, 2016) of the Board of Chancellors of the American College of Radiology, and scientific vice-president and member of the Board of Directors of the National Council for Radiation Protection and Measurements. He earned his M.D. degree at Indiana University and completed his medical residency and fellowship at MGH.

Terry A. Brock *(panelist)* is a senior health physicist with the U.S. Nuclear Regulatory Commission (NRC), where he has worked for over 16 years. He has served as the NRC program manager for the Radiation Exposure Information and Reporting System, the Analysis of Cancer Risks in Populations near Nuclear Facilities study, and the lead for the agency's participation in the One Million U.S. Radiation Workers and Veterans Heath Study. He is a current management board member and past Vice Chair of the Organisation for Economic Co-operation and Development/Nuclear Energy Agency's Information System on Occupational Exposure program. He's the agency liaison with NCRP and the International Commission on Radiological Protection and serves as the NRC representative on the Executive Committee of the Joint Coordinating Committee for Radiation Effects Research (Russian Health Studies). He has served as the project manager for the State-of-the-Art Reactor Consequence Analyses study and on the Risk Task Group that explored risk-informing the radioactive materials arena. Before NRC, he worked in health physics at a commercial nuclear power facility and at two universities. In addition to health physics, Dr. Brock has worked on environmental health and risk communication issues related to pesticides and hazardous substance clean-up sites. Dr. Brock holds a PhD in public health and MS in radiation heath physics and environmental health

from Oregon State University. He holds a BS in health physics and industrial hygiene from Purdue University.

Antone L. Brooks *(presenter)* graduated from Dixie J.C, received BS and MS degrees from University of Utah and a PhD from Cornell University. He is a retired professor from Washington State University. He served on the National Council for Radiation Protection (NCRP) for almost 30 years and was on the Board of directors for that organization, was a member of the EPA science advisory board, was on the National Academy of Science team that produced the BEIR VI report on Radon Health Effects and was the Chief Scientist for the Department of Energy Low Dose Radiation Research Program. He recently published a book "Low Dose Radiation, The history of the U.S. Department of Energy Research Program." He has published over 200 peer reviewed articles and served on many national and international review groups.

Dr. **Donald A. Cool** *(panelist)* is currently the Technical Executive for Radiation Safety with the Electric Power Research Institute, working with member utilities on occupational, public and environmental issues. Before joining EPRI, Dr. Cool served in various senior management and advisory positions with the U.S. Nuclear Regulatory Commission. Dr. Cool is a member of the Main Commission of the International Commission on Radiological Protection and the Chair of Committee 4 on Application of the Commission's Recommendations. He is a Council Member of the U.S. National Council on Radiation Protection and Measurements, and was Co-Chair of Council Committee 1 on Radiation Protection Recommendations. Dr. Cool has more than 36 years of experience in Radiological Protection, and is a Fellow of the Health Physics Society.

Dr. **Francis A. Cucinotta** *(presenter)* is a professor of Health Physics at the University of Nevada, Las Vegas (UNLV). He received his doctorate in nuclear physics from Old Dominion University during 1988. He worked at NASA from 1990-2013 in several positions including research scientist, radiological health officer for spaceflight, and manager and chief scientist for the Space Radiation Research Project. Dr. Cucinotta was NASA's manager for the construction and operation of the NASA Space Radiation Lab at Brookhaven National Laboratory. He developed the astronaut exposure data base of organ doses, and cancer risk estimates for all human missions from Mercury to the International Space Station. He has developed models of cancer, circulatory disease and non-cancer risks to the blood forming organs, and central nervous system for understanding the risks to cancer patients and radiation workers. He led NASA's biodosimetry program for the International Space Station and discovered the association of increased incidence of cataracts in past space missions.

Dr. Cucinotta's biophysical models are applicable to radiation exposures on Earth, to radiation workers and patients, and for astronauts in space. He developed space radiation quality factors and risk models that were approved for use at NASA. National Research Council and National Council on Radiation Protection and Measurements (NCRP) have reviewed his work in dedicated reports. Dr. Cucinotta has published 370 peer reviewed journal articles, numerous book chapters, and NASA technical reports on nuclear and space physics, shielding, DNA damage and repair, biodosimetry, systems biology, cancer and central nervous system risk assessment models. He has published extensively including in *Reviews of Modern Physics*, *Science*, *Nucleic Acids Research*, *Nature Reviews Cancer*, and *the Lancet Oncology*. His work has been cited more than 18,000 times with an h-index of 66 on Google Scholar. He has won research grants from NASA, the Department of Energy and the National Cancer Institute. He earned numerous NASA awards for his efforts, received the 2015 Scholar award from the School of Allied Health Sciences, and UNLV's 2018 Barrick Scholar Award. Dr. Cucinotta served as president of the Radiation Research Society during 2014 and received its highest scientific achievement award, the Failla Award, during 2018. He is serving a second, six-year

term as an elected council member of the NCRP, and has served on special committees for the NCRP and International Commission on Radiological Protection (ICRP).

Lawrence T. Dauer, Ph.D, DABHP *(panelist)* is a medical health physicist specializing in radiation protection at Memorial Sloan Kettering Cancer Center. He is an Associate Attending Physicist in the Departments of Medical Physics and Radiology, and serves as the Corporate Radiation Safety Manager and Chair of the Emergency Management Committee Officer. He has spent more than 30 years in the field of radiation protection and health physics, including radiation protection programs for nuclear energy and industrial sectors as well as operations and research in medical health physics. Larry served as Chair and Vice Chair of the Radiation Safety Committee of the AAPM, President and Executive Council Member of the Medical Physics Section of the HPS, President of the Greater NY Chapter of the HPS, and Board Member of the Radiological and Medical Physics Society of NY, as well as a member of the ICRP Committee 3–Radiation Protection in Medicine. He is currently a Council and Board member of the NCRP and a member of the Science Committee of the IOMP. Larry has received both the Elda Anderson and the Fellow Award from the Health Physics Society. He was co-Chair of NCRP SC 1-23 who produced NCRP Commentary No. 26 – Guidance on Radiation Dose Limits for the Lens of the Eye. He was also co-Chair of NCRP SC 1-25 who produced NCRP Commentary No. 27 – LNT and Radiation Protection.

Sadik Esener *(presenter)* is the director of the OHSU Knight Cancer Institute Cancer Early Detection Advanced Research Center (CEDAR), the Wendt Family Endowed Chair in Early Cancer Detection, and Professor in the Biomedical Engineering Department at OHSU. His research focus has involved projects in multiple scientific fields relevant to cancer early detection, including electrical and optical engineering, nano-engineering and material sciences for biomedical applications. In addition, he has made many pioneering contributions to the fields of optical interconnects, light modulation, optical data storage, biophotonics as applied to gene chips, cell sorting and manipulation, and heterogeneous integration of photonics, electronics and biological components. More recently his work has focused on the synthesis and application of nanoparticles delivery of biologics for cancer therapies, brain mapping and in vivo imaging. Dr. Esener received his Ph.D. in applied physics and electrical engineering from the University of California, San Diego. He has published more than 375 journal and conferences articles, and made more than 250 presentations in international scientific meetings, 60 of which were invited. He holds 23 issued patents, has authored several book chapters, and organized and chaired scientific international conferences. Esener co-founded and served on the board of directors and scientific advisory boards of several companies.

Dr. **Silvia Formenti** *(presenter)* is the Chair of Radiation Oncology at Weill Cornell Medical College and the Associate Director of the Cancer Center. Trained as a medical and radiation oncologist she devoted her career to translate novel preclinical information to the clinic. Key to her formation was a year spent in Malcolm Mitchell's laboratory at USC, in cancer immunology. Her initial research on how to best combine radiation and systemic therapy, both pre-clinically and clinically evolved on focusing on the systemic effects of radiotherapy, particularly on the immune system. Her lab's original demonstration that the abscopal effect of radiotherapy is immune-mediated has opened a fertile field of research to understand the immune-stimulatory and immune-suppressive effects of ionizing radiation, and to develop strategies directed at harnessing anti-tumor immunity in irradiated subjects. This work has introduced a paradigm shift in radiation and cancer biology. In this novel application, radiotherapy contributes at recovering an immunological equilibrium in the setting of metastatic cancer, by converting an irradiated metastasis into an in situ, individualized vaccine in the presence of immune checkpoint blockade (anti-CTLA4, anti-PDL-1). Once successfully immunized against the irradiated site, the

host can develop an anti-tumor immune response capable to reject the other metastases. In some patients with metastatic disease the combination of radiation and immune checkpoint blockade has resulted in complete remissions, sustained for years after treatment (without any other additional interventions). Dr. Formenti's work has been funded by grants from NIH, DOD, ACS and Breast Cancer Research Foundation and is currently leading four investigator-initiated clinical trials of immunotherapy and radiotherapy.

Albert J. Fornace Jr., MD, *(presenter)* is a Professor in the departments of Oncology; Biochemistry and Molecular & Cellular Biology; and Radiation Medicine at Georgetown University. He was the first recipient of the Molecular Cancer Research Chair at Lombardi Comprehensive Cancer Center, joining Georgetown in 2006 from the Harvard School of Public Health, where he was the director of the John B. Little Center for the Radiation Sciences and Environmental Health. Earlier, he was Chief of the Gene Response Section at the National Cancer Institute. He is the 2015 recipient of the Radiation Research Society Failla Gold Medal. Research from the Fornace laboratory has included discovery of some of the first radiation-inducible genes including the gadd gene group of growth-arrest and DNA-damage inducible genes. His studies in this area led to the landmark paper where they and their collaborators at Johns Hopkins demonstrated the radiation-responsive ATM-p53-Gadd45a pathway, and showed for the first time that p53 could bind and induce a cellular gene. This was followed by a large series of important reports by their laboratories and others that elucidated the major contribution of the tumor suppressor p53 as a transcription factor in its role as a 'guardian of the genome.' Fornace's research has shown that stress-related signals inside the cell alter the expression of multiple genes involved in cell-cycle control, programmed cell death, DNA damage processing, metabolism, pro-inflammatory signaling, among others. Radiation signaling events were shown by his laboratory to occur at surprisingly low doses of radiation. His laboratory has contributed to our understanding of the key roles for important stress-signaling pathways in cancer prevention as well as their perturbations that contribute to tumor development after exposure to radiation. His radiobiology studies also include high-energy ion radiation where he leads a NASA Specialized Center of Research (NSCOR) in gastrointestinal carcinogenesis by low-dose space radiation.

In addition to his research on the molecular pathways of radiation-inducible genes, Fornace has also studied cellular stress responses at broader levels. His laboratory at NCI was the first in collaboration with NHGRI to assess genome-wide responses to radiation using a transcriptomics approach. His omics studies were then extended to the small molecule level, i.e. metabolomics, and his team along with collaborators developed the field of radiation metabolomics, and have demonstrated low-dose radiation effects on at the metabolomic level. Fornace currently directs the Waters Center of Innovation for Metabolomics at Georgetown.

Dr. **Charles Gawad** *(presenter)* is an Assistant Member in the departments of Oncology and Computational Biology at St. Jude Children's Research Hospital. He received his medical degree from the University of Arizona in 2006, followed by clinical training in pediatrics and pediatric oncology at UCLA and Stanford University, respectively. He then received a PhD in Cancer Biology from Stanford in the laboratory of Patrick O. Brown, followed by postdoctoral training in the department of Bioengineering under the mentorship of Stephen Quake. His lab focuses on the development and application of new technologies to improve human health, with a focus on single-cell genomics. He is a recipient of the Scholar Award from the American Society of Hematology, Special Fellow Award from the Leukemia and Lymphoma Society, Career Award for Medical Scientists from the Burroughs Wellcome Fund, and NIH Director's New Innovator Award.

Hailing from San Antonio, Texas, **John Gilstad** *(panelist)* graduated from the United States Naval Academy in May 1987 with a bachelor's degree in English and proceeded to medical school at the Uniformed Services University of the Health Sciences (USU). Following initial postings in Quantico, Virginia and Roosevelt Roads, Puerto Rico, he completed a clinical fellowship in geriatrics at Johns Hopkins University and worked as an internist and geriatrician at the National Naval Medical Center, and aboard USNS COMFORT in support of Operation Iraqi Freedom. Following a tour at Naval Hospital Yokosuka, Japan, he reported to the Armed Forces Radiobiology Research Institute (AFRRI) in 2009 for three years assignment as Department Head for Scientific Research. Captain Gilstad was subsequently selected as Executive Officer of the Navy Medical Research Unit 2 (NAMRU-2) in Hawaii and Singapore, and as Commanding Officer of NAMRU-3 in Cairo, Egypt, both of which focused on infectious disease surveillance and regional partnerships for capacity-building and scientific collaboration. Returning to AFRRI from Cairo, CAPT Gilstad served as Chief, Military Medical Operations before being selected as Institute Director, beginning April 2018. His current lines of effort at AFRRI include strategic integration of the AFRRI directed-science mission into USU and new approaches to the military problems of radiological and nuclear medical readiness.

Jenny Goodman *(panelist)* obtained a B.S. in Biochemistry from Rutgers University in 1980 and a M.S. in Radiation Science from Rutgers University in 1987. Ms. Goodman has been with the NJ Department of Environmental Protection (DEP) since 1985 and prior to that she was a Health Physicist with the US Environmental Protection Agency. At the DEP, Ms. Goodman has worked on nuclear emergency response, radon, radiologically contaminated site evaluations, decommissioning, radioactive materials licensing and inspection, and radionuclides in water. She is currently the Manager of the Bureau of Environmental Radiation at the DEP.

Joe W. Gray *(committee chair, presenter, and session moderator)* is the Director, Oregon Health and Science University Center for Spatial Systems Biomedicine, and Associate Director for Biophysical Oncology, Knight Cancer Institute. He applies 'omic and multiscale molecular imaging technologies to elucidate mechanisms by which cancers arise, progress and become resistant to treatment and uses this information to develop therapeutic strategies to more durably control cancers with emphasis on breast cancer. He serves on the Board of Counselors for the Radiation Effects Research Foundation. He has more than 500 publications and 80 US patents. Major awards include the E.O. Lawrence Award, U.S. Department of Energy; Curt Stern Award, American Society for Human Genetics; the Alfred G. Knudson Award in Cancer Genetics, National Cancer Institute; election as a Fellow of the American Institute for Medical and Biological Engineering and the American Association for Cancer Research; and election to the National Academy of Medicine.

Dan Greenbaum *(presenter)* is President and Chief Executive Officer of the Health Effects Institute. In that role, Greenbaum leads HEI's efforts, supported jointly by government and industry, to provide public and private decision makers – in the US, Asia, Europe, and Latin America - with high quality, impartial, relevant and credible science about the health effects of air pollution to inform air quality decisions in the developed and developing world. Greenbaum has been a member of the U.S. National Academies *Board of Environmental Studies and Toxicology* and vice chair of its *Committee for Air Quality Management in the United States*. He is currently Serving on the *NASEM Committee for the Environmental Health Matters Initiative* and recently served on the NASEM Committee on *Grand Challenges for Environmental Engineering*. In May, 2010, Greenbaum received the *Thomas W. Zosel Outstanding Individual Achievement Award* from the U.S. EPA for his contributions to advancing

clean air and in June 2017 he received the *Haagen Smit Award* from the California Air Resources Board for his and HEI's contributions to air pollution science and policy. Greenbaum has over four decades of governmental and non-governmental experience in environmental health. Just prior to coming to HEI, he served as Commissioner of the Massachusetts Department of Environmental Protection where he was responsible for the Commonwealth's response to the Clean Air Act, as well as its award-winning efforts on pollution prevention, water pollution and solid and hazardous waste. Greenbaum holds Bachelor's and Master's degrees from MIT in City Planning.

Janet Hall (PhD) *(presenter)* is a Research Director at INSERM (The French National Institute of Health and Medical Research). Before moving to the Cancer Research Centre of Lyon, in January 2015, she was Director of the Unit of Genotoxicology, Signalisation and Experimental Radiotherapy at Institut Curie in Orsay, France and from 1999 - 2006 Head of the DNA Repair Team at the International Agency for Research in Cancer in Lyon, where she had been an IARC research scientist since 1988. Her research focuses on the impact on cancer risk of the modulation of DNA repair processes by genetic and environmental factors and viral infections, and how these changes can be exploited for therapeutic purposes. She was a member of the High Level Expert Group on European Low Dose Risk Research and is a co-author of several reviews on biomarkers for low dose ionizing radiation exposure.

Kathryn D. Held *(panelist)* is President of the NCRP after being the NCRP Executive Director and Chief Science Officer from 2016 to 2018, on the NCRP Board of Directors from 2008 to 2014 and on a number of NCRP committees. Dr. Held is also Associate Radiation Biologist in the Department of Radiation Oncology, Massachusetts General Hospital, Associate Professor of Radiation Oncology at Harvard Medical School and Distinguished Visiting Professor at Gunma University, Japan. Dr. Held's research interests are in molecular mechanisms for the induction of cell-cell signaling by radiation, including high energy particles, and characterization of charged particle-induced DNA damage responses and cell killing. Dr. Held also teaches radiation biology to radiation oncology medical and physics residents and graduate students. Dr. Held earned her PhD from the University of Texas, Austin. She has served on review panels and committees for numerous federal agencies including NIH, NASA, DOE and the U.S. DOD and other organizations such as RSNA and NAS.

Dr. **Nolan Hertel** *(panelist)* is a Professor Nuclear and Radiological Engineering at Georgia Institute of Technology. He earned his B S and MS degrees in Nuclear Engineering from Texas A&M University and his PhD from the University of Illinois at Urbana-Champaign. He previously served as a faculty member at the University of Texas at Austin from 1979-1992. Dr. Hertel is currently the President of the Health Physics Society. He received the HPS Distinguished Scientific Achievement Award in 2016 and the American Nuclear Society Radiation Protection and Shielding Division's Rockwell Lifetime Achievement Award. Dr. Hertel holds a joint faculty appointment in the Center for Radiation Protection Knowledge t Oak Ridge National Laboratory. He is also an affiliated faculty of the Georgia Tech Center for International Strategy, Technology and Policy of the Sam Nunn School of International Affairs

Professor **Randy Jirtle** *(presenter)* headed the epigenetics and imprinting laboratory at Duke University until 2012. He is now a Professor of Epigenetics in the Department of Biological Sciences at North Carolina State University, Raleigh, NC, and a Senior Scientist in the McArdle Laboratory for Cancer Research at the University of Wisconsin, Madison, WI. Jirtle's research interests are in epigenetics, genomic imprinting, and the fetal origins of disease susceptibility. He has published over 200 peer-reviewed articles, and was a featured scientist on the *NOVA* television program on epigenetics entitled *Ghost in Your Genes*. He was honored in 2006 with

the Distinguished Achievement Award from the College of Engineering at the University of Wisconsin-Madison. In 2007, Jirtle was nominated for *Time Magazine's* "Person of the Year." He received the Linus Pauling Award from the Institute of Functional Medicine in 2014. He will receive the Alexander Hollaender Award this Fall from the Environmental Mutagenesis and Genomics Society.

Michaela Kreuzer *(committee member, presenter, and session moderator)* obtained a diploma in statistics from the Ludwig-Maximilians-University (LMU) in Munich in Germany in 1987 and a PhD in epidemiology in 1996. Since 2004 she is member of the Medical Faculty of the LMU ("Habilitation") and private teacher (Priv.-Doz.) in epidemiology. Michaela Kreuzer started her scientific career in 1988 as epidemiologist at the Institute of Occupational Medicine, Heinrich-Heine University of Düsseldorf. In 1990 she moved into the research field "indoor radon and lung cancer" at the University of Wuppertal, Germany and the Institute of Epidemiology at the HelmholtzZentrum Munich (HMGU), Germany. Since 1998 she is working at the Federal Office for Radiation Protection (BfS) in Neuherberg in Germany, where she was previously heading the working group "Radiation Epidemiology" and is now heading the division "Effects and risks of ionizing and non-ionizing radiation". She is principal investigator of the German uranium miner cohort study with nearly 60.000 radon-exposed miners. Michaela Kreuzer is member of the European research platform "Multidisciplinary European Low Dose Initiative (MELODI)", which was founded in 2010. From 2014-2017 she was chair of the working group "Strategic Research Agenda (SRA)" and since 2018 vice-chair.

Dmitry Klokov *(presenter)* obtained a PhD in Radiobiology from Moscow State University in 2000. He is currently a head of Radiobiology section at Canadian Nuclear Laboratories and an Adjunct Professor at the Department of Biochemistry, Microbiology and Immunology of University of Ottawa. He has published over 45 papers in peer reviewed literature. His research interests encompass various fields of Radiobiology, including effects of low doses on DNA damage and repair, epigenetics, microenvironment and carcinogenesis in somatic and stem cells.

Ourania (Rania) Kosti, Ph.D *(staff member)* is a senior program officer at the Nuclear and Radiation Studies Board (NRSB) of the National Academies of Sciences, Engineering, and Medicine. Dr. Kosti's interests within the NRSB focus on radiation health effects, and she is the principal investigator for the Academies' Radiation Effects Research Foundation Program that supports studies of the atomic bombing survivors in Japan. Prior to her current appointment, she was a postdoctoral fellow at the Lombardi Comprehensive Cancer Center at Georgetown University Hospital in Washington, D.C., where she conducted research on biomarker development for early cancer detection using case-control epidemiological study designs. She focused primarily on prostate, breast, and liver cancers and trying to identify those individuals who are at high risk of developing malignancies. Dr. Kosti also trained at the National Cancer Institute (2005–2007). She received a B.Sc. in biochemistry from the University of Surrey, UK, an M.Sc. in molecular medicine from University College London, and a Ph.D. in molecular endocrinology from St. Bartholomew's Hospital in London, UK.

In the years since being diagnosed with Renal Cell Carcinoma (RCC) in 1997, **Mike Lawing** *(panelist)* has become very involved with cancer survivorship and advocacy for patients and their caregivers in a number of ways. He frequently challenges the newly diagnosed and their families that he encounters with a statement by Dr. Norman Cousins; "Don't deny the diagnosis; try to defy the outcome". Lawing is a co-host of the Powerful Patient, an internet podcasting organization dealing with medical issues of interest and is co-chair of the Patient Advisory Board of KCCure. He has served as a member of the Board of Directors of The Kidney Cancer

Association and is the author of the KCA book *We Have Kidney Cancer: Survivor Stories*. He serves regularly as a Consumer Reviewer for the Department of Defense Peer-Reviewed Cancer Research Program; has served as an NCI SPORE Grant Review panelist; served as a patient advocate on a joint SPORE application for M.D. Anderson, UNC and Stanford; is an affiliate member of the American Association for Cancer Research and is an alumnus of their Scientist-Survivor Program. He has served on the Patient Advisory Committee for one of the largest pharmaceutical companies, has given presentations and served on panels of numerous cancer organizations including the International Kidney Cancer Coalition and the National Comprehensive Cancer Network, and has served on several committees with the North Carolina Comprehensive Cancer Program and the South Carolina Cancer Alliance. He was a facilitator for *Survivin'*; a general cancer and caregiver support group at the Rutherford Regional Cancer Outreach Center and is actively involved with several cancer support groups in the Carolinas. In addition to his involvements with cancer organizations and survivorship issues at several levels, Mike is active in his community; conducting programs for the elderly and the terminally ill at local rest homes and the area Hospice House as well as making presentations on cancer awareness, caregiving and survivorship, and related topics to local and regional organizations, support groups, churches, and other venues. Since 1977 he has been a volunteer with The Church of The Exceptional, Henrietta, NC a church for the physically and mentally challenged; one of the few ministries of its kind in the US.

Dr. **Ted Lazo** *(presenter)* holds Bachelors and Master's degrees in Nuclear Engineering, and a PhD in Radiation Protection, and has been focused in all his professional positions on the practical application of knowledge and experience. His experience has included applied decommissioning at Three Mile Island, environmental restoration at contaminated US DOE sites, operating laboratory and accelerator radiation protection at Brookhaven National Laboratory, and operational radiation protection at French nuclear power stations with FRAMATOME (now AREVA) and EDF. Since 1993 he has been with the NEA's Division of Radiation Protection and Radioactive Waste Management, where he is the Scientific Secretariat of the NEA's Committee on Radiation Protection and Public Health (CRPPH), and is responsible for all sub-groups (totaling approximately 250 experts from 33 countries). His work at the NEA has focused on the evolution of the system of radiological protection, radiological risk assessment and management, radiological protection technical and social science, stakeholder involvement and risk governance, radiation protection policy and regulation, nuclear emergency management, occupational exposure at nuclear power plants, and decommissioning. He was the Chair of the International Congress Programme Committee for IRPA13 (Glasgow, 13 – 18 May 2012), and has participated in the work of ICRP Committee 4 as an observer from 1995 to 2017 (as a member of various Task Groups that developed ICRP Publications 101, 109, 111, 124, and 125).

Dr. **Brian Marples** *(panelist)* has 25+ years' research experience in the field of Radiation Biology. In 2016, he relocated to the Department of Radiation Oncology at the University of Miami to become the Director of Radiobiology. His research interests focus on the molecular radiation response of tumor cells and normal tissues, with an emphasis on the biological mechanisms activated by exposure to low and clinically-relevant doses of radiation, and how these events regulate cell death pathways. He served as the Biology Chair of the American Society for Therapeutic Radiology and Oncology (ASTRO) Education Committee and Science Education Program Development (SEPD) committee, and sits on the ASTRO Science Council Steering Committee. He served as the Biology Chair of American College of Radiology Radiation Oncology In-Training Examination (TXIT) committee and now sits on the American Board of Radiology (ABR) Radiation Oncology Biology Committee. He became the Senior

Biology editor of the International Journal of Radiation Oncology Biology Physics (Red Journal) in October 2016.

John Neumann *(presenter)* is a Managing Director of GAO's new Science, Technology Assessment, and Analytics (STAA) team whose work is focused on supporting the science and technology needs of Congress by conducting technology assessments, providing oversight of federal science and technology programs, and developing innovative analytical techniques for carrying out audits and evaluations. John is a 30 year veteran of GAO. Before taking on his current role, he was the Director of Science and Technology issues within GAO's Natural Resources and Environment (NRE) team. Under his leadership, this portfolio of work grew to include a broad array of products evaluating the management of the substantial federal investment in research and development, as well as federal agencies' implementation of an array of programs, policies, and activities to protect intellectual property rights, enhance U.S. competitiveness, and stimulate the adoption of innovative technologies. Examples of current and recent work in this portfolio, which John continues to lead, include the cost and schedule performance of National Science Foundation construction projects, such as telescopes and research ships; reviews of the policies and procedures for federal science agencies to maintain scientific integrity and for science agencies to more effectively deal with allegations of sexual harassment among grant recipients; and considerations for maintaining U.S. competitiveness in transformational research areas, such as quantum computing and synthetic biology. John has received numerous awards, including, most recently, a Distinguished Service Award in 2018 in recognition of his exemplary leadership of NRE's Science and Technology issue area and his commitment to valuing all people. Prior to leading GAO's science and technology oversight work, John was an Assistant Director with agency's Contracting and National Security Acquisitions team, where he managed a diverse portfolio covering government-wide contracting and the U.S. defense industrial base. In particular, he became a recognized expert on export control issues and the protection of militarily critical technology, and the body of work he led resulted in the creation of a High Risk area in 2007 on ensuring the effective protection of technologies critical to U.S. national security interests. Earlier in his career, John spent a year as a detailee to GAO's Office of General Counsel and a year with the Senate Governmental Affairs Committee, where he conducted investigations for the Permanent Subcommittee on Investigations. John earned a Bachelor of Arts in Political Science from the State University of New York at Stony Brook. He also holds a Juris Doctor from Georgetown University Law Center and a Master in Business Administration from American University.

CAPT Michael A. Noska, *(panelist)* is the Senior Advisor for Health Physics, the Agency Radiation Safety Officer and the Team Lead for Radiological Emergency Response at the US Food and Drug Administration. He has been a health physicist with the US Public Health Service for 27 years and has had multiple assignments at the National Institutes of Health and the FDA with a focus on internal radiation dosimetry and radiological emergency preparedness and response. Prior to joining the PHS, CAPT Noska worked as a research assistant in radiopharmaceutical laboratories at Harvard Medical School and Duke University Medical Center developing radiolabeled monoclonal antibodies for the treatment of cancer. He received his M.S. from the University of North Carolina School of Public Health as a Department of Energy Applied Health Physics Fellow. CAPT Noska is a member of the National Council on Radiation Protection and Measurements. He is also the current Chair of the Federal Advisory Team for the Environment, Food and Health and a member of the Federal Radiological Preparedness Coordinating Committee. He is a Past Chair of the Environmental Health Officer Professional Advisory Committee to the US Surgeon General and Past President of the Baltimore-Washington Chapter of the Health Physics Society. CAPT Noska serves on several interagency committees and workgroups related to radiological emergency response. In 2011,

he deployed to Japan as part of a team from the Department of Health and Human Services in support of the US Ambassador following the Great Tohoku Earthquake and the nuclear crisis at the Fukushima Dai-ichi Nuclear Power Station.

Dale L. Preston, Ph.D. *(presenter)* is a biostatistician with almost 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 as a result of the operations of the Russian reactor and plutonium production complex (Mayak). 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 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. Dr. Preston continues to be actively involved in a number of studies of the long-term health effects of radiation including studies in the Russian Federation, Japan, and the US.

David Richardson *(committee member, presenter, and session moderator)* is Associate Professor of Epidemiology in the School of Public Health at the University of North Carolina at Chapel Hill. His research focuses on the health effects of occupational and environmental exposures, particularly with regards to ionizing radiation. He has conducted studies of cancer among nuclear workers in the US and abroad, as well as studied cancer among the Japanese survivors of the atomic bombings of Hiroshima and Nagasaki. He has served as a visiting scientist at the World Health Organization's International Agency for Research on Cancer, the French Institute for Radiological Protection and Nuclear Safety, and at the Radiation Effects Research Foundation in Hiroshima, Japan. Since 2007, he has served as Director of the National Institute of Occupational Safety and Health-funded training program in occupational epidemiology at the University of North Carolina-Chapel Hill. In addition, he is a core faculty member at the Injury Prevention Research Center at the University of North Carolina, and a member of the Exposure and Biomarkers Research Core at the University's Center for Environmental Health and Susceptibility. He is an Associate Editor of the journals Occupational and Environmental Medicine, American Journal of Epidemiology and Environmental Health Perspectives, and is a member of the President's Advisory Board on Radiation and Worker Health. Dr. Richardson's current research includes studies of mortality among nuclear industry workers and uranium miners, and development of innovative methods for occupational cancer studies. Dr. Richardson received a Ph.D. and M.S.P.H., both in epidemiology, from the University of North Carolina.

Since July 2015, Dr. **Andrew Scott** *(panelist)* has served as the primary advisor on health related nuclear and radiation issues to the Chief Medical Officer of the Department of Homeland Security (DHS). Prior to his work at DHS, he served as a US Army Health Physicist for 19 years in a number of administrative and operational capacities. He earned his PhD from Clemson University in 2010 and became a Certified Health Physicist in 2013. Dr. Scott's publications are in the areas of human radiation dose estimation, uranium mobility in the environment, radiation detection instrumentation, radon remediation and environmental sampling and analysis.

Ignacia (Iggie) Tanaka, DVM, Ph.D. *(presenter)* is an Associate Senior Scientist with the Pathology Group of the Radiobiology Department at the Institute for Environmental Sciences (IES). Her current work mainly focuses on the pathology – neoplastic and non-neoplastic diseases, of mice chronically exposed to low dose-rates of gamma-rays. Prior to joining IES, she worked with non-human primates at a contract research organization (CRO), Ina Research Philippines, Inc. She received her degree, Doctor of Veterinary Medicine (DVM) from the University of the Philippines, an M.Sc. in Ruminant Nutrition from Obihiro University, Japan, and a Doctor of Veterinary Science (PhD) in Comparative Pathology from Hokkaido University, Japan.

Dr. **Robert Ullrich** *(presenter)* is the Chief of Research, Vice Chairman, and Executive Director at the Radiation Effects Research Foundation (RERF) in Hiroshima, Japan. Dr. Ullrich initially joined RERF as its Associate Chief of Research in November 2013. Before joining RERF, Dr. Ullrich was the John Sealy Distinguished Chair in Cancer Biology, Director of the Sealy Center for Cancer Biology, and Interim Director of the Cancer Center at the University of Texas Medical Branch in Galveston, Texas. Prior to that he was the Barbara Cox Anthony Distinguished Chair in Oncology at Colorado State University and Director of the Colorado State component of the University of Colorado Consortium Comprehensive Cancer Center. He is recognized internationally for his research on mechanisms and risks of cancer following exposure to ionizing radiation and for his scientific leadership of laboratory, academic, and medical programs. Dr. Ullrich received the Radiation Research Society's Failla Award in 2012 for outstanding research contributions in radiation science.

Alan E. Waltar *(panelist)* past president of the American Nuclear Society, recently retired as Director of Nuclear Energy at the Pacific Northwest National Laboratory (PNNL) after previously retiring as Professor and Head of the Department of Nuclear Engineering at Texas A&M. He holds a PhD in Engineering Science from the University of California, Berkeley. Whereas the bulk of his career focused on fast reactor research and development, he is now focusing on potential upgrades to low dose radiation protection standards. This interest grew out of the unintended consequences of applying the current, ultra conservative standards and the associated ethical issues.

Gayle Woloschak, PhD, *(committee member, presenter, and session moderator)* professor in the Feinberg School of Medicine Departments of Radiation Oncology, Radiology and Cell and Molecular Biology, is currently involved in nine federally funded research studies, acting as the principal investigator on five of them. A renowned scientist, Woloschak has published numerous articles in journals like Molecular Immunology**,** Nature Materials and Proceedings of the National Academy of Sciences **(**PNAS**),** and has her name registered on a long list of inventions. Woloschak has numerous faculty appointments at universities across the world. In addition to her roles at Northwestern, she is also a visiting scientist at the Bundeswehr Institute for Radiobiology in Munich, Germany, lecturer at Rosalind Franklin Medical School in North Chicago, Ill., and visiting professor at Alexandria University in Alexandria, Egypt. Woloschak is co-leader of the Cancer Nano Materials Program in the Robert H. Lurie Comprehensive Cancer Center of Northwestern University, and is a member of the Center for Genetic Medicine, and the Northwestern Comprehensive Center on Obesity. What's more, Woloschak is associate director of the Radiation Oncology Residency Program at Northwestern, and was the recipient of this program's Teacher of the Year Award during the 2005-2006 academic year. Recently, Woloschak's teaching abilities were recognized again when she was awarded the 2010 Rosalind Franklin University Outstanding College of Health Professions Educator Award.

ABSTRACTS

PLENARY SESSION: Setting the Stage

Moderated by Joe Gray, Oregon Health & Science University (OHSU)

Remembering Gilbert Beebe

Dale Preston, Hirosoft International

Gilbert (Gil) Beebe is perhaps best known for his role in the organization of the ongoing and extremely influential studies of radiation health effects on the survivors of the atomic bombings of Hiroshima and Nagasaki carried out by researchers and staff of the Atomic Bomb Casualty Commission and, its binational successor, the Radiation Effects Research Foundation (RERF). Thanks to the well-thought-out and carefully-implemented research plan developed by Gil and Seymour Jablon, with more than 70 years of follow-up, the LSS study continues to provide new insights into the nature of the long-term effects of acute radiation exposure on cancer and non-cancer risks in the survivors. These findings remain central to the quantification of radiation health effects and the development of national and international radiation protection standards. In this presentation we describe how Gil's ideas about cohort study design evolved from his early work on studies of contraception in Depression-era Appalachia and his development of the Medical Follow-up Agency for health studies of World War II veterans. We also touch upon how his early work and experience with these studies and RERF informed his central role in the development of sound and effective designs that have been used for studies of the effects of the Chernobyl accident. Gil's thoughtful approach to the design and implementation of practical, resilient large-scale follow-up studies is one of the main reasons that we are gathered for this conference on the current status and future directions of studies of low-dose radiation effects.

Low Dose Radiation and Societal Decisions

David Brenner, Columbia University

Our main concerns at low radiation doses relate to radiation-induced cancer, but a number of other health endpoints are also not well quantified at low doses. Realistically, radiation epidemiology and radiation biology can provide quantitative data with reasonable confidence limits in the 10 to 100 mSv range (and above), but at lower doses the confidence limits expand markedly. So radiation risk estimates at lower doses require the use of models to extrapolate risks from higher to lower doses. Such models do exist but are based on assumptions which are often questionable. In summary we have major gaps in our understanding of the health effects of low doses of radiation. These gaps have potentially seriously impact on our ability to make science-driven decisions about low-dose radiation issues such as nuclear power, radon in houses, medical imaging, evacuation after a large-scale nuclear event, and cleanup of radiation contaminated sites. As well as health consequences, our uncertainties in regard to low-dose radiation risks often have major economic consequences. For example the current cost estimate for cleanup of the Hanford Nuclear Reservation is $242 billion which is, in significant part, driven by these uncertainties.

Status of Low-Dose Research in the United States
John Neumann, Government Accountability Office

In September 2017, the U.S. Government Accountability Office (GAO) issued a report on the scientific basis for federal protections against the harmful effects of ionizing radiation—particularly low-dose radiation, or below about 100 millisieverts (10 rem). The report provided examples of how federal agencies developed and applied radiation protection requirements and guidance for workers and the public and examined the extent to which federal agencies funded epidemiological and radiobiological research on the health effects of low-dose radiation and their efforts at coordination of this research. The report found that agencies collaborated on individual projects on radiation's health effects but did not have a mechanism to coordinate research priorities. Consequently, GAO recommended that the Department of Energy (DOE) lead the development of a mechanism for interagency collaboration related to research on the health effects of low-dose radiation.

Global Low-Dose Research Coordination
Ted Lazo, Organisation for Economic Co-operation and Development- Nuclear Energy Agency

One of the key radiological protection research areas addresses the need to improve our understanding of radiological health risks that might be caused by exposure to low radiation doses (meaning below to far below about 100 mSv). This vast subject includes addressing such aspects as chronic versus acute exposures, effects of dose level and dose rate, effects of different types of radiation, organ and tissue sensitivity, cellular damage mechanisms and tumour progression pathways, etc. Given the importance placed on such research by government funding organisations, and recognising the enormous amount of research done and continuing in this area across the globe, while noting ongoing efforts to effectively collaborate and coordinate research, it is felt that the global nature of ongoing work merits consideration of some level of global coordination. This paper will present the work of the NEA High-Level Group on Low Dose Research (HLG-LDR) to assist participants to orient their low-dose research programmes in a coordinated fashion, and to make recommendations as to best practices in planning, implementation and reporting results of low-dose research.

SESSION 1: Low-Dose Radiation Programs

Moderated by Michaela Kreuzer, Federal Office For Radiation Protection, Germany

History of the U.S. Department of Energy Low Dose Radiation Research Program
Tony Brooks, Washington State University Tri-Cities

At the time the DOE Energy Research Program was initiated the scientific community had extensive knowledge on the health effects of high doses of ionizing radiation delivered at high dose rates. There was limited information on the biological responses induced by low dose and dose rate exposures. The sequencing of the genome, development gene expression arrays, and multiple cell and molecular biological techniques along with the development of new technology provided the necessary spring board for the Program to measure biological responses in the dose (less than100 mGy) and dose rate (10 mGy/hr) region that was not possible in the past. The need for this information was critical then and remains critical as the use of radiation remains one of our most important tools to combat disease, generate electric

power, protect the environment, workers and public from unnecessary potential risks. By evaluating the state of knowledge in the field of radiation biology Before the Low Dose Program (BLD) and After the Low Dose Program (ALD) this presentation provides a brief review of the accomplishments of the DOE Program. It is also important to review the forces in place to start the Program, and the shortcomings of the Program. Future research to address the most important effect of low doses of radiation (fear) and need to communication of the research results will be briefly covered. The content of the needed future research program must build on the past research to avoid mistakes and take the public perception of radiation hazards, the science of radiation biology and health protection boldly into the future.

The Multidisciplinary European Low Dose Initiative

Michaela Kreuzer, Federal Office For Radiation Protection, Germany

Background: Based on the recommendations of the High Level Expert Group on European Low Dose Risk research, MELODI (http://www.melodi-online.eu) – a European platform dedicated to low dose ionizing radiation risk research - was founded as registered association with 15 members in 2010. To date, MELODI has more than 40 members from national bodies responsible for defining, funding and implementing research in this domain, and universities and research institutes committed to contribute to R&D efforts.
Activities of MELODI: A major activity is the establishment and regular updating of a long-term Strategic Research Agenda (SRA) for research on low dose risk for radiation protection in Europe. The SRA is intended to guide the priorities for national and European research programs and to support competitive open calls at the European level. Furthermore MELODI supports the availability and maintenance of key infrastructures as essential basis for research activities, and the retention and broadening of competences in radiation research and health risk assessment in the long-term via an integrated European approach for training and education.
Research priorities: Three key research questions have been defined by MELODI: 1) Dose and dose rate dependence of cancer risk, 2) Non-cancer effects and 3) Individual radiation sensitivity. The research required to improve the evidence base for each of the key questions is multidisciplinary and given in three research lines: 1) Basic mechanisms, 2) Epidemiological research for health risk evaluation and 3) Impact of different exposure characteristics.
Organization of funding and integration: The European Network of Excellence DoReMi (2010-2016) funded by Euratom FP7 radiation protection programme served as an important initial operational tool for establishing MELODI and setting up the structures for sustainable integration of research on low dose risk in Europe. Subsequently, the OPERRA (Open Project for European Radiation Research Area) (2013-2017) project continued the work in establishing a programme in radiation protection research in Europe and ran several calls for research projects. Currently, radiation protection research in Europe is organized within the CONCERT European Joint Programme Co-fund Action (EJP) (2015-2020). The aim of EJP is to bring together relevant funding agencies from the European Commission (EC) and the Member States to integrate European research and to administer calls for research proposals in radiation protection on behalf of the EC. This activity builds upon the strategic research agendas from five European radiation protection research areas (low-dose, radioecology, emergency management, medicine, dosimetry), and aims to establish interaction and synergies between the different areas of expertise. Competitive calls for research projects – including MELODI priorities - were ran in 2013 and 2014 by OPERRA and 2016 and 2017 by CONCERT. Additionally, in 2017 and 2018 the EC's EURATOM programme ran calls for research in radiation protection.
Dissemination and Progress of MELODI: MELODI organizes regularly scientific and stakeholder workshops in order to promote the visibility of the research area, to summarize the results

obtained so far and to identify further gaps. In addition, MELODI sponsors workshops on specific topics. Outputs and recommendations from all these activities were used to regularly update the SRA and identify priorities guiding next calls.
Literature:
Kreuzer et al. 2018. Multidisciplinary European Low Dose Initiative (MELODI): strategic research agenda for low dose radiation risk research. Rad Environ Biophys 2018;57:5-15.

The Low-Dose Radiation Research Program in Japan
Ignacia Braga-Tanaka III, Institute for Environmental Sciences, Japan

Research on the effects of low dose radiation exposure has never attracted much attention until the nuclear power plant accident in Fukushima in 2011. The Institute of Environmental Sciences was established in 1990 to address the concerns of the local citizens regarding radiation safety in relation to the construction of the Spent Nuclear Fuel Reprocessing Plant in Rokkasho Village. In 1995, the Institute had a purpose-built SPF mouse facility for conducting long-term continuous (chronic) low dose-rate radiation exposures at dose rates of 0.05, 1 and 20 mGy/day. A second mouse facility was built in 2007 to accommodate medium dose rates of 200 and 400 mGy/day in addition to 1 and 20 mGy/day. A summary of completed projects as well as future perspectives for the Institute will be presented. Current projects in other institutions working on low dose radiation in Japan will also be presented. All projects at IES are performed under contract with the Aomori Prefectural Government, Japan.

Low-Dose Radiation Research in Canada
Dmitry Klokov, Canadian Nuclear Laboratories

The international radioprotection system evaluates human health risks based on the Linear-No-Threshold (LNT) hypothesis. The LNT has been widely criticized for not conforming to a large body of scientific evidence showing non-linearity in biological responses of cells and organisms to low-dose radiation (LDR) exposures. This controversy, going decades back, continues to undermine the radioprotection system. Canadian Nuclear Laboratories (CNL), formerly known as Atomic Energy of Canada Limited, began addressing this issue by initiating research on the biological effects of radiation several decades ago, building a strong and rich legacy in radiobiology, in particular low-dose radiobiology. CNL has built a globally unique animal low-dose irradiation facility that has been home to a number of large scale LDR mouse *in vivo* and *in vitro* studies. Having a low-dose irradiation animal facility, combined with a dedicated LDR focused federally funded program, has allowed CNL to carry out large scale complex mouse studies examining early molecular, genetic, epigenetic and immunological changes in relevance to systemic outcomes such as cancer and life span. This unique holistic approach allows for understanding of the biological effects of LDR at broader and deeper levels.

Our recent results showed that in vivo LDR exposure results in the activation of the nucleotide and base excision DNA repair pathways. Consistent with this, cellular aging in LDR exposed cells was delayed. The concomitant changes in microRNA expression profiles suggested a strong role of epigenetic mechanisms in LDR effects. These results were partially reproduced in the *in vivo* mouse model of aging using markers of aging. Additionally, we demonstrated that LDR triggered an overall stimulatory effect on the immune system in mice. Furthermore, our most recent results from studying genetically modified mice that quickly develop and die of intestinal tumors, showed that LDR exposure improved their health conditions and expanded their life span. Lastly, we demonstrated that various types of human stem cells exposed *in vitro* to LDR delayed their aging-related functional decline. Our current studies are aimed at

obtaining an even deeper insight into mechanisms underlying responses to LDR and affecting systemic health risks - through all levels of biological organization, from molecules to tissues. With the closure of the low-dose radiation research program funded by the U.S. Department of Energy, the CNL radiobiology program remains one of the world largest efforts in the field and continues to make significant contributions to advance the understanding of biological effects of LDR. However, there are huge opportunities for combining efforts with other research programs, both within Canada (e.g. the low-dose program at Northern Ontario School of Medicine and a program coordinated by Health Canada and the Canadian Nuclear Safety Commission), and internationally (e.g. the EU MELODI program or a prospective reopened DOE program) – to maximize the output of large scale LDR animal studies.

SESSION 3: Current Directions for Low-Dose Radiation Research

Part A: Contributions from Epidemiological Studies

Moderated by Gayle Woloschak, Northwestern University

Current Research Activities at the Radiation Effects Research Foundation

Bob Ullrich, Radiation Effects Research Foundation

The study of the effects of the atomic bombings of Hiroshima and Nagasaki began in 1948 with the founding of the Atomic Bomb Casualty Commission (ABCC) the predecessor to the Radiation Effects Research Foundation (RERF). More than 40 years ago, in 1975, the ABCC became the RERF as a nonprofit foundation. RERF is a joint U.S.-Japan research organization responsible for studying the medical effects of radiation and associated diseases in humans for the welfare of the survivors and all humankind. These studies have been going on for over 70 years, which makes RERF the only institution that has been conducting epidemiological studies on a population of more than 120,000 individuals for this long. RERF continues to conduct research until this day because the effects of A-bomb radiation on human health have not been fully elucidated. RERF conducts research in multiple fields of science including epidemiology, clinical medicine, genetics, and immunology. Findings from RERF's studies have been used not only for the welfare of the A-bomb survivors but also for the establishment of international radiation protection standards. This presentation will discuss the most recent findings of these studies and describe potential new collaborative research opportunities.

Occupational Studies

David Richardson, University of North Carolina

Millions of workers worldwide are externally exposed to ionizing radiation on the job. This includes people employed in medicine who conduct radiologic procedures, as well as people employed in the nuclear fuel cycle, industrial radiography, and in defense activities. Recognition of external ionizing radiation as an occupational carcinogen follows a classical path taken for the identification of many environmental and occupational carcinogens. Case reports began to appear shortly after the discovery of X-rays and described malignant skin tumors caused by occupational external ionizing radiation exposures. Next followed reports that described the relative mortality of radiation-exposed clinicians compared to their non-exposed peers. However, it was the Manhattan Project that led to large industrial cohorts of radiation-exposed workers and facilitated quantitative analytical studies of health effects associated with occupational external radiation exposures. By the 1970s and 1980s cohorts

had been enumerated at several nuclear facilities, and national cohort were beginning to be assembled based on registries of radiation workers. Pooled analyses of nuclear worker cohorts, such as those from North American and Europe, have suggested positive associations between cumulative external ionizing radiation dose and cancer across relatively low ranges of cumulative doses. Looking forward, epidemiological studies of radiation-exposed workers are likely to reflect, in part, evolution of the exposures and employment over time; the studies will broaden to encompass increasing numbers of female workers in the nuclear industry and reflect other changes in demographics and exposures among radiation workers that will contribute to a fuller understanding of radiation risks. New computational approaches to handling of measurement error and missing data, and new statistical approaches to strengthen inferences in longitudinal analyses, will accompany and strengthen large-scale collaborative studies on this topic. Large cohort studies are likely to be complemented by efficient, nested studies that permit collection of more refined exposure and outcome information.

Environmental Exposure Studies
Dale Preston, Hirosoft International

While the results of studies of radiation health effects in the atomic bomb survivors are central to discussions of the quantitative effects of radiation on cancer and other disease risk, studies of populations with environmental radiation exposures provide what is probably the most directly relevant estimates of radiation health effects. These studies generally involve unselected populations that include men and women of all ages who typically received low and often chronic exposures. There are several studies populations with environmental exposure for which individual / individualized dose estimates are available. These include studies of people with non-occupational exposures as a result of nuclear weapons production or accidental releases from nuclear power plants, of the consequences of natural background exposures and of exposures from other sources. Such studies, while important, present a number of challenges including identification, tracing, and case-finding; potential confounding; dose reconstruction and dose uncertainty; and a likely lack of statistical power. In this presentation I will briefly note several studies carried out in environmentally-exposed populations and discuss, in general terms, the challenges in conducting such studies and interpreting their findings. Despite the difficulties in carrying out these studies, they have the potential to, and probably should, have a more direct impact on the assessment of radiation effects in cancer and other diseases.

Medical Exposure Studies
Amy Berrington de González, National Cancer Institute

There have been increases in ionizing radiation exposure to the general population in the last few decades due to rapid growth in medical radiation, primarily from CT scans. Smaller increases in other higher dose diagnostic exposures, nuclear medicine procedures, and fluoroscopically -guided interventional procedures also contributed. Several important historical cohort studies, such as the Massachusetts and Canadian fluoroscopy cohorts, established that repeated exposure to diagnostic X-rays resulted in an increased risk of cancer. These populations received high cumulative doses of up to 1Gy following hundreds of exposures. More recent cohort studies have also suggested that pediatric CT scans can result in increased cancer risks even when the cumulative doses are much lower (eg 100mGy). Replication of these findings is important and there are large multi-center studies in Europe and North America currently in progress. Future studies will benefit from the increasing feasibility of electronic medical record linkage studies, which enable the conduct of large-scale studies with individualized dose records and detailed medical histories.

Part B: Contributions from Radiation Biology

Moderated by David Richardson, University of North Carolina

Low Dose and Low Dose Rate Responses in Animals

Gayle Woloschak, Northwestern University

Many remarkable and extensive studies pertinent to low dose radiation research were done in a variety of animal model systems. For example, studies from ENEA and SCK/CEN in Europe or ORNL and ANL in USA regularly included cohorts of mice or rats exposed to low dose rate, fractionated and chronic external beam exposures, accumulating to medium total doses of radiation at or below 1.5 Gy (Haley et al., 2015). Similarly, internal emitter studies in US and Europe included low dose rate emitting radionuclides (Puukila, et al 2018, Paunesku et al., 2012). Majority of this work was focused on changes in life expectancy and cancer incidence. In some of the lowest dose exposed animals, in some cases, this was associated with increased life expectancy and change in spectra of cancers and non-cancer diseases.

Partially in response to this work, partially driven by development of reliable and sensitive assays for molecular biology, more recent and current low dose radiation studies included fewer animals but focused on different genetic makeups, or introduction of stresses pre or post low dose radiation exposures. Not surprisingly, this research found that, molecularly and cytologicaly, same effects of low dose radiation exposures can be beneficial in specific disease contexts (e.g. regenerative neovascularization as found by Ministro et al., 2017) and detrimental in others (e.g. neovascularization supporting tumor growth in SCID mice as noted by Sofia Vala et al., 2010). Considering persistent growth of more sensitive and reliable techniques in biology and increasing understanding that sometimes even minor alterations in animal age and environment can have profound effects on animals' health and ability to cope with stresses (Paunesku and Woloschak 2018), we can expect consistent growth of our ability to conduct and interpret sophisticated low dose radiation studies in animal research models.

Molecular Injury Responses Triggered by Low Dose Radiation and Implications for Long-Term Effects in Normal Tissues

Al Fornace, Georgetown University

In the course of our studies on the cellular effects of radiation, we have observed a wide variety of genes whose products are involved in intercellular signaling and tissue injury responses. These studies have included responses in human cell lines, peripheral blood lymphocytes irradiated *ex vivo* and *in vivo* from patients, as well as studies employing mouse models and non-human primates. Cellular responses to radiation injury and other forms of genotoxic stress involve a complex network of signaling processes that contribute to recovery from injury but can also have adverse effects *in vivo*. Interestingly, many of these responses have been shown to be induced even by low dose radiation (LDR) [1], and similar effects were subsequently shown by others. In the case of transcriptional responses, p53 signaling can be induced by doses of 1 cGy or lower [1]. Using genetic and metabolomics approaches, our laboratory has shown that LDR can affect many tissues *in vivo* and can impact immune function and energy metabolism by inhibiting specific signaling pathways [2]. Long-term effects of radiation are known to be associated with immune dysfunction and pro-inflammatory signaling in many tissues, and can lead to incompetent metabolic reprogramming in activated T cells even at low doses [2]. After either low or high LET LDR, our laboratory has shown triggering of long-term stress signaling, elevated oxidative stress, increased senescent cells, and induction of a pro-inflammatory state

characteristic of the senescence-associated secretory phenotype [3]. Radiation-induced premature senescence is well known in the field, and it has been shown that even a very small number of senescent cells can result in physical dysfunction. For example, senescent cells can impact normal somatic stem cell function with a variety of deleterious long-term consequences [3]. Understanding the roles of LDR-induced senescence on metabolism, inflammation, and immune function should help to delineate a systematic view of the physiologic impacts of LDR. Incorporation of state-of-art approaches and models into LDR research offers exciting opportunities to engage top-notch scientists with diverse expertise and to make breakthroughs in a variety of areas from basic mechanistic science to practical applications including risk estimation and potential targets for risk reduction.

1. Amundson, S. A., Do, K. T., and Fornace, A. J., Jr. Induction of stress genes by low doses of gamma rays. Radiat Res *152*: 225-231, 1999. PMID: 10453082
2. Li, H. H., Wang, Y. W., Chen, R., Zhou, B., Ashwell, J. D., and Fornace, A. J., Jr. Ionizing Radiation Impairs T Cell Activation by Affecting Metabolic Reprogramming. Int J Biol Sci *11*: 726-736, 2015. PMID: 26078715
3. Kumar, S., Suman, S., Fornace, A. J., Jr, and Datta, K. Space radiation triggers persistent stress response, increases senescent signaling, and decreases cell migration in mouse intestine. Proc Natl Acad Sci U S A 201807522, 2018. PMID: 30275302

Epigenetic Alterations from Low-Dose Radiation

Randy Jirtle, North Carolina State University

Genes with metastable epialleles have highly variable expressions because of stochastic allelic modifications in the epigenome induced by environmental exposures. The viable yellow agouti (A^{vy}) mouse harbors a metastable *Agouti* gene because of an upstream insertion of a transposable element. We previously used this animal model to demonstrate that nutritional and chemical toxicant exposures during early development induce persistent epigenetic changes at the A^{vy} locus that result in alterations in coat color and adult disease susceptibility. We also showed that low doses of ionizing radiation ($\leq$7.6 cGy) induce a sex and dose dependent positive adaptive phenotype in A^{vy} offspring that results from significant alterations in DNA methylation at the A^{vy} locus; an effect that is block by maternal antioxidant exposure.

SESSION 4: New Directions in Low-Dose Radiation Research

Moderated by Alexandra Miller, Armed Forces Radiobiology Research Institute

Biomarkers for Molecular Epidemiological Studies

Janet Hall, French National Institute of Health and Medical Research (INSERM)

The integration of ionising radiation (IR) biomarkers into epidemiological studies to substantiate the radiation causality of health risks associated with low dose and low dose rate IR exposures and to address the differences in radiation sensitivity between individuals, or groups could be potentially useful and informative. A number of key considerations including the choice of population to be investigated, the type of radiation exposure (radiation quality and dose rate), study design, ethical considerations, the logistics of biological sample collection, processing and storing, the limitations of and thus the choice of the biomarker or bioassay to be used, as well as potential confounding factors need to be taken into consideration (reviewed in Pernot *et al.,* Mutation Res., 751 (2012) 258-286). Given the increased mechanistic understanding of responses to low dose and dose rate radiation, and technological and analytical developments

and cost-reductions that are advancing the development of potential biomarkers, an update of the Pernot *et al.* review was undertaken (Hall *et al.,* Mutation Res., 771 (2017) 59-84). For instance, progress has been made in the identification of potential biomarkers of exposure and late-effects related to advances in metabolomics and transcriptomics and there is great potential to identify genetic and epigenetic biomarkers of individual radiosensitivity. The increasing number of potential new biomarkers underpins the need for guidelines for biomarker validation and deciding which biomarkers to carry forward from discovery to implementation. A roadmap was drawn-up to aid in this decision process of when to progress or drop a biomarker that took into account critical issues such as assay reproducibility, sensitivity and specificity for IR exposure. This roadmap was then used to summarise the current status of proposed biomarkers for epidemiological studies investigating low dose health effects. Based on this evaluation it was concluded that most potential biomarkers remain at the discovery stage and that robust validation will be essential before implementation. For some, there is sufficient evidence that further development for use in low dose radiation molecular epidemiology studies is not warranted.

Technological Advancements
Joe Gray, OHSU

The mechanisms by which radiation and other environmental factors cause disease conditions include cancer include genome and epigenome modifications and direct chemical and physical interactions that compromise the multiscale structures and functions of affected cells and tissues. Importantly, the actual effects of exposure to these factors depend on the biological, physical and chemical environments in which the individual affected cells reside. Technological advances in the last decade have dramatically increased our ability to quantify the components and multiscale architectures of cells and tissues leading to new insights into disease genesis and behavior. This talk will illustrate the utility of several of these technologies by describing their applications to assessment of human cancerous tissues. These include (a) single cell sequencing to study epigenomic differentiation state switching and cancer cell motility, (b) multiplex immunochemical analysis of tissues to assess induced changes in cellular composition including immune status, and (c) 3-dimensional scanning electron microscopy and super resolution fluorescence microscopy to reveal nanoscale structures that influence the inter and intracellular interactions. All featured tools and workflows featured have been applied to human tissues and so can be considered for use in assessment of the sometimes-subtle effects of radiation in exposed individuals.

Sadik Esener, OHSU

Significant advances have been made in understanding the role of various particulates that circulate in body fluids. In blood these include various types of cells and platelets, but also extracellular vesicles (EVs), including nanoscale exosomes and platelet derived particulates as well as free circulating proteins, and DNA and RNA that are often protected within lipid particulates. The analysis of these particulates in blood of patients show significant differences with normal such that these particulates are now being considered as potential biomarkers for diseases such as cancer. In this presentation we will describe methods to isolate and analyze these particulates, and discuss ways by which they might be affected by induced stress including low dose radiation. Recent studies for example suggest that EVs play significant role in mediating radiation-induced bystander signals.

Single Cell Genomics
Charles Gawad, St. Jude Children's Research Hospital

The consequences of exposures to low doses of mutagens on single human cells and how those changes alter tissue health are largely unknown. This has been mainly been due to a lack of technical tools available to study global changes in the nucleic acid content of single cells. In this lecture, I will provide an overview of the recent progress in the development of single-cell sequencing methodologies. I will then discuss our recent development of primary template-directed single-cell whole genome amplification (PTA), which enables the accurate detection of about 85% of genetic variation in each individual cell. We have applied PTA to map genome-wide interactions of mutagens with single living human cells at base-pair resolution, and are currently using PTA to examine the mutagenesis rates and signatures of environmental compounds. I will conclude by exploring how these studies could be expanded to study relationships between low-dose radiation, tissue biology, and disease.

Immune Response
Silvia C. Formenti, Weill Cornell Medicine

Focal radiation therapy (RT) induces both immunogenic and immunosuppressive signals to the tumor and its microenvironment. Preclinical strategies to enhance the formers and/or mitigate the latter have proven the concrete possibility to shift the balance toward a therapeutic success (Formenti S et al, J Natl Cancer Inst. 2013). Preclinical experiments in multiple syngeneic mouse models that mimic the setting of advanced human cancers have demonstrated promise of combining RT with immunotherapy. The preclinical data was consistently confirmed clinically. Particularly, when combined with immune checkpoint blockade (ICB), radiation therapy has demonstrated to be a powerful adjuvant to immunotherapy (Demaria S et al, Clin Cancer Res. 2005;11:728-734). Clinical examples of synergy between radiation and immune checkpoint inhibitors have been reported (Postow M et al, N Engl J Med. 2012; Formenti S et al, Nature Medicine, 2018, etc.) Currently, multiple clinical trials are exploring optimal combinations and scheduling of focal radiotherapy and immunotherapy. Strategies at reducing radiation-induced lymphopenia are warranted to assure adequate availability of naïve T cells when focal radiotherapy is harnessed to convert the tumor into an individualized cancer vaccine. Finally, both dose and fractionation are key at optimizing the combination of RT/ICB (Vanpouille-Box et al, Nature Communications, 2017).

Until now, the immune effects of low dose total body exposure of RT remain poorly understood. For instance, it is unknown whether scattered dose to the rest of the body contributes to systemic effects of RT and ICB. In vitro tumor cell irradiation at sublethal doses of 2 Gy enhances cytotoxic T lymphocytic activity, measured by FACS. Whole body exposures to doses in the range of 50 cGy-100 cGy induce cell death receptors' ligands (TRAIL, FAS-L), but evidence is limited when doses below 10 cGy are used. Recent preclinical evidence suggests that a total body dose of 1-2 Gy can enhance the effect of CAR-T cell therapy (Deselm C et al, Molecular Therapy 26:11, 2018). Local or total body radiation in these dose ranges rendered tumor cells highly vulnerable to TRAIL-mediate death, suggesting a therapeutic opportunity for including RT conditioning during CAR-T therapy.
Research is warranted to test low dose RT in preclinical and other clinical settings, particularly when combined with ICB.

Systems Biology
Francis Cucinotta, University of Nevada, Las Vegas

We discuss applications of systems biology approaches in the study of radiation health effects. Definitions of systems biology range from the description of the behavior of complex biological processes in terms of molecular constituents to the use of functional omics and pathway modeling in multi-scale descriptions of biological processes in cells and tissues. Mathematical approaches using engineering concepts such as motifs, modularity, robustness, and positive and negative feedback controls are commonly used in systems approaches. System models of the DNA damage response in tissues, immune responses to radiation, and low dose radiation effects on cognition are discussed.

Microbiome
Eleanor Blakely, Lawrence Berkeley National Laboratory

This presentation will briefly review what is known about the human microbiome and its association with human disease. The limited information available on the effects of exposures to low radiation doses of various types of radiation on the microbiome will be summarized. The various current approaches and model systems used to investigate the microbiome will be described. Key challenges and opportunities for future low dose radiation research on the microbiome will be outlined, as well as the potential scientific impact of these investigations.

SESSION 5: Models for Coordinated Research

Moderated by Joe Gray, OHSU

Lessons learned from Coordinated Research on the Health Effects of Air Pollution
Dan Greenbaum, Health Effects Institute

The design, funding, and implementation of comprehensive research programs is always a challenge, and can be especially challenging when the topics to be studied are designed to inform potentially controversial policy decisions. This presentation will discuss two successful models for such research programs, implemented to address key questions related to air pollution and health. First, it will discuss the work of NAS Committee on *Research Priorities for Airborne Particulate Matter* which was launched in the wake of controversial 1997 US EPA decisions on air quality standards, and provided a means through four reports over 5 years, to both guide EPA on its research priorities – and then monitor the progress in implementing the research. Second, it will discuss the development and implementation of the Health Effects Institute *Strategic Plan for Understanding the Health Effects of Air Pollution*, a Plan developed every five years – for the past 25 years – to guide the research program of HEI – a research institute funded jointly by the US EPA and the worldwide motor vehicle industry. The presentation will discuss the factors that led to the development of these to models, the practical experience, and potential lessons for other areas such as low dose radiation.

Lessons Learned from Large-Scale Biology Initiatives
Anna Barker, Arizona State University

Early in the 21st Century, it was becoming increasingly apparent that the development of effective interventions to diagnose, treat and prevent cancer, would require understanding

cancer at a more fundamental level – especially alterations in the cancer genome. Fortunately, advances in technologies and the molecular sciences provided the National Institutes of Health (NIH) and the National Cancer Institute (NCI) with opportunities to undertake a number of high priority coordinated (collaborative) large-scale initiatives to address these needs in areas ranging from cancer genomics to nanotechnology, biomarkers and clinical trials.
Two models will be discussed in this presentation; The Cancer Genome Atlas (TCGA), developed and managed as a partnership between the NCI and the National Human Genome Research Institute; and the ISPY 2 trial, a large-scale coordinated/collaborative clinical trial that was designed through the Foundation for the NIH Cancer Biomarker Committee and continues through a non-profit organization (Quantum Leap Healthcare Collaborative). The overall goal of TCGA was to leverage expertise and technologies from the Human Genome Project and cancer genomics through a large network of academic institutions and investigators to identify all the major genomic alterations in most major types of cancer. TCGA was completed in late 2018, having sequenced 33 types of cancer (including 10 rare tumors) and made the data publicly available. In contrast the ISPY 2 trial is an ongoing public-private partnership model that is organized as a large scale adaptive platform trial. To date, the ISPY 2 network has tested 17 cancer therapies and “graduated” 7 agents that can move to phase 3 trials. Both project models have exceeded their original goals and proven transformational in cancer research and well beyond.

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ABOUT THE NUCLEAR AND RADIATION STUDIES BOARD

The mission of the Nuclear and Radiation Studies Board (NRSB) is to (1) provide an open forum for discussion, and (2) organize and oversee studies on safety, security, technical efficacy, and other policy and societal issues arising from the application of nuclear and radiation-based technologies, including:

- Exposure to ionizing and non-ionizing radiation, including assessments and amelioration of biological, health, and other effects.
- Generation, use, remediation, and disposition of nuclear materials and radioactive (including mixed) wastes.
- Malevolent uses of nuclear and radiation-based technologies.
- Risks, benefits, and/or efficacies of nuclear and radiation-based applications, including medical applications.

The board also supports the participation of the United States in the Radiation Effects Research Foundation and sponsors the Gilbert W. Beebe Symposium on radiation health effects.

Learn more about NRSB here: http://dels.nas.edu/nrsb

ABOUT THE GILBERT W. BEEBE SYMPOSIUM

The Gilbert W. Beebe symposium was established by the Board on Radiation Effects Research (now the Nuclear and Radiation Studies Board) in 2002 to honor the scientific achievements of the late Dr. Gilbert Beebe (National Cancer Institute). Dr. Beebe was one of the designers and key implementers of the epidemiology studies of Japanese atomic bombing survivors and organized and led investigations into the Chernobyl accident. The symposium is used to promote discussions among scientists, federal staff, and other interested parties concerned with radiation health effects.

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