

**COOPERATIVE CENTERS FOR  
MEDICAL COUNTERMEASURES AGAINST RADIATION  
(CMCRs)**

**SCIENTIFIC PROGRAM DESCRIPTIONS**



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## **COOPERATIVE CENTERS FOR MEDICAL COUNTERMEASURES AGAINST RADIATION (CMCRs)**

### **PROGRAM OBJECTIVES**

Very few medical products exist to counter the variety of acute and long-term injuries that can result from nuclear or radiological attacks. In addition, there is currently no rapid means to detect the radiation dose that an individual may have received. The threat of nuclear or radiological attacks has grown in recent years, with increased activity of global terrorist organizations and a rise in illicit trafficking of radioactive materials. To expand the medical options available to prevent or treat radiation-induced injury, and thereby help minimize the terrorist threat, as well as develop effective countermeasures and biodosimetry triage tools, the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) established eight cooperative Centers for Medical Countermeasures against Radiation (CMCRs) in September 2005.

The CMCRs are intended to serve as multidisciplinary, extramural research centers comprised of academic, commercial, and government laboratories that are funded to: 1) move candidate countermeasures through the regulatory process into the national stockpile; 2) develop new techniques and devices to provide accurate dose assessment in a triage scenario; 3) conduct basic and translational research to identify new countermeasures; 4) develop and validate new animal models or *in vitro* assays to evaluate countermeasures or underlying biology; and 5) provide new or expanded education resources to improve expertise in radiobiology.

Each CMCR participates as a member of the CMCR network, which includes all CMCR awardees (principal investigators) as well as other NIAID-designated partners such as U.S. federal government laboratories and/or private companies. The CMCR network facilitates interactions among the awardees and assists in interactions with regulatory and public health organizations. The Centers network is governed by a CMCR Steering Committee, charged with coordinating and facilitating research activities for the overall program.

The CMCR program is designed for optimal research flexibility, synergy, and efficiency with the goal of rapidly developing effective countermeasures and/or biodosimetric tools for clinical use. The program is milestone based, and includes the flexibility to quickly redirect or replace research projects during the funding period. The Cooperative Agreement mechanism (U19) is used to support the work of multi-investigator teams with a scope of activities not possible with other funding mechanisms. Synergistic interaction with other Centers and the NIH will be a key feature. Each Center provides unique and complementary strengths in terms of technical potential and specific areas of investigation, and all Centers share responsibility for program development and resource coordination *via* the CMCR Steering Committee. When appropriate, and in accordance with NIH policies, project personnel are expected to collaborate; share novel reagents, assays, and animal models; and share both positive and negative results that would help guide the research and development activities of other CMCR network members.

Each CMCR consists of four components: (1) A minimum of three RO1-like research projects focused on mechanisms of radiation damage, biodosimetry to determine radiation dose received or countermeasure testing and/or development; (2) core facilities to support the research projects or to facilitate management of the CMCR; (3) short-term pilot projects; and (4) an education component focused on short-term training in the technical or theoretical aspects of radiation biology. The projects and cores (except the Administrative, Pilot Research Projects and Training and Education Cores) for each CMCR are summarized below.

**BRENNER, David**

**U19 AI067773-01**

**Center for High Throughput, Minimally Invasive, Radiation Biodosimetry**

Locations

**Columbia University Medical Center, New York, NY**

Arizona State University (ASU), Tempe, AZ

Charles University, Prague, Czech Republic

Harvard School of Public Health, Boston, MA

National Cancer Institute, Bethesda, MD

Sionex Corporation, Waltham, MA

TGen, Phoenix, AZ

University of Pittsburgh, Pittsburgh, PA

Key Personnel

Sally Amundson\*

Michael Bittner

William Bonner

David Brenner\*

Bruce Demple

Albert Fornace\*

Charles Geard

Frank Gonzalez

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Gary Johnson

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Gerhard Randers-Pehrson

Jeffrey Trent

Carl Yamashiro

Y. Lawrence Yao

Frederic Zenhausern\*

\*In attendance at this meeting

<b>Brenner, David</b> <b>Center for High Throughput, Minimally Invasive, Radiation Biodosimetry</b>		
Brenner, David (Columbia)	Automated robotically-based high-throughput radiation biodosimetry	<ul style="list-style-type: none"> <li>❖ Analysis of micronuclei, H2AX-loci from lymphocytes, reticulocytes &amp; exfoliated buccal or urinary bladder cells</li> <li>❖ Develop HTP robotics controlled automated image acquisition (30,000 samples per day)</li> <li>❖ Device development, fabrication optimization, calibration and testing of biological samples under cGLP, cGMP, FDA regulatory requirements</li> </ul>
Zenhausen, Frederic (ASU)	Biodosimetry with a fully integrated biochip using gene expression signatures	<ul style="list-style-type: none"> <li>❖ Develop module for blood sample collection from a finger prick</li> <li>❖ Fabricate and validate channel chips with integrated oligo array &amp; pump</li> <li>❖ Develop an integrated micro/nano fluidic cartridge for RNA extraction from whole blood</li> <li>❖ Incorporate radiation-related gene-expression signatures into microarrays</li> <li>❖ Integrate blood collection, RNA extraction &amp; hybridization microchannel modules</li> <li>❖ Validate with <i>ex vivo</i> irradiated cells &amp; human blood</li> <li>❖ Integrate &amp; evaluate reagent storage; develop integrated control electronics</li> <li>❖ Verify that the device meets product requirements</li> </ul>
Fornace, Albert (Harvard)	Non-invasive radiation biodosimetry through metabolomics	<ul style="list-style-type: none"> <li>❖ Develop a metabolomics-based portable biodosimeter</li> <li>❖ Analyze urine, blood, serum, sweat, and saliva to identify dose &amp; time-dependent mouse metabolomics signatures</li> <li>❖ Study radiation-induced metabolomics and expression signatures in mice with altered radiation injury responses</li> <li>❖ Identify and validate metabolomics signatures in humans undergoing TBI - compare with mouse data</li> <li>❖ Transfer technology from large scale UPLC-MS to miniature and bench top MS</li> <li>❖ Build and test a breadboard and handheld device</li> </ul>
Yamashiro, Carl (ASU)	CORE: Product development	<ul style="list-style-type: none"> <li>❖ Facilitate product development activities of the CMCR</li> <li>❖ Approach: concept/discovery, feasibility, development, transition and launch</li> <li>❖ Use experience of the Center for Applied Nano-Bioscience (ANBC) at ASU</li> <li>❖ Follow requirements for cGLP and cGMP</li> </ul>
Amundson, Sally (Columbia)	CORE: Functional genomics	<ul style="list-style-type: none"> <li>❖ Establish gene expression signatures diagnostic of human radiation exposure and dose</li> <li>❖ Compare gene expression method with micronuclei and urinary metabolomics</li> <li>❖ Provide experimental design &amp; training in genomics</li> <li>❖ Develop diagnostics gene expression signatures</li> <li>❖ Testing and validation to increase throughput</li> </ul>
Trent, Jeffrey (TGen)	CORE: Informatics, biostatistics and data management	<ul style="list-style-type: none"> <li>❖ Provide informatics and biostatistical support</li> <li>❖ Provide experimental design and data analysis</li> <li>❖ Provide secure data exchange among CMCR members</li> </ul>

**CHAO, Nelson**  
**U19 AI067798-01**  
**Center for Medical Countermeasures against Radiation**

Locations

**Duke University School of Medicine, Durham, NC**

Defence R & D Canada, Ottawa, Ontario, Canada

National Center for Toxicological Research/ US Food and Drug Administration, Jefferson, AK

Oak Ridge National Laboratory (ORNL), Oak Ridge, TN

Oklahoma State University, Stillwater, OK

University of Arkansas for Medical Sciences (UAMS), Little Rock, AK

University of North Carolina at Chapel Hill (UNC), Chapel Hill, NC

Wake Forest University Health Sciences, Winston-Salem, NC

Key Personnel

Ines Batinic-Haberle

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Willie Brickey

Carl Cerniglia

Nelson Chao\*

John Chute\*

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Michael Robbins

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Robert Storms

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Junru Wang

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Albert Zimmerman

\*In attendance at this meeting

<b>Chao, Nelson</b> <b>Centers for Medical Countermeasures against Radiation</b>		
Eckerman, Keith (ORNL)	Post exposure injury assessment tool	<ul style="list-style-type: none"> <li>❖ Develop a biodosimetry tool based on radiation dose to teeth by optical stimulation of luminescence (OSL)</li> <li>❖ Design a portable device to measure doses of 0.5 to 10 Gy</li> <li>❖ Develop Monte Carlo calculations to convert tooth dose to organ or tissue dose for photon and neutron radiation</li> <li>❖ Determine dose response based on age and gender using porcine molars</li> <li>❖ Modify OSL equipment for fiber optic measurements to teeth</li> </ul>
Nevins, Joe (Duke)	A molecular signature of radiation injury	<ul style="list-style-type: none"> <li>❖ Develop a biodosimetry tool based on the gene expression profiles of exposed individuals</li> <li>❖ Characterize radiation-induced changes in gene expression in mouse peripheral blood and bone marrow mononuclear cells</li> <li>❖ Study different doses, times, strain variability &amp; age variability after <i>E. coli</i> LPS injection and neutron exposure in mice</li> <li>❖ Compare mouse results with human data (human blood analyzed before and after radiation in bone marrow transplant patients)</li> <li>❖ Validate profiles for mouse and human with unknown samples</li> <li>❖ Develop a portable biomarker based instrument in collaboration with LLNL</li> </ul>
Hauer-Jensen, Martin (UAMS)	Somatostatin analogues as countermeasures against intestinal radiation toxicity	<ul style="list-style-type: none"> <li>❖ Assess efficacy of somatostatin analogs (octreotide &amp; SOM230) for treatment of GI injury: optimal dose, duration, and therapeutic window</li> <li>❖ Determine DRF for octreotide &amp; SOM230 in GI radiation injury, bacterial translocation, and lethality after irradiation</li> <li>❖ Assess optimal post-radiation time window after TBI for octreotide therapy</li> <li>❖ Determine if octreotide exerts GI effects by reducing pancreatic proteases, and if the effect is reversible</li> </ul>
Vujaskovic, Zeljko (Duke)	Radiation protection with SOD mimetics	<ul style="list-style-type: none"> <li>❖ Evaluate the efficacy of two already established Mn porphyrins to prevent and/or treat radiation-induced lung injury</li> <li>❖ Test optimum time of administration of the compound</li> <li>❖ Test the most effective compound in a NHP model</li> <li>❖ Develop 3 pegylated Mn porphyrin compounds and compare with lead compound</li> </ul>
Chao, Nelson (Duke)	Human growth hormone for radiation exposure	<ul style="list-style-type: none"> <li>❖ Characterize human growth hormone (HGH) ability to accelerate hematopoietic recovery in irradiated animals</li> <li>❖ Determine if HGH exerts its effects <i>via</i> hematopoietic stem cell self-renewal or progenitor cell activation</li> <li>❖ Characterize the activity of HGH in enhancing T and B cell function and thymopoiesis after radiation</li> <li>❖ Test HGH efficacy in a cynomolgus monkey model</li> </ul>

Reya, Tannishtha (Duke)	Hematopoietic repair following radiation injury	<ul style="list-style-type: none"> <li>❖ Evaluate the role of Wnt signaling in repair of HSC damage</li> <li>❖ Determine if Wnt pathway activation induces <i>in vitro</i> expansion of human HSCs for stem cell based repair</li> <li>❖ Define if activation of Wnt signaling in human HSCs leads to functional expansion in xenotransplant NOD/SCID model</li> <li>❖ Determine if <i>in vivo</i> activation of Wnt pathway enhances regeneration</li> <li>❖ Determine whether direct delivery of Wnt activators enhances regeneration</li> </ul>
Chute, John (Duke)	Endothelial cell factors mediate the repair of the irradiated hematopoietic compartment	<ul style="list-style-type: none"> <li>❖ Assess efficacy of endothelial cells (EC) and conditioned medium (CM) to treat radiation-induced hematopoietic damage</li> <li>❖ Characterize the mechanisms by which primary ECs or EC-CM accelerate <i>in vivo</i> hematopoietic recovery after irradiation</li> <li>❖ Identify the molecules that contribute to hematopoietic recovery by gene expression analysis and siRNA loss of function</li> <li>❖ Characterize and initiate pre-clinical development of factors produced by endothelial cells that mediate repair of the hematopoietic system after radiation injury</li> </ul>
Ting, Jenny (UNC)	Inflammation and radiation-induced lung injury	<ul style="list-style-type: none"> <li>❖ Assess roles of a TLR signaling molecule, MyD88, in radiation induced pneumonitis</li> <li>❖ Assess role of CIAS1 in radiation-induced pneumonitis &amp; study nucleotide-binding properties of CIAS1</li> <li>❖ Evaluate the role of CIITA in radiation-induced pneumonitis and delineate the nucleotide-binding properties of CIITA</li> </ul>
Sartor, Balfour (UNC)	Regulation of ionizing radiation induced gastrointestinal damage by innate immune response to commensal bacteria	<ul style="list-style-type: none"> <li>❖ Assess role of enteric microbes in radiation-induced GI injury; develop therapeutics to treat GI damage</li> <li>❖ Determine the role of commensal bacteria in the pathogenesis and treatment of radiation-induced enteropathy and develop optimal antibiotic and probiotic therapeutic regimens to treat radiation-induced GI injury</li> <li>❖ Determine mechanisms by which bacterial adjuvants induce and prevent radiation-induced GI injury, identify key endogenous inhibitors of inflammation, and develop agonists and inhibitors to treat GI injury</li> </ul>
Kepler, Thomas (Duke)	CORE: Computational medicine	<ul style="list-style-type: none"> <li>❖ Develop information sharing system for CMCR staff</li> <li>❖ Acquire and develop computational tools</li> <li>❖ Provide support for data analysis and experimental design</li> </ul>
Sempowski, Gregory (Duke)	CORE: Immune monitoring core	<ul style="list-style-type: none"> <li>❖ Provide flow cytometry support: high speed sorting and multi-color analysis of cellular subsets</li> <li>❖ Provide multiplex protein array profiling of biological samples using BioPlex Luminex bead array system</li> <li>❖ Provide quantitative real-time-PCR multiplex gene expression analysis</li> </ul>
Cline, Mark (Wake Forest)	CORE: Primate studies	<ul style="list-style-type: none"> <li>❖ Acquire and maintain NHPs; expose animals to radiation and administer therapeutic interventions</li> <li>❖ Provide clinical and pathological assessments of treatment outcomes including post-mortems, tissue collection, assessment of radiation responses &amp; mitigating interventions</li> <li>❖ Provide data management service for primate studies</li> </ul>

**D'ANDREA, ALAN**

**U19 AI067751-01**

**Dana-Farber/Harvard Center for Medical Countermeasures against Radiation**

Locations

**Dana-Farber Cancer Institute, Boston, MA**

Brigham and Women's Hospital, Boston, MA

Harvard University Medical School, Boston, MA

Key Personnel

Jon Clardy

Alan D'Andrea\*

Stephen Elledge

Kalindi Parmar\*

Cindy Matheson\*

Peter Mauch

Caroline Shamu

Piotr Sicinski

\*In attendance at this meeting

<b>D'Andrea, Alan</b> <b>Centers for Medical Countermeasures Against Radiation</b>		
D'Andrea, Alan (Dana-Farber)	Cell-based, small molecule screens for novel radioprotective agents	<ul style="list-style-type: none"> <li>❖ Identify novel radioprotective agents using cell-based small molecule drug screens</li> <li>❖ Evaluate the efficacy of WW-85 (ROS scavenger) for improved survival, decreased tissue damage, and improved bone marrow stem cell survival in mouse model and human bone marrow cells</li> </ul>
Elledge, Stephen (Brigham)	Genetic screens for radiation resistance	<ul style="list-style-type: none"> <li>❖ Identify genes that act as drug targets to promote survival, using genome-wide RNAi screens and cDNA library over-expression</li> <li>❖ Screen for genes responsible for radiation resistance, oxidative stress resistance, hematopoietic stem cell maintenance/proliferation/differentiation and apoptosis control</li> <li>❖ Screens for chemicals that disrupt radiation damage pathways</li> <li>❖ Investigate pathways involved in radio-resistance</li> </ul>
Sicinski, Piotr (Dana-Farber)	Cyclins and cyclin-dependent kinases as targets for protection against radiation-induced apoptosis	<ul style="list-style-type: none"> <li>❖ Determine the role of cyclins and cyclin dependent kinases in radiation-induced apoptosis in hematopoietic cells using mice lacking D and E-type cyclins, and D and E-cyclin dependent kinase (CDK) catalytic partners (CDK2, 4, 6),</li> <li>❖ Determine whether acute shutdown of particular cyclins after radiation exposure protects animals from radiation-induced apoptosis, using conditional knockout strains of D or E cyclins</li> <li>❖ Evaluate the efficacy of cyclin-CDK inhibitors in protecting against radiation-induced apoptosis</li> </ul>
Mauch, Peter (Dana-Farber)	CORE: Mouse biology and stem cell	<ul style="list-style-type: none"> <li>❖ Provide hematopoietic cell culture and murine assays</li> <li>❖ Evaluate normal and mutant mice for LD50, tissue pathology, and chromosomal aberrations</li> <li>❖ Evaluate candidate radioprotective agents in mice</li> </ul>
Clardy, Jon (Harvard)	CORE: Small molecule screening and medicinal chemistry	<ul style="list-style-type: none"> <li>❖ Provide resources, instruments, and expertise for HTP screening of small molecule libraries</li> <li>❖ Provide facility to screen protein and cell-based assay systems</li> <li>❖ Facilitate discovery of small molecule research tools to study radiobiology related biological processes</li> <li>❖ Provide medicinal chemistry expertise for acceleration of interesting "hit" compounds into therapeutic leads</li> </ul>

**GEORGES, GEORGE**  
**U19 AI067770-01**  
**Radiation Dose-Dependent Interventions**

Locations

**Fred Hutchinson Cancer Research Center, Seattle, WA**  
University of Washington, Seattle, WA

Key Personnel

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George Georges\*  
Scott Graves  
Shelly Heimfeld  
Christian Kuhr  
Marco Mielcarek\*  
Amanda Paulovich\*  
Mark Phillips  
Jerald Radich  
Jeffrey Schwartz  
Derek Stirewalt  
Rainer Storb  
Barry Storer  
Beverly Torok-Storb  
Barbara Varnum-Finney  
Scott Wilbur  
Murad Yunusov

\*In attendance at this meeting

**Georges, George**  
**Radiation Dose-Dependent Interventions**

<p>Paulovich, Amanda (Fred Hutchinson)</p>	<p>Protein biomarker dosimetry</p>	<ul style="list-style-type: none"> <li>❖ Develop protein-based, lateral flow diagnostics that can be deployed “in the field” to assess radiation exposure immediately (assays and reagents for quantifying radiation-induced protein changes)</li> <li>❖ Screen 200-300 protein radiation biomarker candidates using commercially available antibodies and identify 5 promising protein markers.</li> <li>❖ Develop monoclonal antibodies to each of the 5 promising protein markers and develop ELISA for quantifying these targets in high throughput from PBMCs, plasma or urine</li> <li>❖ Construct detailed dose-response curves for the 5 protein markers in dog PBMCs irradiated <i>ex vivo</i> and <i>in vivo</i></li> <li>❖ Correlate canine dosimetry to human dosimetry with human PBMCs exposed <i>ex vivo</i> and <i>in vivo</i></li> </ul>
<p>Stirewalt, Derek (Fred Hutchinson)</p>	<p>Quantitative RT/PCR- based radiation dosimetry</p>	<ul style="list-style-type: none"> <li>❖ Develop RNA based dosimetry assays using GenXpert</li> <li>❖ Characterize dose dependent gene expression changes after <i>in vitro</i> irradiation of human blood</li> <li>❖ Determine which genes display <i>in vivo</i> dose-dependent expression changes in plasma and blood cells in canine <i>in vivo</i> exposure model</li> <li>❖ Repeat studies with blood and plasma from transplant patients and correlate with canine dosimetry</li> </ul>
<p>Mielcarek, Marco (Fred Hutchinson)</p>	<p>Cell therapy for transient hematopoietic recovery</p>	<ul style="list-style-type: none"> <li>❖ Determine maximum radiation dose at which survival can be achieved with transplant of non-matched hematopoietic cells, with and w/out growth factors in a canine model</li> <li>❖ Conduct <i>ex vivo</i> expansion of canine myeloid progenitor cells from blood, bone marrow or cord blood</li> <li>❖ Increase production under GMP conditions; test stability and survival of cells by different methods of cryopreservation</li> <li>❖ Determine if infusion of <i>ex vivo</i> expanded myeloid progenitor allows autologous recovery</li> <li>❖ Determine if immunosuppressive treatments are needed</li> <li>❖ Develop a combined regimen of cytokines and expanded cell products to obtain optimum survival</li> </ul>
<p>Georges, George (Fred Hutchinson)</p>	<p>Transplantation of cord blood</p>	<ul style="list-style-type: none"> <li>❖ Develop canine model for UCB transplant</li> <li>❖ Facilitate engraftment of the partially DLA-matched, low cell dose UCNB (umbilical cord neonatal blood) graft by co-infusion with three distinct hematopoietic cell sources</li> <li>❖ Supplement UCNB graft with 1, 5, 10 units of cryopreserved DLA-mismatched UCNB to overcome resistance</li> <li>❖ Supplement graft with <i>ex vivo</i> expanded myeloid progenitors</li> <li>❖ Define conditions for <i>ex vivo</i> expansion of UCNB CD34+ cells using cytokines and Notch-1 ligand</li> <li>❖ Test efficacy of <i>ex vivo</i> expanded CD34+ cells with UCNB</li> <li>❖ Determine if UCNB infusion will rescue if delayed 4 days</li> </ul>

Kuhr, Christian (Fred Hutchinson)	Stem cell rescue for radiation accident victims	<ul style="list-style-type: none"> <li>❖ Optimize hematopoietic cell transplant (HCT) with HLA-mismatched or HLA-haploidentical donors in dogs</li> <li>❖ Study effects of dose, dose rate and timing on HCT</li> <li>❖ Study effects of agents that suppress host NK cell, T cell or both NK and T cell on HCT</li> <li>❖ Develop strategies to prevent GVHD</li> </ul>
Schwartz, Jeffrey (U Washington)	CORE: Radiation resource	<ul style="list-style-type: none"> <li>❖ Provide dosimetry, access to low and high LET sources</li> <li>❖ Coordinate irradiation protocols</li> <li>❖ Supervise irradiations with Cs-137 &amp; alpha source</li> </ul>
Torok-Storb, Beverly (Fred Hutchinson)	CORE: Canine resource	<ul style="list-style-type: none"> <li>❖ Provide canines and canine tissue to all research projects</li> <li>❖ Schedule irradiations, pre/post irradiation treatments, sample acquisition</li> <li>❖ Distribute and maintain database</li> <li>❖ Tissue type for class I and II MHC antigens, and harvest cord blood</li> </ul>
Heimfeld, Shelly (Fred Hutchinson)	CORE: Cell therapy resource	<ul style="list-style-type: none"> <li>❖ Provide optimal cryopreservation, storage, cell selection, and flow cytometry analysis</li> <li>❖ Store peripheral blood and sera from dogs and humans exposed to various doses of irradiation</li> <li>❖ Create a canine cord blood bank; enrich canine CD34+ cells to initiate <i>ex vivo</i> expanded myeloid progenitor cells</li> </ul>

**GREENBERGER, JOEL**

**U19-AI068021-01**

**Mitochondrial Targeting against Radiation Damage**

Locations

**University of Pittsburgh, Pittsburgh, PA**

Carnegie Mellon University, Pittsburgh, PA

Fluorous Technologies, Pittsburgh, PA

Key Personnel

Andrew Amoscato

Chao Cai

Richard Chaillet

Michael Epperly\*

Mitchell Fink

Joel Greenberger\*

Valerian Kagan\*

Paul Karol

John Lazo

Linda Pearce

James Peterson\*

Douglas Potter

James Schlesselman

Hong Wang

Peter Wipf

Jack Yalowich

Wei Zhang

\*In attendance at this meeting

<b>Greenberger, Joel</b> <b>Development of new ionizing radiation protectors and damage mitigators</b>		
Greenberger, Joel (U Pittsburgh)	Mn-SOD transgenes & SOD mimetic small molecules mediate protection & mitigation by stabilizing mitochondria	<ul style="list-style-type: none"> <li>❖ Optimize SOD therapy for radiation protection and mitigation; verify that MnSOD plasmid liposomes (PL) are protective</li> <li>❖ Measure ROS production, changes in thiols and antioxidant pools in tissues in MnSOD-treated and transgenic mice</li> <li>❖ Show SOD mimetics synergize with MnSOD-PL gene therapy</li> <li>❖ Develop a systemic oral or skin patch</li> <li>❖ Show nitroxide, catalase, glutathione peroxidase help protect</li> </ul>
Kagan, Valerian (U Pittsburgh)	Prevention of cardiolipin oxidation in irradiation apoptosis	<ul style="list-style-type: none"> <li>❖ Determine mechanism of damage to electron transport chain (ETC); ROS production, activation of cardiolipin (CL)/cytochrome c, oxidized CL, release of pro-apoptotic factors</li> <li>❖ Show electron acceptors, peroxidase quenchers, lipid &amp; enzyme antioxidants, scavengers &amp; diet manipulations prevent apoptosis</li> <li>❖ Conduct <i>in vitro</i> &amp; <i>in vivo</i> mouse studies: assess lung, GI, oral mucosa, bone marrow for reduced CL oxidation &amp; apoptosis</li> </ul>
Peterson, James (U Pittsburgh)	Development of sm. molecule targets for radiation protection by elaborating mechanism of radiation damage to mitochondrial ETC	<ul style="list-style-type: none"> <li>❖ Identify mitochondrial sites of initial superoxide production</li> <li>❖ Identify mitochondrial sites damaged by ROS/RNS (chronic superoxide generation); devise strategies to deactivate sites</li> <li>❖ Assess peroxynitrite and hydrogen species in post-irradiation damage of the ETC</li> <li>❖ Develop agents to prevent ROS/RNS formation in mitochondria</li> <li>❖ Study efficacy and toxicity of compounds within the ETC</li> </ul>
Chaillet, Richard (U Pittsburgh)	CORE: Transgenic animal	<ul style="list-style-type: none"> <li>❖ Generate transgenic and KO mice to understand effects of different agents in radiation protection</li> <li>❖ Help design experiments and animal care protocols</li> <li>❖ Generate mice, provide tissues, derive lines for <i>in vitro</i> testing</li> <li>❖ Evaluate study results, propose experimental direction</li> <li>❖ Maintain NHPs</li> </ul>
Lazo, John (U Pittsburgh)	CORE: Innovative medicinal chemistry: discovery and screening	<ul style="list-style-type: none"> <li>❖ Prepare peptide mimetics-time-release ROS scavenger derivatives</li> <li>❖ Synthesize cell permeable peptide antioxidants targeted to the inner mitochondrial membrane</li> <li>❖ Analyze agents in cells; formulate for <i>in vivo</i> IV and oral use</li> <li>❖ Evaluate extraction methods to prepare samples for analysis</li> </ul>
Zhang, Wei (Fluorous)	CORE: Chemical process development	<ul style="list-style-type: none"> <li>❖ Produce early, mg scale chem libraries; scale-up to g quantities</li> <li>❖ Provide guidance &amp; design</li> <li>❖ Oversee outsourcing of any synthesis</li> <li>❖ Design linking strategy to prepare dual-action NOS inhibitor/antioxidants with targeting peptides</li> <li>❖ Design EP, UHDBT &amp; MOAS analogs</li> </ul>
Schlesselman, James (U Pittsburgh)	CORE: Biostatistics	<ul style="list-style-type: none"> <li>❖ Contribute statistical expertise on project development</li> <li>❖ Perform data analyses for <i>in vitro</i> and <i>in vivo</i> studies</li> <li>❖ Perform data collection and database development</li> <li>❖ Assist with progress reports, publications &amp; presentations</li> </ul>
Epperly, Michael (U Pittsburgh)	CORE: Radiobiological standardization	<ul style="list-style-type: none"> <li>❖ Standardize <i>in vitro</i> cultures, DNA damage quantitation and comparative analysis of products</li> <li>❖ Provide <i>in vitro</i> &amp; animal responses to drugs</li> <li>❖ Standardize <i>in vitro</i> and <i>in vivo</i> radiobiology testing</li> </ul>

**MCBRIDE, WILLIAM**  
**U19 AI067769-01**  
**UCLA Center for Biological Radioprotectors**

Location

**University of California David Geffen School of Medicine, Los Angeles, CA**

Key Personnel

Kenneth Bradley  
Liutao Du  
Richard Gatti  
Keisuke Iwamoto  
Owen Kelly  
Joseph Loo  
William McBride\*  
Colin McLean  
Rachel Ogorzalek-Loo  
Frank Pajonk  
P. Nagesh Rao  
Dorthe Schae  
Robert Schiestl\*  
Michael Teitell  
Jullian Whitelegge  
H. Rodney Withers

\*In attendance at this meeting

**McBride, William**  
**UCLA Center for Biological Radioprotectors**

Schiestl, Robert	Radioprotection of acute and persistent DNA deletions	<ul style="list-style-type: none"> <li>❖ Identify small molecules from compound libraries that counteract cytotoxicity and frequency of DNA deletions in yeast when added before or after radiation exposure</li> <li>❖ Develop a bioluminescent, high-throughput version of the yeast assay</li> <li>❖ Test agents for reduction of radiation hyper-recombination</li> <li>❖ Determine the efficacy of selected agents in reducing the frequency of radiation-induced DNA deletions <i>in vivo</i> in mice</li> <li>❖ Determine whether any of the three selected potent radioprotectors protect against radiation-induced cancer in mice</li> </ul>
McBride, William	Radioprotection of the immune system	<ul style="list-style-type: none"> <li>❖ Screen compounds using HTP cell viability assay to identify agents that will increase the survival of murine T lymphocytes when added before or after irradiation</li> <li>❖ Determine which agents inhibit radiation-induced lymphocyte cytotoxicity &amp; activate protective signaling pathways in dendritic cells</li> <li>❖ Investigate the ability of select compounds to modulate radiation-induced changes in protein expression</li> <li>❖ Examine the ability of select agents to reverse radiation-induced immune suppression and defects in non-immune tissues in mice</li> </ul>
Gatti, Richard	Human models of radioprotection	<ul style="list-style-type: none"> <li>❖ Assess <i>in vitro</i> effects of selected agents on normal human cells &amp; cells from patients with known or undiagnosed DNA repair disorders</li> <li>❖ Evaluate the mechanisms of action of select agents in normal and radiosensitive human cells</li> <li>❖ A panel of &gt;40 radiosensitive cell lines will be used</li> </ul>
Withers, Rodney	CORE: Mouse	<ul style="list-style-type: none"> <li>❖ Breed and maintain mice (transgenics, knockouts, other immune competent and deficient strains)</li> <li>❖ Provide cesium source &amp; level II Biohazard facility</li> <li>❖ Assist in obtaining study approval; monitor animal health; design and perform animal irradiations; help analyze and interpret results</li> </ul>
Loo, Joseph	CORE: Proteomics	<ul style="list-style-type: none"> <li>❖ Provide mass spectrometry and expertise in protein characterization and post-translational modifications</li> <li>❖ Assist in profiling changes in protein expression</li> </ul>
Rao, Nagesh	CORE: Genomic instability	<ul style="list-style-type: none"> <li>❖ Provide cytogenetics support: karyotyping, chromosome/ chromatid breakage studies, micronuclei analysis &amp; FISH</li> <li>❖ Determine effects of radio-modulator compounds on chromosome aberrations in mouse embryonic cells &amp; normal and radiosensitive human cells</li> </ul>

**MOULDER, JOHN**

**U19 AI067734-01**

**Post-Irradiation Intervention to Mitigate and Treat Non-Hematological Injuries**

Locations

**Medical College of Wisconsin (MCW), Milwaukee, WI**

Proteome Systems, Inc., Woburn, MA

Henry Ford Health System, Detroit, MI

University Health Network, Ontario Cancer Institute, Princess Margaret Hospital, University of Toronto,  
Toronto, Ontario, Canada

Key Personnel

Ossama Abu-Hatoum

Stephen Brown\*

Eric Cohen

Susan Doctrow\*

David Gutterman

Carol Gloff

William Hendee

Richard Hill\*

Elizabeth Jacobs

Kenneth Jenrow

Jae Ho Kim

X. Allen Li

Timothy Lowry

Mie Lu

Meetha Medhora

Robert Molthen

John Moulder\*

Mary Otterson

Mukut Sharma

Janet Smart

Robert Truitt

Wen-Chen Yeh

\*In attendance at this meeting

<b>Moulder, John</b> <b>Post-Irradiation Intervention to Mitigate and Treat Non-Hematological Injuries</b>		
Ottersson, Mary (MCW)	Post-irradiation modulation of GI injury	<ul style="list-style-type: none"> <li>❖ Study high &amp; low dose-rate radiation effects on early &amp; long-term GI motility, enteric, neural &amp; microvascular changes in rat &amp; dog</li> <li>❖ Evaluate angiotensin converting enzyme (ACE) inhibitors, N-methyl-D-aspartate (NMDA) receptor inhibitors &amp; SOD/catalase mimetics as mitigating agents for GI injury</li> </ul>
Moulder, John (MCW)	Post-irradiation intervention to mitigate and treat chronic renal injuries	<ul style="list-style-type: none"> <li>❖ Evaluate ACE inhibitors and angiotensin II receptor antagonists (AII blockers) for mitigation and treatment of renal radiation injury &amp; determine mechanisms of action</li> <li>❖ Test efficacy of SOD/catalase mimetics &amp; nitroxide antioxidants for mitigation and treatment of renal radiation injury &amp; determine mechanisms of action</li> <li>❖ Evaluate the best of the above agents for mitigation of renal radiation injury in a dog model</li> <li>❖ Determine if the <i>in vitro</i> glomerular leakage assay can be used as an HTP screen to identify new mitigators of renal injury</li> </ul>
Medhora, Meetha (MCW)	Modulation of post-irradiation changes in pulmonary vasculature	<ul style="list-style-type: none"> <li>❖ Develop a lung injury model with non-invasive endpoints for single-dose irradiation of the whole thorax in rat</li> <li>❖ Test efficacy of ACE inhibitors and AII blockers for mitigating and treating radiation-induced lung injury</li> <li>❖ Define the mechanisms of action of these agents</li> </ul>
Hill, Richard (Toronto)	Mitigating and treating effects of radiation on lung	<ul style="list-style-type: none"> <li>❖ Test mitigating and therapeutic efficacy of SOD/catalase mimetics and genistein (in rats and in normal and knock-out mice), alone and in combination with ACE inhibitors and AII blockers</li> </ul>
Kim, Jae Ho (Henry Ford)	Mitigating and treating radiation-induced CNS injury with ACE inhibitors and statins	<ul style="list-style-type: none"> <li>❖ Assess efficacy of ACE inhibitors, AII blockers, statins &amp; SOD/catalase mimetics to mitigate &amp; treat radiation-induced CNS injury</li> <li>❖ Determine the influence of antioxidant therapies on neurogenesis following whole brain irradiation in adult rats</li> <li>❖ Endpoints in rat model: cognitive, visual tests; MRI imaging blood-brain barrier; histopathology of vascular, neuronal, glial cells</li> </ul>
Li, X. Allen (MCW)	CORE: Irradiator	<ul style="list-style-type: none"> <li>❖ Provide irradiation and dosimetry services for the projects</li> <li>❖ Develop QA procedures to ensure GLP-like standards</li> <li>❖ Perform daily, monthly &amp; annual QA measurements for irradiators that are used for the projects</li> <li>❖ Perform 3D dose calculations based on CT or MRI images using Monte Carlo technique if necessary</li> </ul>
Doctrow, Susan (Proteome Systems, Inc.)	CORE: Development and analysis of SOD/Catalase mimetics	<ul style="list-style-type: none"> <li>❖ Develop and refine methods for analyzing biological samples for SOD/catalase mimetics</li> <li>❖ Select and synthesize other SOD/catalase mimetics and assess their suitability for testing <i>in vivo</i> as mitigation or treatment agents in the GI, renal, lung and CNS projects</li> <li>❖ Analyze tissues and samples for compound levels to characterize biodistribution and pharmacokinetics</li> <li>❖ Provide R &amp; D expertise on SOD/catalase mimetics, including cGMP and cGLP activities</li> </ul>

**OKUNIEFF, PAUL**

**U19 AI067733-01**

**Center for Biophysical Assessment and Risk Management Following Irradiation**

Locations

**University of Rochester Medical Center, Rochester, NY**

Dartmouth Medical School, Hanover, NH

Defense Research and Development Canada, Ottawa Ontario, Canada

Health Canada, Radiation Protection Bureau, Ottawa, Ontario, Canada

Litron Laboratories, Rochester, NY

McMaster University, Hamilton, Ontario, Canada

National Center for Toxicological Research/US Food and Drug Administration, Jefferson, AK

Resonance Research, Billerica, MA

Trinity College, University of Dublin, Dublin, Ireland

Uniformed Services University for Health Sciences, Bethesda, MD

University Health Network, Ontario Cancer Institute, Princess Margaret Hospital, University of Toronto,  
Toronto, Ontario, Canada

Key Personnel

Douglas Boreham

Paul Okunieff\*

Robert Bristow

Louis Pena

Yuchyau Chen

Derick Peterson

John Coey

Alexander Romanyukah

Eugene Demidenko

Piotr Starewicz

Stephen Dertinger

Artur Sucheta

Bruce Fenton

Harold Swartz\*

Jacob Finkelstein\*

Sarah Thurston

David Gladstone

Nancy Wang

Robert Heflich

Ruth Wilkins

Richard Hill

Diana Wilkinson

Ollivier Hyrien

Jacqueline Williams\*

Peter Keng

David Wu

Piotr Lesniewski

Zhenyu Xiao

James MacGregor

Andrei Yakovlev

James McNamee

Shanmin Yang

Chad Mitchell

Lurong Zhang

Tim Mosmann

Gunther Oberdorster

\*In attendance at this meeting

<b>Okunieff, Paul</b> <b>Center for Biophysical Assessment and Risk Management Following Radiation</b>		
Okunieff, Paul (Rochester)	Inflammatory molecules in radiation risk assessment: preclinical drug testing for mitigation	<ul style="list-style-type: none"> <li>❖ Show that alteration of inflammatory molecules (IM) mitigates radiation damage</li> <li>❖ Characterize/quantify IM by protein array after TBI in mice</li> <li>❖ Test anti-oxidants, anti-apoptotics, anti-inflammatories &amp; growth factors to mitigate early and late IM toxicity</li> <li>❖ Investigate combined agents (e.g. vitamin C, curcumin, IL-1Ra, EsA, triptolide, FGF) to mitigate inflammation and fibrosis:</li> </ul>
Finkelstein, Jacob (Rochester)	Pulmonary response to external and internal exposure: model for dispersion event	<ul style="list-style-type: none"> <li>❖ Study role of immune and inflammatory systems in development of late lung effects after low dose radiation and internal exposure</li> <li>❖ Study modulation of the cytokine cascade</li> <li>❖ Assess late fibrotic lung changes after low dose irradiation</li> <li>❖ Study effects of inhalation of radio-labeled cesium on cytokines and lung toxicity; compared to external beam irradiation</li> <li>❖ Deliver cesium in aerosol and soluble form; create a model for inhaled insoluble alpha-emitting nuclides (e.g. americium)</li> <li>❖ Assess efficacy of anti-cytokines, chemokines, &amp; prostaglandins</li> <li>❖ Create an inhaled particulate model for children using mice pups</li> <li>❖ Test drugs such as statins, celebrex &amp; curcumin</li> </ul>
Swartz, Harold (Dartmouth)	<i>In vivo</i> EPR for after-the-fact measurement of dose	<ul style="list-style-type: none"> <li>❖ Establish an EPR facility to measure within 5 minutes the radiation dose received by individuals (threshold = 50-100 cGy)</li> <li>❖ Develop a transportable dosimeter</li> <li>❖ Increase accuracy, lo-wer threshold, decrease measurement time</li> <li>❖ Develop a portable, hand-held dosimeter for use in the field</li> <li>❖ Develop methods to measure dose from nails, hair &amp; tooth chips</li> </ul>
Chen, Yuchyan (Rochester)	Validation of quantitative, high throughput <i>in vivo</i> and <i>ex vivo</i> assays of bone marrow genotoxicity after radiation exposure	<ul style="list-style-type: none"> <li>❖ Develop HTP assay to measure hematopoietic cytogenetic damage</li> <li>❖ Validate micronucleated reticulocyte (MN-RET) measurements by flow cytometry in mouse, rat and human</li> <li>❖ Perform measurements after inhalation high LET and low LET exposures and treatments; perform inter-laboratory comparisons</li> <li>❖ Optimize 3D marrow cultures to characterize radio-sensitivity of multi-lineage system in mice, rat and human bone marrow</li> </ul>
Hill, Richard (Toronto)	Assessing skin exposure by measuring DNA damage in skin cells	<ul style="list-style-type: none"> <li>❖ Establish methods to assess immediate or late radiation dose</li> <li>❖ Establish methods to measure micronuclei (MN) from skin biopsies of different mice strains, ages, gender &amp; analysis time</li> <li>❖ Measure radiation induced foci (RIF) of nuclear proteins using immunohistochemistry of skin biopsies</li> <li>❖ Compare RIF data with MN measurements</li> <li>❖ Repeat the same studies with high LET thermal neutrons</li> <li>❖ Compare with tooth biodosimetry and MN in reticulocytes</li> </ul>
Thurston, Sally (Rochester)	CORE: Biostatistics	<ul style="list-style-type: none"> <li>❖ Provide personnel and knowledge to analyze data</li> <li>❖ Provide input on statistical issues, from study design to data collection, and inferential statements made from that data</li> <li>❖ Offer data management &amp; analysis, develop new methodologies</li> <li>❖ Develop and test new software to identify cytokines with good predictive abilities from high dimensional array data</li> </ul>