RITN
RADIATION INJURY TREATMENT NETWORK

Medical and Organizational Challenges Resulting from a Radiological/Nuclear Emergency

The RITN is a cooperative effort of the National Marrow Donor Program® (NMDP)/Be The Match and the American Society for Blood and Marrow Transplantation (ASBMT).

Jointly Provided by:

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Radiation Countermeasures Center of Research Excellence
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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
REMM
RADIATION EMERGENCY MEDICAL MANAGEMENT
Guidance on Diagnosis & Treatment for Health Care Providers

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NP20443; JUL 2015

Program Overview

Title: Medical and Organizational Challenges Resulting from a Radiological/Nuclear Emergency

Program Description:

The workshop will include highlight the most recent research of medical countermeasures and developments in the field of radiological/nuclear emergencies, including the Federal Concept of Operations, patient movement, the Public Health Emergency Medical Countermeasure Enterprise (PHEMCE), operational best practices, and biodosimetry.

Target Audience:

Physicians, and other clinicians, support staff, emergency managers, research scientists, and appropriate federal agency staff involved in radiation response and treatment of patients with bone marrow toxicity.

Learning Objectives:

At the completion of this workshop, attendees will be able to:

1. Discuss progress in research on radiological countermeasures and biodosimetry.
2. Explain best practices from RITN hospitals.
3. Evaluate medical and societal effects from a pertinent recent event.
4. Describe federal objectives for radiological/nuclear disaster response.
5. Identify key lessons from a real-world ARS treatment case study.

National Marrow Donor Program (NMDP):

The NMDP facilitates unrelated marrow, PBSC and cord blood transplants. The NMDP also provides research, medical education and patient advocacy to extend and improve lives through innovations in transplantation.

Non-Endorsement of Products:

The opinions expressed in this program are those of the participating faculty. Approval of this program does not imply endorsement by the program provider, the approver (MCW) or ANCC/ACCME of any commercial products discussed.

Verification of Participation and Continuing Education:

To receive continuing education credit for this meeting, attendees must attend the meeting sessions and complete the **Activity Evaluation and Verification of Participation** online by August 7th. Credits will not be granted retroactively. Certificates will be sent to participants following completion of the evaluation.

Continuing education credit is available for:

- **Physicians**:

  This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Medical College of Wisconsin and the NMDP. The Medical College of Wisconsin (MCW) is accredited by the ACCME to provide continuing medical education for physicians.

  AMA Credit Designation Statement:
  The Medical College of Wisconsin designates this Live Activity for a maximum of 9.5 *AMA PRA Category 1 Credit(s) ™.* Physicians should claim only the credit commensurate with the extent of their participation in the activity.

- **Nurses:**

  The National Marrow Donor Program is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation (COA).

  Up to 9.5 contact hours may be claimed for this educational activity.

- All other health care professionals requesting continuing education credit for this activity will be issued a certificate of attendance.

Speaker/Planner Disclosures

It is the policy of the providers of this program to ensure balance, independence, objectivity, scientific rigor and content that is free of commercial bias and outside the control of persons or organizations with an economic interest in influencing the content in all of its sponsored educational activities. Therefore, all planning committee members and speakers are required to disclose their relevant financial relationships and any or apparent conflicts of interest to the content of their presentations have been identified and resolved. The audience shall be informed of all relevant financial relationships, including the source of any commercial support for this forum.

Speakers/Planners:

These speakers/planners disclosed the following pertinent financial relationships:

William F. Blakely, PhD	Research Collaboration: Meso Scale Diagnostics
Michael Epperly, PhD	Patent issued for JP4-039 as a radiation mitigator
Joel S. Greenberger, MD	Patent issued for JP4-039 as a radiation mitigator
Zoya Gluzman-Potorak, PhD, MBA	Employment: Neumedicines
Lewis Rubinson, MD, PhD	Research Funding: FDA/BARDA
	Consultant/Advisory Board: GlaxoSmithKline
	Consultant/Advisory Board: Phillips
Daniel Weisdorf, MD	Consultant/Advisory Board: Amgen

Upon review of these disclosures, it was determined that these financial relationships either do not relate to the educational assignment or have been resolved by program planning staff prior to the activity.

Conference Planning Committee

David Weinstock, M.D.
RITN Medical Advisor
Dana-Farber Cancer Institute

Cullen Case Jr. CEM, CHEP
RITN Program Manager
National Marrow Donor Program

Nelson Chao, M.D.
RITN Executive Committee
Duke University

Dennis L. Confer, M.D.
RITN Executive Committee
National Marrow Donor Program

Daniel Weisdorf, M.D.
RITN Executive Committee
University of Minnesota—Fairview

John Chute, M.D.
RITN Executive Committee
UCLA

Robert Krawisz, M.B.A.
RITN Executive Committee
ASBMT

Julie Wilhauk, D.N.P.
RITN Executive Committee
ASBMT

Mary Horowitz, M.D.
University of Wisconsin

Martha Lassiter, RN, MSN, AOCNS, BMTCN
Duke University

Lyndsey S. Aspaas, BS, CHTC
National Marrow Donor Program

Agenda

Day One – July 14, 2015		
10:30-12:30	**Registration Opens/Box Lunch Available (at noon)**	
12:30	**Welcome: Dennis Confer, MD**	
12:30-1:00	A Decade of RITN	Bob Hartzman, MD
Session Chair: Cullen Case		
1:00-1:25	Review of Dangerous Radioisotopes: What is Available in Practice, What Should We be Concerned About?	Carl Curling, Sc.D
1:25-1:50	FEMA's Planning and Coordination Activities for Public Health and Medical Response after an IND	Dwayne Myal, MPH
1:50-2:15	New Federal ConOps for Lab Surge and Triage	John Koerner, MPH
2:15-2:40	PHEMCE & How it Will Support Medical Response	Norm Coleman, MD
2:40-2:55	**Q & A**	
2:55-3:15	**Break**	
Session Chair: David Weinstock, MD		
3:15-3:40	Progress and Achievements in Radiation Nuclear MCM Development by the NIAID Radiation Nuclear Countermeasures Program	Bert Maidment, PhD
3:40-4:05	Emergency Biodosimetry	William F. Blakely, PhD
4:05-4:30	Capability of the Bundeswehr Rad Medical TF	Andreas Lamkowski, MD
4:30-4:45	**Q & A**	
4:45-4:55	**Closing Comments**	
5:00-6:30	**Reception** - Cash Bar and Hors d'oeuvres	

Day Two – July 15, 2015		
8:30-12:00	**Track 1: Research Updates**	**Track 2: Preparedness Operations**
Session Chair: John Chute, MD		**Session Chair: Cullen Case, BS**
8:30-8:42 - Niche-Derived Mitigators for Acute Radiation Injury (Chute, MD)		**8:30-8:50 -** The Dana-Farber/Brigham and Woman's Cancer Center Full Scale Exercise: Planning, Implementation, and Lessons Learned (McCullen, MS & Tierney, MPH)
8:42-8:54 - Importance of CaMKK2 as a Regulator of HSC Regeneration in Vivo (Racioppi, MD)		
8:54-9:06 - Fibrinogen-Coated Nanospheres Improve Hemostasis and Prevent Fatal Hemorrhage from Radiation-Induced Thrombocytopenia (Chen, MD)		**8:50-9:10 -** Conducting a Radiological Full Scale Exercise – Mayo (Teske, MS)
9:06-9:18 - Radioprotective Efficacy of Tocols is Mediated Through Induction of Granulocyte Colony-Stimulating Factor (Romaine, BA)		
9:18-9:30 - The THBD-aPC Pathway in Radiation Mitigation (Geiger, PhD)		**9:10-9:30 -** RITN Incidents and the Use of eEmergency (Schlosser, NREMT-P)
9:30-9:42 - Abrogation of TGFB Signaling Does Not Rescue the Radiosensitive Phenotype or Hematopoiesis Smad3-/-Fancd2-/- Double Knockout Mice (Zhang, MD)		**9:30-9:50 -** Geographical Relation of RITN Centers to Medical Toxicology and Disaster Management Resources (Davlantes, MD & Kazzi, MD)
9:42-9:54 - Tissue-Specific Endothelial Cell Transplantation for Mitigation of Radiation-Induced Fibrosis and Injury (Rafii, MD)		
9:54-10:14 – Break		**9:50-10:10 – Break**

Day Two – July 15, 2015 (cont.)	
Session Chair: Nelson Chao, MD	**Session Chair: David Weinstock, MD**
10:14-10:26 - Advanced Development of HemaMax for Mitigation of HSARS Under the FDA Animal Rule (Gluzman-Poltorak, PhD)	**10:10-10:25 -** National Alliance for Radiation Readiness: Leveraging Partnerships to Increase Preparedness (Allen, PhD)
10:26-10:38 - PHD Inhibition Mitigates and Protects Against Radiation-Induced Gastrointestinal Toxicity Via HIF2 (Giaccia, PhD)	**10:25-10:40 -** A Strategic Approach to National Radiation Emergency Medical Education & Training (MAJ Vanhorne-Sealy, MS)
10:38-10:50 - Animal Models, and the Role of Acute Injury Associated with Late Effects (Cohen, MD)	**10:40-11:00 –** Lessons Learned from the Aurora Theater Mass Casualty on Engaging Staff for Preparedness Efforts (Conroy, MA)
10:50-11:02 - Role of Prostaglandin E2 in Mitigation in Radiation-Induced Hematopoietic Injury (Calvi, MD)	
11:02-11:14 - Administration of Two Radiation Mitigators: GS Nitroxide JP4-039 and Water Soluable Oxetanyl Sulfoxide MMS-350 Improves Total Body Irradiation Survival Superior to One Alone (Greenberger, MD)	**11:00-11:20 -** Increasing RITN Awareness in PH Circles (Rose, PhD)
11:14-11:26 - An Attempt to Potentiate the Radioprotective Efficacy of Countermeasures by Utilizing a Combination of Modalities: Gamma-Tocotrienol and Amifostine (Newman, BA)	
11:26-11:38 - Mitochondrial Targeted Glutathione Peroxidase 4 Mimic Mito-ebselen Mitigates Irradiation Damage (Stoyanovsky, PhD)	**11:20-11:40 -** Promoting Involvement in RITN: How to Generate Interest and Get the Right Players to the Table (Satterlee, BA & Davis, BA)
11:38-11:50 - Circulating IL-18BP and IL-18 as Dual Biomarkers for Radiation Dose and Injury Assessment in Mice After Total Body Radiation Exposure (Xiao, MD)	
11:50-12:00 – Final Q & A	**11:40-12:00** – Discussion of How to Best Engage RITN Staff to Be Prepared Despite a Lack of an IND (Weinstock, MD)
12:00-1:00 – Lunch (Buffet in Hallway)	
Rejoin as One Group	
Session Chair: Dennis Confer, MD	

1:00-1:30	Patients with Hematopoietic Syndrome of ARS: FDA's Perspective on the Dose Selection for Filgrastim	Lian Ma, PhD
1:30-2:00	Our Experience in Tokai-mura Nuclear Accident	Shin Mineshi, MD
2:00-2:30	Improvements in Radiation Medical Countermeasures for ARS Through BARDA's Funding	Richard Hatchett, MD
2:30-2:40 – Break		
2:40-3:10	Japan's 3.11 Earthquake, Tsunami, and Nuclear Crisis: Life at the Intersection of Danger and Opportunity	Ken Nollet, MD
3:10-3:40	Crisis Standards of Care: Lessons from the Recent Ebola Outbreak in Africa	Lewis Rubinson, MD
3:40-4:00	**Recap and Close**	Dennis Confer, MD

Poster Session: Poster will be located in the Plaza Ballroom

Poster # 1501: Microneedle Arrays Topically Deliver Radiomitigators at Different Time Points

Review of Dangerous Radioisotopes: What is Available in Practice, What Should We be Concerned About? Carl Curling, Sc.D

A discussion the applicability of using current casualty estimation methodologies to develop planning parameters for tactical and terroristic threats of the use of radiation exposure devices (RED), radiation dispersal devices (RDD), and improvised nuclear devices (IND), as well as conventional nuclear weapons.

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This presentation identifies and illustrates the applicability of using current casualty estimation methodologies to develop planning parameters for tactical and terroristic threats of the use of radiation exposure devices (RED), radiation dispersal devices (RDD), and improvised nuclear devices (IND), as well as conventional nuclear weapons.

The first part of the analysis was a study to identify the radioisotopes of interest from within the full spectrum of radiological threats. Thirty one radioisotopes were evaluated for their credibility as radiological weapons under seven different routes of exposure (or types of radiological weapons), including external irradiation from a point source or contaminated ground; aerosol exposure by inhalation, ingestion, contamination, and submersion in contaminated air; and immersion in a radioactive gas. Radioisotopes modeled in HPAC included Strontium-90, Cesium-137, Plutonium-238, and Americium-241. Additionally, a 10KT generic fission device with a height of burst (HoB) = 1m ("Surface Burst") was selected as representative of an IND, and the same weapon with a HoB = 129m ("Low Air Burst") was selected as a conventional nuclear weapon.

The second part of the study estimated casualties from radiological and nuclear weapons under scenarios selected to illustrate a potential range of casualties which might be of interest. The "Military" tactical scenario involves a light infantry battalion task force in defense of an airfield. The "Domestic" scenario used civilian population data. The location was selected to include a popular and high visibility public event which might be considered at risk from a terrorist attack with nuclear or radiological weapons.

Examples of the casualty estimates for radiological and nuclear events are provided, considering conditions of no response, medical treatment, and different routes of exposure for RDDs.

FEMA's Planning and Coordination Activities for Public Health and Medical Response after an IND.
Dwayne Myal, MPH

This session will describe FEMA's Public Health and Medical coordination activities with interagency partners and various community stakeholders to improve our readiness to respond to an IND.

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The Federal Emergency Management Agency (FEMA) Response Directorate, CBRNE Office, is actively engaged in Interagency coordination to facilitate the planning and response to catastrophic scenarios, such as the detonation of an Improvised Nuclear Device (IND). For this work, FEMA has five working groups (WG), including a Public Health and Medical (PHM) WG which enlist the support of interagency and stakeholder communities to identify and resolve gaps in IND preparedness planning. The PHM WG is co-chaired with the US Department of Health and Human Services (HHS) Assistant Secretary for Preparedness and Response (ASPR) and is composed of federal representatives, state/local stakeholders, and subject matter experts who facilitate communication and collaborate on issues relevant to IND public health and medical preparedness and response planning. Expertise in the group includes physicians, nurses, emergency response personnel, policy developers, and response planners at all levels, as well as support from a variety of professional organizations. The WG has recognized a number of gaps such as the need for better medical countermeasures, surge capacity for diagnostics, education and training needs, and strategies for handling this type of mass casualty event. Ongoing activities by different stakeholder partners that address gaps are related back to the group to facilitate information exchange between communities. Achievements by the WG itself to date include Fast Fact sheets for Emergency Medical Technicians (EMTs) and ER doctors and nurses. One activity the WG is currently engaged in is the development of Concept of Operations for Early Screening and Triage after an IND. Schematics for PHM response after an IND have been developed with interagency support to facilitate and conceptualize the time dependent needs and patient flow after the incident. The WG members are currently working on the development of concepts of operations (CONOPS) for the different public health and medical functions required early after the incident which will facilitate the decisions made at each node in the system and the directed flow of patients and populations through these nodes. In conclusion, FEMA, through the PHM WG and other activities, facilitates communication and coordination among all levels of government as well as with private and other stakeholders. These activities strengthen our country's response capabilities and our resilience.

New Federal ConOps for Lab Surge and Triage. John Koerner, MPH

This session introduces a National concept of operations for nuclear detonation being developed to incorporate mass triage and a novel Integrated Clinical Diagnostics System (ISDC) to assess radiation injury. The goal is to provide evidence-basis to maximize lives saved in the resource constrained environment anticipated following a nuclear detonation.

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In the event of a nuclear detonation in a US city, hundreds of thousands of people will require assessment, diagnosis, and medical treatment for trauma and/or radiation exposure. Medical countermeasures for radiation injury are likely to be in short supply and must be utilized within a medically relevant timeframe. In the National Planning Guidance for Response to a Nuclear Detonation (White House National Security Staff, 2nd Edition, June 2010) national experts have determined that the National medical and public health response capacity to assess and treat casualties is likely to be far exceeded. This session introduces a National concept of operations for nuclear detonation being developed to incorporate mass triage and a novel Integrated Clinical Diagnostics System (ISDC) to assess radiation injury. The goal is to provide evidence-basis to maximize lives saved in the resource constrained environment anticipated following a nuclear detonation. Casualty assessment criteria and triage early in the incident and in the field or healthcare facilities close to the detonation will primarily focus on physical trauma, burns, emergent medical conditions, and various acute exposures (e.g. chemical, smoke inhalation, etc.). After the first few days and further from the incident, for surviving casualties, radiation assessment and triage will be more important to understand survivability of patients and focus clinical interventions. Since this will likely be a resource constrained environment, critical triage decisions must be made that are fair, widely used, and ensure care is provided in a manner that will save the most lives. To support triage decisions and the provision of care, laboratory surge will be required at as many points of care as possible. To do this, this session will introduce a concept that is being developed that integrates the Radiation TRiage, TRansport, and TReatment functional model (Hrdina CM, et al: The “RTR” medical response system for nuclear and radiological mass-casualty incidents: A functional TRiage-TRansport-TReatment medical response model. Prehospital Disast Med 2009;24(3):167–178.) with an accepted biodosimetry architecture (Sullivan JM, Prasanna PG, Grace MB, Wathen LK, Wallace RL, Koerner JF, Coleman CN. Assessment of Biodosimetry Methods for a Mass-Casualty Radiological Incident. Health Physics 105.6 (2013): 540-54.) to create an Integrated Clinical Diagnostics System (ICDS) (Coleman CN, Sullivan JM, Bader JL, Murrain-Hill P, Koerner JF, Garrett AL, Weinstock DM, Case C Jr, Hrdina C, Adams SA, Whitcomb RC, Graeden E, Shankman R, Lant T, Maidment BW, Hatchett RC. Public health and medical preparedness for a nuclear detonation: the nuclear incident medical enterprise. Health Phys. 2015 Feb;108(2):149-60.) to support the massive surge for assays such as lymphocyte depletion kinetics (CBC Diff), dicentric analysis (cytogenetics), radiobioassay, and other novel assays and diagnostics under development. Importantly, the national concept of operations and ICDS recognize that the role of clinical diagnostics will differ depending on location and goals of care and will change over time and location with triage first (trauma, then radiation focused triage), support for medical management next, and later for epidemiology and risk assessment. This presentation will focus on the triage and early medical management functions.

PHEMCE & How it Will Support Medical Response. Norm Coleman, MD

Session will be presented from this abstract: Public health and medical preparedness for a nuclear detonation: the nuclear incident medical enterprise.ublic health and medical preparedness for a nuclear detonation: the nuclear incident medical enterprise. Health Phys. 2015 Feb;108(2):149-60.

Resilience and the ability to mitigate the consequences of a nuclear incident are enhanced by (1) effective planning, preparation and training; (2) ongoing interaction, formal exercises, and evaluation among the sectors involved; (3) effective and timely response and communication; and (4) continuous improvements based on new science, technology, experience, and ideas. Public health and medical planning require a complex, multi-faceted systematic approach involving federal, state, local, tribal, and territorial governments; private sector organizations; academia; industry; international partners; and individual experts and volunteers. The approach developed by the U.S. Department of Health and Human Services Nuclear Incident Medical Enterprise (NIME) is the result of efforts from government and nongovernment experts. It is a "bottom-up" systematic approach built on the available and emerging science that considers physical infrastructure damage, the spectrum of injuries, a scarce resources setting, the need for decision making in the face of a rapidly evolving situation with limited information early on, timely communication, and the need for tools and just-in-time information for responders who will likely be unfamiliar with radiation medicine and uncertain and overwhelmed in the face of the large number of casualties and the presence of radioactivity. The components of NIME can be used to support planning for, response to, and recovery from the effects of a nuclear incident. Recognizing that it is a continuous work-in-progress, the current status of the public health and medical preparedness and response for a nuclear incident is provided.

Progress and Achievements in Radiation Nuclear MCM Development by the NIAID Radiation Nuclear Countermeasures Program. Bert Maidment, PhD

The Department of Health and Human Services (HHS) is charged with protecting civilian populations by providing leadership in research, development, acquisition, deployment, and use of effective medical countermeasures (MCMs) for weapons of mass destruction. Among the top priorities identified by the HHS PHEMCE Implementation Plan are MCMs against radiological and nuclear threats. HHS delegated the responsibility to the National Institute for Allergy and Infectious Diseases (NIAID) to develop and manage a comprehensive research and translational program focused on the identification, development and licensure of radiation/nuclear MCMs and diagnostics. Over the last ten years, NIAID has implemented its strategic plan and research agenda to achieve the objectives. NIAID established a multi-element program of grants, cooperative agreements, contracts, corporate partnerships, and intra and inter-agency agreements. Priority objectives are to develop:

- Infrastructure and expertise for research, development, and translation
- Safe and effective MCMs to increase survival in a radiation public health when administration is delayed at least 24 hours post-radiation exposure;
- Safe and effective oral radionuclide decorporation agents to expedite removal of internal contamination of various radionuclides; and
- Biodosimetry devices and biomarkers of radiation-induced tissue injury for use in radiation public health emergencies for triage, dose assessment, and monitoring.

Information on building a research infrastructure and a cadre of investigators/developers with radiation/product development expertise; and data on progress in identifying, developing, and licensing MCMs and biodosimetry methods and devices.

Emergency Biodosimetry. William F. Blakely, PhD

• What are the current recommended applications of biodosimetry in a nuclear power plant accident for workers, accident responders, and general public that are suspected of exposure to radiation?
• Describe the concept of operations for biodosimetry.
• What are the current limitations and gaps in biodosimetry?

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Early emergency response for a radiological accident involves a multiple-parameter biodosimetry diagnostic strategy, since no single assay is sufficient to address all potential radiation scenarios including partial-body exposures. The accepted generic multiple-parameter approach includes: measuring for radioactivity associated with the exposed individual; observing and recording prodromal signs and symptoms; obtaining serial complete blood counts with white blood cell differential; sampling blood for the chromosome-aberration cytogenetic bioassay using the “gold standard” dicentric assay (or other suitable cytogenetic chromosome aberration assay) for dose assessment; bioassay sampling from various sources (i.e., urine, fecal, blood, nasal, oral, etc.), if appropriate, to determine radionuclide contamination; biosampling blood for measurement of proteomic and gene expression radiation-responsive biomarkers; biosampling nail clippings for measurement of free radicals by electron paramagnetic resonance (EPR) for dose assessment; and using other available dosimetry approaches. Life-saving procedures in the medical management of the radiation accident patient take precedent to biodosimetry assessments. Radioactivity assessment and decontamination procedures are then typically followed by the generic early-phase biodosimetry procedures as described above. In the case of radiological mass-casualty incidents, a diagnostic triage system should be setup where rapid sentinel biodosimetry tests are used to prioritize casualties for subsequent confirmatory radiation injury and dose diagnostic tests to develop guidance for medical management treatment decisions.
Readiness for a potential nuclear reactor accident dictate that local resources need to have prior established and exercised medical triage competency including radiation injury and dose assessment capability. This capability should be broadly based and include: access to radiation detection devices; stockpiling of supply materials and protocols for appropriate biosampling; and reagents and devices supporting point-of-care triage diagnostics for measurement of a complete blood cell count, C-reactive protein, and amylase activity. Prior arrangements for reach-back diagnostic support to include: i) establishing deployable (i.e., hematology and biodosimetry) laboratories and reference (i.e., cytogenetic biodosimetry, radiation bioassay, EPR biodosimetry) laboratories are essential. Recording dynamic medical and other radiological relevant data to support dose reconstruction is an important component of an effective response to a suspected radiation overexposure incident. This is especially important in cases of the general population, who are potentially exposed to low doses in the local area of a nuclear reactor accident, where the low doses are below the limit of detection of current biodosimetry assays. Research efforts to focus on early and rapid assessment of partial-body exposures are needed, since this is critical for early-phase medical management treatment decisions. "The views expressed do not necessarily represent the Armed Forces Radiobiology Research Institute, the Uniformed Services University of the Health Sciences, or the Department of Defense."

Capability of the Bundeswehr Rad Medical Task Force. Andreas Lamkowski, MD

The Radiological Nuclear Medical Task Force (RN Medical Task Force) of the Bundeswehr Institute of Radiobiology affiliated to the University of Ulm represents an operational element specialized in medical care and treatment of soldiers who have been exposed to ionizing radiation.
In order to ensure the individual and case-related assessment of irradiated patients directly on site, the RN Medical Task Force can be deployed world-wide within 3 days.
The Task Force Team consists of physicians with profound knowledge in the assessment of radiation- induced damages and technical assistants who are trained to operate radiation measurement detectors.
Based on the findings of the in-depth medical examinations, the RN Medical Task Force diagnoses radiation-related disorders and provides an early estimate of patients' prognosis according to the severity of clinical signs and symptoms (e.g. by prodromi or peripheral blood cell counts).
All information concerning physical and clinical data are gathered in a database, allowing the subsequent analysis of the cases in order to provide recommendations for further treatment.
In cases of suspected exposure to ionizing radiation, blood samples are collected and sent to the Biological Dosimetry Labs of the Bundeswehr Institute of Radiobiology. The RN Medical Task Force also elevates the status of external contamination and performs the preliminary assessment of incorporation (e.g. by saliva measurements and spectrum analyses). If incorporation of radionuclides has occurred, decorporation therapy must be performed, immediately. For this reason, the RN Medical Task Force stockpiles an assortment of common decorporation agents.

Niche-Derived Mitigators for Acute Radiation Injury (Chute, MD)

The bone marrow microenvironment or niche regulates the maintenance and regeneration of hematopoietic stem cells (HSCs). We hypothesize that cells within the HSC niche elaborate soluble factors which promote HSC regeneration following acute radiation injury. Using cell-specific genetic models, we have discovered several niche-derived paracrine factors which appear to be necessary for normal hematopoietic recovery after radiation injury. These factors can be translated as candidate mitigators to improve hematopoietic recovery and survival following radiation injury.

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Ionizing radiation can induce hematopoietic failure via damage to both hematopoietic stem cells (HSCs) and the niches wherein HSCs reside. We hypothesized that soluble factors elaborated by niche cells in the bone marrow (BM) might regulate HSC regeneration following acute radiation injury. We utilized Cre-LoxP technology to delete specific genes in VEcadherin+ BM endothelial cells (ECs) and osterix+ BM osteolineage progenitors and evaluated the effects on HSC regeneration after radiation injury. These genetic models led to our discovery of 3 secreted factors: pleiotrophin (PTN), epidermal growth factor (EGF) and Dikkopf-1 (DKK1) which are secreted by BM niche cells and regulate HSC regeneration. Interestingly, each of these niche-derived proteins regulates HSC regeneration via unique mechanisms. Furthermore, systemic administration of each factor markedly improves both the hematopoietic reconstitution and overall survival of lethally irradiated mice. Broadly, our research suggests that the BM microenvironment is a rich resource for discovery of extrinsic mechanisms which regulate HSC fate determination. Further, our results suggest that niche-derived growth factors can be developed for therapeutic purposes: both for the mitigation of acute radiation sickness and to accelerate hematopoietic reconstitution in patients receiving myelosuppressive chemotherapy or undergoing myeloablative stem cell transplantation.

Importance of CaMKK2 as a Regulator of HSC Regeneration in Vivo (Racioppi, MD)

Long-term hematopoietic stem cells (HSCs) are predominantly quiescent in adults, but become proliferative in response to blood and bone marrow injury. Herein, we demonstrate that Ca2+/Calmodulin (CaM)-dependent protein kinase kinase 2 (CaMKK2) is an important regulator of HSC regeneration in vivo. We analyzed Camkk2-EGFP reporter bone marrow cells and found robust Camkk2 expression in all progenitors and long-term HSCs. To test the functional role of CaMKK2 in regeneration we examined Camkk2 -/- mice and identified accelerated hematopoietic recovery and increased HSC proliferation in vivo following radiation injury. Mechanistically, our data demonstrate that CaMKK2 is required for coupling radiation signaling with AMP-activated protein kinase (AMPK). Thus, in response to radiation Camkk2 -/- HSCs accumulated less phospho-AMPK and more phospho-S6 ribosomal protein (pS6rp) than control HSCs. Finally, pharmacological blockade of CaMKK2 improved hematologic regeneration in vivo in mice and stimulated colony formation by human CD34+ hematopoietic cells in vitro. Cumulatively, our data establish CaMKK2 as critical regulator of HSC regeneration and identify CaMKK2 inhibition as a novel approach to HSC expansion.

Fibrinogen-Coated Nanospheres Improve Hemostasis and Prevent Fatal Hemorrhage from Radiation-Induced Thrombocytopenia (Chen, MD)

Radiation-induced thrombocytopenia may cause life-threatening bleeding. Fibrinogen-coated nanospheres (FCN) may bind to platelets, contributing to hemostasis. Data from our murine model of radiation-induced thrombocytopenia suggest that administration of FCN shortens bleeding times and improves survival by preventing fatal gastrointestinal and intracranial hemorrhage.

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Introduction: Radiation-induced thrombocytopenia (TCP) may cause severe and life-threatening bleeding. While complications may be prevented by platelet transfusions, transfusions are associated with significant costs and complications, and supply may be limited in the setting of a radiation catastrophe. We hypothesize that fibrinogen-coated nanospheres (FCN) may bind to platelets through fibrinogen-GPIIb/IIIa interactions, contributing to hemostasis in the setting of TCP.

Methods: FCN are made of human albumin polymerized into a sphere and coated with fibrinogen; the average size is 400 nm. They are stored in suspension at 20°C and are stable up to 2 years. We evaluated the safety and efficacy of FCN in four murine models of radiation-induced thrombocytopenia: in the first two, BALB/c mice received 7.25 Gy total body irradiation (TBI) and C57BL/6 mice (which are more radioresistant) received 8.25 Gy TBI; in the second, a lower dose of radiation (7.0 Gy BALB/c, 8.0 Gy C57BL/6) was combined with an anti-platelet antibody to induce severe thrombocytopenia. We also assessed the impact of FCN on various hemostatic mechanisms using a variety of ex vivo and in vitro assays.

Results: In all four murine models of radiation-induced TCP, administration of FCN (8 mcg/g, i.v., at Day 1, 5, and 10) significantly improved survival compared to saline control (BALB/c TBI 7.25 Gy, n=20/arm: survival was 75% with FCN vs. 40% with control, p=0.029; BALB/c TBI 7.0 Gy + Ab, n=25/arm: 56% FCN vs. 12% control, p=0.004; C57BL/6 TBI 8.25 Gy: 40% FCN vs. 0% control, n=10/arm, p=0.0131; C57BL/6 TBI 8.0 Gy + Ab, n=15/arm: 73% FCN vs. 0% control, p<0.0001). All deaths were due to gastrointestinal or intracranial hemorrhage. Furthermore, FCN shortened bleeding times in a platelet-concentration dependent manner in a murine model of radiation-induced thrombocytopenia as well as a murine model of antibody-induced thromobcytopenia.

There were no clinical signs of thrombosis or laboratory signs of disseminated intravascular coagulation after FCN, nor were microthrombi or embolism found on histological examination of lung, liver, brain, heart, spleen, and kidney tissue. In further support of safety, in vitro studies suggest that FCN only bind to platelets upon platelet activation (e.g., in the presence of collagen), suggesting that they would only clump in the setting of endothelial injury but would not cause spontaneous thrombosis.

Interestingly, no differences in platelet aggregation or clot strength were detectable on light aggregometry (PAP-8E), impedance aggregometry (Multiplate), or thromboelastography (TEG, ROTEM). Nor were differences seen in fibrin formation. However, using a flow-based model of hemostasis (Cellix), in which blood is flowed across a biochip that has been pre-coated with collagen, addition of FCN to blood samples taken from thrombocytopenic patients was found to improve platelet adhesion and aggregation compared addition of saline (p=0.014).

Conclusion: FCN may prevent thrombocytopenia-related bleeding by interacting with platelets and inhibiting clot lysis. FCN may be helpful in many disorders including primary (immune thrombocytopenia) as well as secondary thrombocytopenia (cancer, chemotherapy, trauma, radiation injury), potentially reducing platelet transfusions, particularly in situations where platelets may not be readily available.

Radioprotective Efficacy of Tocols is Mediated Through Induction of Granulocyte Colony-Stimulating Factor (Romaine, BA)

Presentation of a recent mice study investigating cytokine induction by tocols and the role of granulocyte colony-stimulating factor in radioprotection against lethal radiation dose.

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The aim of this study was to determine the role of granulocyte colony-stimulating factor (G-CSF), induced by the tocols, (gamma tocotrienol (GT3), delta-tocotrienol (DT3) and tocopherol succinate (TS)), in survival after exposure to a lethal dose of radiation, using the murine model. CD2F1 mice were injected with a tocol and a G-CSF antibody then monitored for 30 d for survival. Cytokines from serum samples were analyzed using Multiplex Luminex. Our results demonstrate that all three tocols significantly protected mice against ionizing radiation, and induced high levels of G-CSF in peripheral blood, 24 h after administration. Injection of a G-CSF neutralizing antibody resulted in complete neutralization of G-CSF and abrogated the radioprotective efficacy of tocol administration. G-CSF antibody administration did not affect the levels of other cytokines induced by tocols. Our results suggest that tocols protect against lethal radiation damage by inducing G-CSF. Similar observations have been made with additional radiation countermeasures confirming the radioprotective role of G-CSF.

The THBD-aPC Pathway in Radiation Mitigation (Geiger, PhD)

Tissue damage induced by ionizing radiation in hematopoietic and gastrointestinal/epithelial systems is the major cause of lethality in radiological emergency scenarios, and underlies deleterious side effects in patients undergoing radiation therapy. Identification of target-specific interventions that confer radio-mitigating activity are largely unmet challenges. Based on a forward genetic approach, we identified the thrombomodulin (Thbd)–activated protein C (aPC) pathway as a novel mechanism for mitigation of total body irradiation (TBI)-induced mortality. Therapeutic administration of recombinant, soluble Thbd or aPC to lethally irradiated wild type mice resulted in the accelerated recovery of hematopoietic progenitor activity in bone marrow and mitigation of lethal TBI. Starting infusion of aPC as late as 24 hours after exposure to radiation was still sufficient for mitigating radiation-induced mortality. These findings suggest that pharmacologic supplementation of the protein C pathway activity by Thbd or aPC might offer a rationale approach towards the mitigation of tissue injury and lethality caused by ionizing radiation.

Abrogation of TGFB Signaling Does Not Rescue the Radiosensitive Phenotype or Hematopoiesis Smad3-/- Fancd2-/- Double Knockout Mice (Zhang, MD)

Enhanced Fanconi Anemia bone marrow inhibition by irradiation- induced TGF-β may explain irradiation sensitivity. A novel DKO mouse was developed to determine if abrogation of the TGF-β signaling pathway altered the Fancd2-/- mouse phenotype. Comparisons between parent and DKO bone marrow cells and derived cell lines for phenotype changes were made.

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Purpose: Fanconi Anemia (FA) mice represent a valuable model system in which to test effectiveness of new radiation countermeasures in radiosensitive individuals. Enhanced FA bone marrow hematopoietic cellular inhibition by irradiation- induced TGF-β may explain total body irradiation sensitivity. To determine if abrogation of the TGF-β signaling pathway altered the Fancd2-/- mouse phenotype, we generated a novel DKO mouse strain. FA (Fancd2-/-) mice on the C57Bl/6 background which are radiosensitive, as are derived marrow stromal cell lines (Berhane et al., Rad Res, 181(1):76-89,201 and Berhane et al., Rad Res: 182:35-49, 2014) were crossed with Smad3-/- mice (129/Sv) which display bone marrow stromal cell radioresistance (Epperly et al., Rad Res:165:671-677, 2006). We tested DKO mouse fresh bone marrow cells, long term bone marrow cultures (LTBMCs) and derived cell lines for phenotype compared to parent strain Fand2-/- mice and Smad3-/- mice.

Methods: (Smad3-/- (129/Sv) Fancd2-/-(C57Bl/6)) DKO mice were derived by breeding double heterozygotes. LTBMCs were established from DKO and control mice and bone marrow stromal cell lines were obtained from each genotype culture. Sensitivity of each genotype bone marrow to irradiation and to TGF-β was determined in the presence or absence of TGF-β receptor antagonist SD-208.

Results: DKO pups were small at birth. Fresh marrow displayed lower numbers of CFU-GM, BFUe and CFU-GEMM similar to Fancd2-/- mouse marrow. DKO marrow showed decreased duration of hemopoiesis in LTBMCs similar to Fancd2-/-mouse cultures. Hemopoiesis ceased by week 10, consistent with reduced primitive stem cell numbers. In contrast Smad3-/- mouse marrow showed increased duration of hemopoiesis in LTBMCs consistent with stem cell resistance to negative regulation by TGF-B (Epperly et al., Exp Hematol 33:352-362, 2005). DKO fresh marrow colony forming cells were resistant to TGF-B. In contrast TGF-β inhibition of colony forming cells was intact in SMAD3+/+ and in Fancd2-/- bone marrow. Colony forming cell survival fraction dropped from 1.00 ± 0.09 at 0 ng/ml to 0.81 ± 0.5 ($p = 0.0232$) and 0.75 ± 0.07 ($p = 0.0168$) in 20 and 50 ng/ml TGF-β, respectively. SD-208 increased the survival of colony forming cells from Smad3+/+ and Fancd2-/- marrow in the presence of added TGF-β (1.01 ± 0.03 ($p = 0.0033$) and 0.96 ± 0.03 ($p = 0.042$) at 20 and 50 ng/ml, respectively). In contrast DKO mouse marrow was resistant to TGF-B or to SD-208. DKO mouse bone marrow stromal cells were still radiosensitive (Do = 1.41 ± 0.03 Gy) similar to Fancd2-/- cells (Do = 1.46 ± 0.10) and dissimilar from radioresistant Smad3-/- or Smad3+/+ Fancd2+/+ cells (Do=2.25 ± 0.14 or 1.59 ± 0.03 Gy, respectively, $p \leq 0.0418$).

Conclusions: DKO mice show the predominant phenotype of Fancd2-/- mice, while maintaining resistance to TGF-B. DKO mouse marrow showed reduced stem cell numbers, decreased longevity of hemopoiesis of explanted marrow in LTBMC and radiation sensitivity. These mice should be valuable for study of the complex interactions of the TGF-β signaling pathways with the defective DNA response to oxidative stress in Fancd2-/- mice.

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Tissue-Specific Endothelial Cell Transplantation for Mitigation of Radiation-Induced Fibrosis and Injury (Rafii, MD)

Radiation injury to various organs is particularly aggravated by damage to the vasculature that are exquisitely sensitive to irradiation. Exposure of capillary blood vessels to radiation induces rapid apoptosis of endothelial cell (ECs) lining the blood vessels, leading to vascular thrombosis, impaired organ repair, hypoxia and aberrant healing by maladaptive fibrosis. Scarring of various organs not only lead to dysfunction but also predisposes to tumorigenesis. Therefore restoration of vascular function by transplantation of the endothelial cells will provide a novel means to promote organ repair without scarring.

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Shahin Rafii MD, Bi-Sen Ding, and Jason M Butler
Weill Cornell Medical College, Angiocrine Bioscience, Ansary Stem Cell Institute, New York, NY

Organ specific endothelial cells (ECs) are not just passive conduits to deliver oxygen and nutrients, but also establish an instructive vascular niche, which by elaboration of specific paracrine trophogens, (known as angiocrine factors), directly balance the rate of stem cell self-renewal and differentiation. Activation of Akt-mTOR pathway in the sinusoidal ECs (SECs) stimulates expression of angiocrine factors, including Notch-ligands, Wnts, FGFs and TGF-modulators, that induce expansion of authentic hematopoietic stem cells (1). After partial hepatectomy, SECs within the liver stimulated regeneration by angiocrine expression of Wnt2 and HGF (2) without provoking fibrosis (3). Pulmonary capillary ECs (PCECs) by deploying MMP14 and release of EGF-ligands sustain lung regeneration without instigating aberrant pro-fibrotic changes (4). Most importantly, intravenous transplantation of tissue-specific ECs into mice restores organ regeneration after radiation-induced injury. Transplantation of the marrow derived cells accelerated hematopoietic recovery after exposure of the mice to total body irradiation. These data establish the previously unappreciated tissue-specific vascular heterogeneity in orchestrating organ regeneration (5). Indeed, each organ is arborized with specialized capillary ECs endowed with unique repertoire of angiocrine factors (5). Notably, as ECs can be provoked to instigate pro-fibrotic changes, we need to manufacture and transplant tissue-specific ECs that drive organ regeneration without promoting maladaptive fibrosis.

For clinical translation, we have differentiated human and mouse embryonic stem and iPSC cells into induced vascular ECs (iVECs). However, iVECs (like iPSC-derived cells) are unstable and upon further stressful stimuli differentiate into other non-vascular cells. To circumvent this hurdle, we have developed new strategies by transcriptional (short term ETV2+Fli1+Erg1+TGFβ inhibition) reprogramming of mid-gestation amniotic cells into vascular ECs (rAC-VECs) without employing pluripotent transcription factors (TFs) (6). rAC-VECs phenocopy the specialized tissue-specific function of ECs, supporting long-term expansion of repopulating cells, such as hematopoietic stem cells in xenobiotic-free conditions.

We show that once transplanted intravenously, rAC-VECs home to regenerating tissues reconstructing a vascular niche that by production of specific angiocrine factors promote organ regeneration and repair without fibrosis. Since rAC-VECs can be HLA-typed, cryopreserved, and publicly banked, these cells establish an inventory for generating abundant vascular niche cells for organ repair.

Finally, we have shown that transition through a pluripotent state results in poorly engraftable hematopoietic cells. To resolve this hurdle, we have transduced adult human or mouse ECs with Runx1/Spi1/Gfi1/FosB TFs along with vascular niche-induction allowing for conversion of these ECs into stable and long-term engraftable hematopoietic stem and progenitor cells (7).

In summary, we propose that timely transplantation of even allogeneic tissue-specific endothelial cells after exposure to radiation results in the engraftment of these endothelial cells into

injured tissues and by producing specific angiocrine factors promotes organ regeneration and repair without provoking maladaptive scarring. We have devised strategies to engineer and manufacture endothelial cells that will enable translation of this innovative approach to the clinical setting.

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Advanced Development of HemaMax for Mitigation of HSARS Under the FDA Animal Rule (Gluzman-Poltorak, PhD)

Overview and recent advances in HemaMax (rHuIL-12) development, a front-line Rad-MCM

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HemaMax (aka rHuIL-12) is being developed under the FDA Animal Rule to prevent or reduce mortality and morbidity associated with HSARS. Efficacy has been evaluated in non-human primates (NHP) and safety in humans. Three studies in irradiated NHP have demonstrated the ability of single, low doses (50-500 ng/kg) of HemaMax to induce recovery of hematopoietic tissue and to decrease the incidence of hemorrhage and infections, leading to a substantial increase in survival. HemaMax significantly improved survival in a head to head study relative to G-CSF, the currently recommended drug for treatment of HSARS in victims of a radiation disaster (Basile 2012; Gluzman-Poltorak 2014a and b). The efficacious effects of HemaMax have been demonstrated in a surrogate species, namely C57Bl/6J mice using murine IL-12. The PK and PD of IL-12 has been characterized in irradiated and non-irradiated rhesus monkeys and mice.

A recent meta-analysis of three NHP studies shows that the level of the nadir of lymphocytes, neutrophils, and platelets is significantly higher in animals who remained alive at day 60 following TBI. Thus, animals with higher nadirs have an improved chance of survival. The nadir for lymphocytes appears to be the strongest and most consistent predictor of death, in agreement with METREPOL human database (Fliedner 2007). Thus, the significant increase in early bone marrow regeneration in HemaMax-treated animals, resulting in increases in nadir values for all major blood cell types, is an important mechanism of action by which HemaMax mitigates the lethality of HSARS.

A toxicology study with seven repeat doses of HemaMax administered every other day at 3 dose levels (100, 316 and 1000 ng/kg/dose) along with cardio-vascular and respiratory safety studies were conducted in rhesus monkeys. The no observed adverse effect level (NOAEL) was 1000 ng/kg/dose, and a no observable effect limit (NOEL) could not be established.

Clinical safety of HemaMax has been established in two Phase 1 blinded randomized placebo-controlled studies in 92 healthy volunteers in which HemaMax, at single unit doses up to 12 µg (~170 ng/kg) , has been shown to trigger multilineage hematopoietic and immune-mediated effects without undue toxicity (Gokhale 2014). An ongoing placebo-controlled multicenter Phase 2 study is being performed to confirm the safety and tolerability of a single 12 µg SC unit dose of HemaMax in healthy subjects considered representative of the US population. To date 111 subjects had been enrolled and treated and the safety data is under evaluation.

Dose translation from monkeys to humans was proposed based on the PK exposure and qualitative similarity of PD responses. Noncompartmental PK analysis showed that there were no obvious species differences in PK exposure between rhesus monkeys and humans. Simulations included impact of radiation, species differences, PK variability, and distribution of human body weights over normal strata. Initial analysis of exposure-survival relationship in irradiated NHP shows an apparent lack of dose response from 50 to 500 ng/kg as evidenced by the plateau in % increase in survival. An additional exposure-survival NHP study at the dose range 50-150 ng/kg is ongoing.

PHD Inhibition Mitigates and Protects Against Radiation-Induced Gastrointestinal Toxicity Via HIF2 (Giaccia, PhD)

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The overall goal of radiotherapy is to eradicate the tumor and spare normal tissue damage. My research interests have focused on understanding the molecular mechanisms underlying the response of tumors and normal tissue to a reduced oxygen environment (hypoxia). Tumor hypoxia reduces the efficacy or radiotherapy and chemotherapy and increases the invasive and metastatic behavior of tumor cells. This talk is based on data from our studies on how the HIF/VHL pathway affects normal tissue responses, in particular the gastrointestinal tract. We have found that inhibition of PHD activity and increased HIF activity in the GI tract results in an increase in intestinal regeration and increased survival following lethal doses of irradiation to the abdomen. We have a great deal of expertise with the PHD/HIF pathway and feel that these studies represent a new approach to protecting and/or rescuing the bone marrow after exposure to ionizing radiation.

Animal Models, and the Role of Acute Injury Associated with Late Effects (Cohen, MD)

For presentation at sessions on animal models, and the role of acute injury associated with late effects

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Acute kidney injury in a non-human primate model of high-dose, partial-body irradiation (PBI).

Eric P Cohen, Kim G Hankey, Alexander Bennett, Sean R Kearney, Ann M Farese, Thomas J MacVittie.
University of Maryland, School of Medicine, Baltimore, MD

Chronic kidney disease occurs after total-body irradiation (TBI) in clinical hematopoietic stem cell transplantation (HSCT) and in rodent models of TBI/HSCT or leg-out TBI. Acute kidney injury (AKI) is reported after radiation accidents and has yet to be identified in a large animal model of the ARS or delayed effects of acute radiation exposure (DEARE). Its occurrence after HSCT is ascribed to multiple nephrotoxins. Occurrence of AKI after total- or PBI may greatly influence survival, the occurrence of multiple organ injury (MOI) and use of mitigators. We evaluated its occurrence in a PBI with approximately 5% bone marrow (BM5)-sparing model in non-human primates (NHP). NHP (n=22) underwent 10 Gy (n=8) or 11 Gy (n=14) PBI/BM5 with moderate supportive care for up to 180 days, as described previously (Health Phys 103:427, 2012). Renal function was assessed at euthanasia using blood urea nitrogen (BUN) and renal histology. BUN rose to a maximum of 99 mg/dL at nine days after PBI (normal 14 to 24 mg/dL). BUN progressively decreased over the ensuing 50 days. Semi-quantitative histology for tubular injury, glomerular thrombosis, and medullary congestion—each scored as 0, 1, or 2—showed a cumulative maximum score of 5 at nine days after PBI and progressively declined over the ensuing 50 days. There were no features of radiation nephropathy such as mesangiolysis and there was no fibrosis. BUN correlated with the histologic score ($r = 0.5$, $p = 0.03$). Neither BUN nor histology scores differed between the 10 Gy and 11 Gy irradiated-NHP. This AKI occurred concurrently with the acute gastrointestinal syndrome and during the latent period for evolving lung and cardiac injury characteristic of the DEARE. The AKI did not have the histological appearance of radiation nephropathy and appeared to resolve within 50 days after PBI, which is consistent with the time scale for acute tubular necrosis and its recovery. It is possible that this AKI potentiates later pulmonary and/or renal DEARE. It is likely that the pharmacology of radiation mitigators used in NHP or in humans will be significantly affected by this AKI. The clinical and histological definition of acute organ-specific effects supports a more strategic approach to medical countermeasure efficacy and the connection between the ARS and DEARE.

Role of Prostaglandin E2 in Mitigation in Radiation-Induced Hematopoietic Injury (Calvi, MD)

Data presentation on murine models of radiation injury and mitigation.

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Acute mortality after radiation injury is often mediated by acute hematopoietic failure.Hematopoietic stem and progenitor cells (HSPCs), which continuously maintain all mature blood cells, are regulated within the marrow microenvironment. One microenvironmental factor that regulates HSPCs is prostaglandin E2 (PGE2). Prostaglandins are synthesized by many cell types in the marrow microenvironment, including osteoblastic cells. PGE2 and other metabolites in the prostaglandin pathway expand the HSPC pool through activation of the EP2 and EP4 receptors and thereby improve their repopulating ability. We previously reported that pharmacologic treatment of naïve mice with PGE2 expands HSPCs. Data from our laboratory and others demonstrate that these effects are mediate both through direct action of PGE2 on HSCs and through the HSC microenvironment. PGE2 treatment in naïve mice inhibits apoptosis of HSPCs without changing their proliferation rate. In a murine model of sub-lethal total body irradiation (TBI), in which HSPCs are rapidly lost, treatment with a long-acting PGE2 analogue (dmPGE2) reversed the apoptotic program initiated by TBI. dmPGE2 treatment in vivo decreased the loss of functional HSPCs following radiation injury, as demonstrated both phenotypically and by their increased reconstitution capacity. DmPGE2 treatment does not impair the ability of HSCs to differentiate in vivo, resulting instead in improved hematopoietic recovery after TBI, particularly for platelets and red blood cells. Based on these data, we hypothesized that dmPGE2 would be an effective mitigator, and found indeed that when administered acutely after radiation, PGE2 mitigates acute mortality. To define the mechanism of mitigation, we explored its effects on HSCs and the microenvironment. dmPGE2 enhanced the bone marrow microenvironmental response to TBI, increasing microenvironmental cyclooxygenase-2 expression. Based on these data and data by, in vivo treatment with PGE2 agonists may be particularly beneficial to HSPCs in the setting of injury by targeting them both directly and also through their niche, therefore it is a promising mitigation strategy for radiation injury.

Administration of Two Radiation Mitigators: GS Nitroxide JP4-039 and Water Soluable Oxetanyl Sulfoxide MMS-350 Improves Total Body Irradiation Survival Superior to One Alone (Greenberger, MD)

Multiple drug administration may be required for radiation mitigation. The mitochondrial targeted GS-nitroxide, JP4-039, acts as a free radical scavenger. The oxetanyl sulfoxide, MMS350, acts as a hydroxyl radical scavenger. Both drugs individually mitigate irradiation damage. We tested the effect of both compounds together a mouse TBI irradiation model.

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Purpose: Multiple drug administration at 24 hr or later after irradiation may be required for effective mitigation. The mitochondrial targeted GS-nitroxide, JP4-039, acts as a free radical scavenger. The oxetanyl sulfoxide, MMS350, acts as a hydroxyl radical scavenger. Both drugs individually mitigate acute total body irradiation damage and with MMS350, also, late radiation pulmonary fibrosis (Kalash, Epperly, Cao et. al., Radiation Research 180:474-490, 2013). We tested the effect of both compounds together in the C57BL/6NTac mouse TBI irradiation model.

Methods: Irradiation survival curves with murine hematopoietic progenitor cell line 32D cl3 in vitro showed both drugs were mitigators. JP4-039 (10 μM) or MMS350 (100 μM) were incubated with the cells one hour before irradiation or added 30 min following irradiation ranging from 0 to 8 Gy. The irradiated cells were plated in methylcellulose, incubated for 7 days at 37oC, and colonies of greater than 50 cells counted. The data was analyzed using linear quadratic or single hit, multi-target models. C57BL/6NTac mice were irradiated to 9.25 Gy total body irradiation and injected intravenously 24 hr later with JP4-039 (20 mg/kg) in F14 emulsion, MMS350 (20 mg/kg) or both JP4-039 (20 mg/kg) + MMS350 (20 mg/kg). Mice were followed for development of the hematopoietic syndrome (irradiation induced bone marrow failure) and sacrificed according to IACUC Institutional rules.

Results: An irradiation survival curve demonstrated that both JP4-039 and MMS350 protected and mitigated 32D cl 3 cells by increasing the shoulder on the clonagenic survival curves. The shoulder on survival curve for 32D cl 3 cells was 2.0 ± 0.3 compared to 3.8 ± 0.5 when JP4-039 was administered pre irradiation ($p = 0.0092$), 5.4 ± 0.5 when JP4-039 was administered post irradiation ($p = 0.0002$), 3.5 ± 0.3 for cells incubated with MMS350 pre irradiation ($p = 0.0104$) or 5.3 ± 1.5 when MMS350 was ministered post irradiation ($p = 0.0096$). Mice treated with JP4-039 at 24 hours after TBI had increased survival at 60 days following 9.25 Gy from 20% for control irradiated compared to 65% ($p = 0.0092$) for JP4-039 treated. Mice treated with MMS350 showed an increased survival of 55% ($p = 0.0097$). The combination of JP4-039 and MMS350 was additive and increased survival to 95% ($p < 0.0001$).

Conclusions: JP4-039 and MMS-350 were each effective irradiation mitigators. The combination of JP4-039 and MMS350 further increased mitigation. The data indicate that drug combinations may be required to optimize radiation mitigation.

Supported by NIAID/NIH U19-A1068021.
Conflict of Interest: Michael Epperly, Peter Wipf and Joel Greenberger have a conflict of interest due to a patent issued for use of JP4-039 as a radiation mitigator.

An Attempt to Potentiate the Radioprotective Efficacy of Countermeasures by Utilizing a Combination of Modalities: Gamma-Tocotrienol and Amifostine (Newman, BA)

Presentation of recent NHP study utilizing a combination of two drugs (amifostine and Gamma-tocotrienol) at low dose administration to reduce drug side effects and potentiate radio-protective efficacy.

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The purpose of this study was to potentiate the protection afforded by amifostine against total body irradiation (TBI) using the novel approach of combining two drugs, with different mechanisms of action, to reduce adverse and potentially incapacitating side effects. Mice were administered amifostine and/or GT3, then exposed to 9.2 Gy Co-60 gamma-irradiation and monitored for survival for 30 days. To investigate cytokine stimulation, mice were administered amifostine or GT3; serum samples were collected and analyzed for cytokines by multiplex Luminex. In vitro experiments were performed by exposing human fetal lung fibroblasts (HFL-1) to GT3 or amifostine treatment and analyzing supernatant for cytokines. Survival studies show single treatments of GT3 or amifostine significantly improved survival, compared to the vehicle, and also showed that the combination treatments resulted in significantly higher survival compared to single treatments. In vivo studies with GT3 confirmed prior work indicating GT3 induces granulocyte colony-stimulating factor (G-CSF). Amifostine did not induce G-CSF either in the in vivo or in vitro studies. This approach, the combination of amifostine and GT3, which act through different mechanisms, shows great promise and should be investigated further as a potential treatment for ARS.

Mitochondrial Targeted Glutathione Peroxidase 4 Mimic Mito-ebselen Mitigates Irradiation Damage (Stoyanovsky, PhD)

Following irradiation, there is an increased production of mitochondrial H2O2 resulting in apoptosis and necroptosis. GPX4 is very efficient in the reduction of lipid hyperoxides and H2O2 and should be an effective mitigator. We have developed a mitochondrial targeted GPX4 mimic (mito-ebselen) and tested it as a radiation mitigator.

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Purpose: Following ionizing irradiation of cells, there is an increased production of mitochondrial hydrogen peroxide (H2O2) resulting in intrinsic apoptosis and necroptosis. Glutathione peroxidase 4 (GPX4) is very efficient in the reduction of lipid hyperoxides and H2O2 and should be an effective mitigator of irradiation damage. We have developed a mitochondrial targeted GPX4 mimic (mito-ebselen) and tested its potential as a radiation mitigator.

Methods: Mito-ebselen was developed by attaching a mitochondrial targeting group, triphenylphosphonium, to a GPX4 mimic (ebselen). Using mouse embryonic cells (MEC) toxicity was tested in concentrations ranging from 0 to 20 uM. Radiation protection and radiomitigation were analyzed by adding mito-ebselen or ebselen 10 min before or 30 min after irradiation of 10 Gy to MECs and the percent of dead cells determined 24 hr later. Mito-ebselen block of apoptosis was determined by irradiating MECs to 10 Gy and assaying for caspase 3 activation using an EnzChek Caspase 3 Assay Kit. Mito-ebselen (20 uM) or 3-hydroxypropyl(triphenyl)phosphonium chloride, which structurally mimics the triphenylphosphonium moieties (20 uM) were added 10 min before or 30 min after irradiation. In vivo radiation mitigation was determined by total body irradiation of C57BL/6NTac mice to doses of 9.1 or 9.25 Gy. Twenty-four hours later, a subgroup of mice was injected intravenously with mito-ebselen in F14 emulsion and followed for development of the hematopoietic syndrome at which time they were euthanized.

Results: In MECs no toxicity was demonstrated with mito-ebselen at concentrations up to 20 uM. At higher concentrations of 40 uM some toxicity was seen. Irradiation of MECs to 10 Gy resulted in 28% of the cells dying within 24 hr. Addition of mito-ebselen but not ebselen 10 min before irradiation resulted in 50% reduction in cell death. Pretreatment with mito-ebselen also inhibited apoptosis following 10 Gy as demonstrated by a reduction of caspase 3 activity from 10.2 ± 1.5 fold increase in caspase 3 activity to 4.8 ± 1.0 fold increase in caspase 3 activity. In vivo survival curves also demonstrated mitigation by mito-ebselen where C57BL/6NTac mice irradiated to 9.1 Gy showed a survival fraction of 25% at 30 days compared to 52% for mice treated at 24 hr after irradiation with mito-ebselen ($p = 0.0237$). Mice irradiated to 9.25 Gy did not survive past day 15 following irradiation. Mice treated with mito-ebselen 24 hrs after 9.25 Gy had 50% survival at day 15 and 20% survival at day 30 after irradiation ($p = 0.0200$).

Conclusion: Mito-ebselen is a potent radiation migitator in vitro and in vivo.

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Circulating IL-18BP and IL-18 as Dual Biomarkers for Radiation Dose and Injury Assessment in Mice After Total Body Radiation Exposure (Xiao, MD)

Evaluation of radiation-induced IL-18 and IL-18BP in serum by ELISA is a rapid, non invasive, reliable, easy to-use, and inexpensive procedure which can be used as a biomarker for triage and track casualties after radiological accidents as well as for therapeutic radiation exposure.

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Previous studies of biological dosimetry diagnostic system using in vitro and in vivo animal models suggest a multibiomarkers role in radiation assessment. However, biomarkers that specifically and significantly release upon the development of pathology after radiation exposure are not available. Radiation-induced massive release of proinflammatory cytokines will induce apoptosis, senescence, or necrosis in irradiated cells. In this sense, acute radiation syndrome (ARS) can be considered an acute inflammatory disease. We recently reported that the circulating interleukin-18 (IL-18) can be used as a biomarker to assess therapeutic radiation exposure and track casualties after radiological accidents in mice, minipigs and nonhuman primates. Here, we further determined the serum levels of IL-18 binding protein (IL-18BP), a circulating antagonist of the IL-18, in CD2F1 mice after 1 to 13 days subjected to different doses (5-10 Gy) of total-body gamma irradiation (TBI). We compared the changes in the well-known hematological radiation biomarkers including lymphocyte, neutrophil, and platelet counts, with the changes in IL-18BP and IL-18 in mouse blood, and evaluated the significance, sensitivity and specificity of radiation-induced IL-18BP alteration. The 30-day survival studies showed LD25/30 (lethal radiation dose that results in the mortality of 25% of mice in 30 days), LD70/30 and LD90/30 in 8, 9 and 10 Gy of TBI mice, respectively. Radiation doses at 5 and 7 Gy did not cause CD2F1 mice death (sublethal). After 5-10 Gy of TBI, IL-18 increased by 3-20 fold and stably elevated in mouse serum from day 1 up to 13 days in a radiation dose-dependent manner. IL-18BP increased rapidly in these mice's serum on day 1 after TBI (25-62 fold, $p<0.001$). However, the IL-18BP levels returned to baseline within 3 days after 5 to 7 Gy and within 7 days after 8 Gy of TBI, and was unaltered thereafter ($p=0.392$ and 0.103, radiation vs. sham-control, respectively). Consistent with IL-18BP levels returned to normalcy, the neutrophil counts in mouse blood started recovering 9 days after 5 Gy-TBI, and platelet counts were higher in 5 and 7 Gy irradiated mice than in those receiving the lethal doses. In contrast, high doses of radiation (9 and 10 Gy) significantly sustained a higher level of IL-18BP in mouse serum and later, induced a second phase increase of IL-18BP on day 9 through day 13 after irradiation, which coincided with the start of animal mortality ($p<0.001$, AUC=1.0). Our data showed that IL-18BP increase was tightly associated with lethal radiation doses. Radiation-induced differential elevation of IL-18BP and IL-18 in animal serum is a dynamic and discriminative indicator of the severity and lethality of irradiation. The findings support the inclusion of the dual markers IL-18BP and IL-18 into the development of a multifactorial strategy for radiation dose and injury assessment.

The Dana-Farber/Brigham and Woman's Cancer Center Full Scale Exercise: Planning, Implementation, and Lessons Learned (McCullen, MS & Tierney, MPH)

A review of the full scale exercise conducted by Dana-Farber/Brigham and Woman's Cancer Center during 2013 and 2014. The planning process, implementation of modules, and lessons learned throughout the process will be discussed.

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The Dana-Farber/Brigham and Woman's Cancer Center conducted a yearlong exercise program that culminated in a multi-agency, multijurisdictional, multi-discipline Full Scale Exercise (FSE). The exercise program was designed with eight separate modules - one training, three tabletops, two drills, one functional and one full scale exercise. Each of the eight modules were connected to a master scenario, but each one had separate timeframes and injects, requiring different personnel to act and make decisions regarding command and control, tactical and operational planning around a surge of patients, and recovery. Small tabletops and drills were run to test assumptions and verify process and workflow throughout the year and culminated in a week-long "real time" exercise.

- Module 1: Operation NIRVE – Demonstrated the needed steps to make medical logistics available for both inpatient and outpatient issues during an RITN activation.
- Module 2: Communications Drill – RITN Activation and Notification Test
- Module 3: Operation Moose Tracks - Tabletop demonstrated the key intersection of technology, family reunification, patient records and maintaining patient privacy during RITN activation.
- Module 4: Test of RITN Activation and Communications Drill
- Module 5: REAC/TS onsite training "Radiation Emergency Medicine"
- Module 6: Operation Lifeline Full Scale Exercise demonstrated patient movement in support of RITN operations using existing NDMS protocols
- Module 7: Operation Lifeline Functional exercise looked at medical triage, records transfer, and management of RITN patients
- Module 8: Operation Lifeline – Tabletop focused on management, logistics and support of outpatients and family assistance. Risk Communication exercised with mock press conference.

The Exercise looked at the following FEMA Homeland Security Exercise Evaluation Program (HSEEP) Core Capabilities:

- Medical Surge Management
- Chemical, Biological, Radiation, Nuclear, Explosion (CBRNE) Detection
- Information Gathering & Recognition of Indicators and Warnings

In addition to internal participants, the exercise involved significant collaboration with many external partners including Brigham and Woman's Hospital, Boston Children's Hospital, Fairbanks Memorial Hospital, Boston University School of Medicine, the City of Boston Public Health Commission, the Boston Medical Intelligence Center, Massport (Logan Airport) and the Boston VA/NDMS.

Lessons learned and opportunities for further exercises will be discussed by the panel, in addition to the exercise design process and implementation.

Conducting a Radiological Full Scale Exercise – Mayo (Teske, MS)

Lesson's learned from the Mayo Clinic of Rochester, MN exercise in 2013

RITN Incidents and the Use of eEmergency (Schlosser, NREMT-P)

Avera is fortunate to have a facility in Sioux Falls that provides Electronic care through eEmergency, eICU, and ePharmacy; and the system is now including eConsult to this program. We have worked with eCare staff and the South Dakota Air National Guard Emergency Management wing to develop a process to incorporate eEmergency assessment tools in an RITN event.

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Incorporating the eCare concept of eEmergency into assessing possible victims arriving at Sioux Falls Regional Airports by utilizing video feed from the reception site at the airport back to the Emergency Dept. Physicians; as well as other specialists present at eCare to assist with the Triage and processing of Patients to Inpatient admissions or Outpatient care; all with the assistance of the South Dakota Air National Guard and eCare.

Geographical Relation of RITN Centers to Medical Toxicology and Disaster Management Resources (Davlantes, MD & Kazzi, MD)

We examine the geographic location of medical toxicology and disaster management resources with regards to existing RITN transplant centers.

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Background: The Radiation Injury Treatment Network (RITN) consists of centers across the United States that are poised to care for victims of a radiation emergency. The network is organized around bone marrow transplant centers because these facilities have expertise both in radiation medicine and in the care of patients with bone marrow depression. RITN centers may further expand their capabilities by partnering with medical toxicologists as well as federal disaster management agencies. Medical toxicologists possess training in radiation injury management and expertise in the management of internal contamination. Local emergency management agencies, including National Disaster Medical System (NDMS) Federal Coordinating Centers (FCCs) and United States Air Force bases, play a critical role in the government's response to a radiation emergency. NDMS is a partnership between several federal agencies to coordinate medical care during disasters. FCCs work with local and state emergency management and health departments to facilitate the distribution of patients to non-federal NDMS-participating hospitals. The Department of Defense and the VA organize the movement of patients in the NDMS system, using Air Force bases as hubs for long-distance transport.

Methods: We examined the geographic location of medical toxicology and disaster management resources with regards to existing RITN transplant centers. Specifically, we looked at medical toxicology fellowships, inpatient toxicology services, outpatient toxicology clinics, poison control centers, NDMS FCCs, and United States Air Force bases. We also evaluated the proximity of RITN centers to nuclear power plants to loosely assess the likelihood of a radiation emergency occurring nearby. Data were derived from public sources.

Results: The majority of RITN centers do not have a medical toxicology fellowship, an inpatient toxicology service, or an outpatient toxicology clinic within the same institution. However, 57% of RITN centers have at least one of these resources located in the same city, and 73% have at least one of these resources or a poison center within the same city. 82% of centers are in the same city as a FCC, and 32% of RITN centers are within 50 miles of a United States Air Force Base. 36% of RITN centers are located within 50 miles of a nuclear power plant; 6.7% are within 25 miles, and none are located within 10 miles of a nuclear power plant.

Discussion: Most RITN centers are in the same city as at least one medical toxicology resource. As toxicology resources can supplement the capabilities of RITN centers in a radiation emergency, medical toxicologists and RITN centers should collaborate during further planning and response efforts. Most RITN centers are also located in the same city as a FCC, allowing for easier communication and coordination during a large-scale disaster. However, few centers are close to air force bases; perhaps additional means of inter-facility transport may need to be explored.

National Alliance for Radiation Readiness: Leveraging Partnerships to Increase Preparedness (Allen, PhD)

This presentation will introduce you to the NARR and its member organizations, it will provide you with an overview of how the NARR utilizes its member organizations to enhance preparedness by developing products and opportunities for inclusion.

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The National Alliance for Radiation Readiness (NARR) is a collective of 17 national member organizations that have banded together to serve as the collective "voice of health" in radiological preparedness through the:

- Participation in national dialogues on radiological emergency issues
- Provision of thoughtful feedback on documents, policies, and guidelines
- Convening of partners to raise awareness of and resolve radiological emergency issues

The NARR benefits from the intersection of public health, radiation control, and emergency management professionals; all with an interest in bolstering the nation's preparedness for a radiological or nuclear incident. The NARR is able to provide a unique perspective on radiological and nuclear preparedness by creating multi-disciplinary workgroups to develop guidance, recommendations, and provide subject matter feedback.

The NARR aims to build response and recovery capacity and capabilities by supporting the sharing resources and tools, including technical methods and information through the development of an online clearinghouse. The NARR also aims to identify and disseminate of best practices, along with define and educate on the roles and responsibilities of local, state, and federal government and the numerous agencies involved with the response to a radiological emergency.

Following the Fukushima incident, the NARR led a review of the US public health and medical response to domestic concerns. The NARR leveraged this information to develop a table top exercise testing the current passenger screening guidelines that were developed following Fukushima. Due to the lessons learned from the exercise, the NARR has drafted expanded traveler screening guidance for ports of entry. In addition to passenger screening, the NARR has developed a list of considerations for prioritization of laboratory samples following a radiological event. This list was created to help jurisdictions plan for the surge of samples that would present at labs following a radiological event. Additionally, ASTHO is developing a framework for a concept of operations to assist state health departments in planning to distribute anti-neutropenics following an improvised nuclear device detonation.

This presentation will not only introduce you to the NARR and its member organizations, it will provide you with an overview of how the NARR utilizes its member organizations to enhance preparedness by developing products and opportunities for inclusion.

A Strategic Approach to National Radiation Emergency Medical Education & Training (MAJ Vanhorne-Sealy, MS)

A comprehensive approach to meeting the specific educational needs of our nation's medical providers and all levels of support staff, throughout the Nation. This presentation proposes federal interagency developed a multi-modal framework to build and maintain competence in working with patients who have encountered radioactive material, in order to maximize lifesaving when dealing with radiological or nuclear mass casualty situations.

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The current lack of adequate radiation training for medical responders to nuclear and radiological incidents is widely acknowledged and well documented by national standard organizations (NCRP 2005, 2010) and in the academic literature (Mettler et al. 2005; Reilly et al. 2007; O'Sullivan et al. 2008). The medical response to nuclear or radiological terrorism or accident is a capability gap that for many years has not been fully addressed by the medical community. The competing priorities and lack of adequate funding for training the broad audience in the healthcare community has made it difficult to develop the leadership, expertise, and programs to fully address the issue. Past incidents have demonstrated that, both during and after the response to radiation accidents, unprepared and untrained medical personnel struggled to provide adequate care for the patients and avert undue stress to the population (IAEA 2012). In the case of a nuclear detonation, the provision of life-saving medical interventions for tens of thousands of people would similarly be substandard, worsening an already devastating event and impairing and prolonging recovery. This strategy focuses on a five-pronged strategic approach and acknowledges that we must tap into existing systems to full address this issue. This strategy proposes: an introduction of radiological mass casualty events in all medical and allied health schools; triennial exercises in accredited medical facilities; a requirement of 20% to 30% of trained hospital staff (all levels); an online occupationally focused training tool; and just-in-time training with job sheets. A strategic approach is necessary to full address the noted shortages in training and education in this arena.

Lessons Learned from the Aurora Theater Mass Casualty on Engaging Staff for Preparedness Efforts (Conroy, MA)

This session will review the experiences of the University of Colorado Hospital in preparing for, responding to, and recovering from a catastrophic event. The circumstances surrounding the July 2012 Aurora Theater Shooting will serve as the case scenario for this discussion,

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The University of Colorado Hospital has maintained an active and robust emergency preparedness program for many years. This program includes multiple table top, functional, and full scale exercises each year, active engagement in planning efforts at the local, regional, state and national level, and very strong senior executive support. This support has allowed us to send over forty management team members across multiple disciplines to training programs such as the Health Care Leadership Course at the Center for Domestic Preparedness in Anniston, AL.

Over the years this level of preparedness has proven itself to be effective in multiple situations. As a Trauma Center and the only academic medical center in the region with unique service lines that are not available elsewhere, we frequently become involved in high-profile situations. This was never more evident than on July 20, 2012 when UCH was confronted with the tragedies associated with the Aurora Theater Shooting.

By the end of that night UCH received twenty-three victims from the shooting. The majority of the most critical patients arrived in the back of police cars. This would have been a major event for any hospital however on that evening UCH had a totally full Emergency Department and had actually been on EMS divert since the previous evening.

Despite these odds the staff at UCH responded in an extraordinary fashion to an extraordinary event. Much of the success that we experienced that evening in dealing with this incident though can be directly attributed to the preparedness efforts that we had undertaken in the prior years.

While there were many lessons to be learned from this event, and new processes and procedures that have had to be implemented, this level of engagement of staff in preparedness, response and recovery activities is essential to any large medical campus.

Increasing RITN Awareness in PH Circles (Rose, PhD)

This session will provide a broad overview of how the National Association of County and City Health Officials is working with its members to increase preparedness levels for radiological/nuclear incidents.

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In the United States alone there are 100 nuclear reactor facilities which comprise nearly 20 percent of the country's domestic power created annually. These reactors are dispersed over 31 states often in groups of two per site. Should a nuclear incident occur in the US at nuclear reactor facility, individuals at the local level will require immediate aid. This presentation will describe how the National Association of County and City Health Officials is actively undertaking activities to elevate public health preparedness coordinators nuclear incident planning practices, awareness, and their familiarity with the RITN.

Promoting Involvement in RITN: How to Generate Interest and Get the Right Players to the Table (Satterlee, BA & Davis, BA)

How do you get people excited about, (or at least invested in), your organization's involvement in RITN? Like everything else - it is all about networking! We hope to illustrate how to reach out not only to your own staff, but how to get city, county and state emergency/medical management resources to the table.

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Promoting Involvement in RITN: How to generate interest and get the right players to the table

As a specialty cancer care center in the Northwest, (with a strong emphasis on hematopoietic stem cell transplant), it was not surprising that the National Marrow Donor Program reached out to us in the beginning, to see if we would like to participate in the in the Radiation Injury Treatment Network. At the time, we had no idea what this would involve, or what it would grow in to, but it sounded interesting and we just thought it was the right thing to do. Our first tabletop exercise consisted of 4 staff members. We spent about an hour pondering the unthinkable scenario, and came to the conclusion that this was actually kind of a bigger deal than we had anticipated.

In this session, we hope to walk you through our center's journey in regards to our involvement with the RITN, what we learned along the way, and our discovery that networking is critical to advancement.

Just like planning a party, you need to invite the right people, (don't be afraid to mix it up a little!). From the start, we reached out to as many different internal staff members as we could, and asked them to recommend others who might be interested. It was in this way that we made huge leap in our journey when it was suggested that we reach out to local and state government agencies to get their input. Originally that included representatives from Seattle police and fire, and later grew to include members of our state government and personnel from Joint Base Lewis McChord.

From those relationships, we evolved our planning from assuming care of victims and families upon arrival in Seattle, to extensive plans for tapping into an already existing network of emergency management. In return, outside groups and organizations began to invite us to their planning sessions, so that they could learn more about RITN and radiation related injuries in general.

In conclusion, these efforts have somewhat brought us full circle - our current planning brings the focus back to our clinical expertise. Because we are a specialty care clinic, our plans now include creation of a command center that would disseminate knowledge to our community partners and hospitals, where we would partner with them to address the medical issues for each patient.

Patients with Hematopoietic Syndrome of ARS: FDA's Perspective on the Dose Selection for Filgrastim.
Lian Ma, PhD

Filgrastim is a recombinant human granulocyte colony-stimulating factor initially approved in the United States for use in patients receiving myelosuppressive anticancer drugs associated with a clinically significant risk of febrile neutropenia (administered at a dose of 5 μg/kg/day). Filgrastim is also approved in additional indications, including reducing the duration of neutropenia and neutropenia-related clinical sequelae in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation with approved dosing regimen of 10 μg/kg/day.

On March 30, 2015, FDA approved Filgrastim (Neupogen®) for the treatment of patients acutely exposed to myelosuppressive doses of radiation. Since human clinical trials cannot be ethically conducted in HS-ARS setting, approval was based on data from an efficacy study in irradiated non-human primates (NHPs).2 In this National Institute of Allergy and Infectious Disease (NIAID) sponsored study, NHPs were treated with 10 μg/kg/day filgrastim through neutrophil recovery, after receiving lethal irradiation. The filgrastim treated group showed significantly reduced 60-day mortality and decreased duration of neutropenia compared to the control group. Based on the totality of evidence from clinical and non-clinical data, along with dose selection considerations on the guidance for product development under the animal rule1, a dose of 10 μg/kg/day in humans was approved for the HS-ARS indication.

Summarized below is the rationale for approving the 10 μg/kg/day dosing regimen in humans for HS-ARS indication. Firstly, according to the dose selection considerations based on the "Animal Rule", because of the uncertainty associated with extrapolating animal efficacy data to humans, human dose should provide exposures that exceed those observed in animal efficacy studies with fully effective dose. Upon FDA's request, pharmacokinetic simulations incorporating the between-subject variability were conducted by the applicant that indicated that 5 μg/kg dose may not be adequate to produce optimal benefit in humans exposed to radiation because it did not exceed the exposures associated with the effective dose (10 μg/kg) in NHPs. Based on the simulation results, a higher dose, 10 μg/kg/day in humans, is expected to provide exposures that exceed those observed in the NHP studies. Secondly, from a benefit prospective, 10 μg/kg/day is supported by the dose-dependent increase in absolute neutrophil count (ANC) response observed in both human and animals. Thirdly, from a safety perspective, there is clinical experience with a dose of 10 μg/kg/day for two of the filgrastim indications. The safety of this higher dose in humans is also supported by a published meta-analysis in literature.3

References:

1. Guidance for industry: Product development under the animal rule, http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm399217.pdf

2. Farese AM, Cohen MV, Katz BP et al. Filgrastim improves survival in lethally irradiated nonhuman primates. Radiat Res. 2013;179:89-100.

3. Pulsipher MA, Chitphakdithai P, Logan BR et al. Lower risk for serious adverse events and no increased risk for cancer after PBSC vs BM donation. Blood. 2014; 123:3655-3663.

Our Experience in Tokai-mura Nuclear Accident. Shin Mineshi, MD

Will talk about the experience to take care of nuclear accident victims who underwent allogeneic stem cell transplant in the effort to save their lives.

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Tokai-mura Nuclear accident occurred in 1999 in Japan. Doctors have tried to save the lives of the victims, and perfomed allogeneic stem cell transplant for two of them. Engraftment was successful and hematopoietic recovery was observed but unfortunately both patients died because of non-hematologic causes. I was working at National Cancer Center Hospital in Tokyo, and was involved in taking care of one of these patients. I will share our experience with you, show you how the treatment and radiation injury progressed, and discuss about the indication of stem cell transplant in this kind of situations.

Improvements in Radiation Medical Countermeasures for ARS Through BARDA's Funding. Richard Hatchett, MD

Dr. Hatchett will provide an update on radiation medical countermeasures in the Strategic National Stockpile and describe ongoing efforts to develop new products to treat various components of Acute Radiation Syndrome.

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The approval of filgrastim (granulocyte colony-stimulating factor, or G-CSF) as a treatment for the hematopoietic component of acute radiation syndrome (ARS) on March 30, 2015, represents a major milestone in the development of radiation medical countermeasures. Filgrastim is the first medical product to receive FDA approval, licensure, or clearance for the treatment or diagnosis of acute radiation syndrome and its approval establishes the product as an important component of standard therapy for persons receiving more than 2 Gy irradiation.

Filgrastim and sargramostim (granulocyte macrophage colony-stimulating factor, or GM-CSF) were procured under Project BioShield for the Strategic National Stockpile in 2013 and were previously available for the treatment of ARS under FDA's Emergency Use Authorization authority. Both products received the endorsement of the FDA Medical Imaging Drugs and Oncologic Drugs Advisory Committees for this indication at a joint public meeting held in May, 2013. The data presented at and outcomes of this meeting will be reviewed.

In addition to filgrastim and sargramostim, the U.S. Government is supporting the development of a number of other products to facilitate the diagnosis and treatment of ARS following the accidental or deliberate exposure of civilians to high doses of ionizing radiation. Dr. Hatchett will provide an overview of these efforts, a progress report on their status, and describe the strategic and operational considerations that inform the composition of BARDA's current portfolio.

Japan's 3.11 Earthquake, Tsunami, and Nuclear Crisis: Life at the Intersection of Danger and Opportunity. Ken Nollet, MD

Attendees will hear a first-hand account of Fukushima Medical University's response to the Great East Japan Earthquake of March 11, 2011, including specific activities and the latest results of the Fukushima Health Management Survey.

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Four nuclear plants on the Pacific coast of Japan went into automatic shutdown in response to the earthquake and tsunami of March 11, 2011. One, Fukushima Daiichi, lost backup power, and 3 of 6 cores melted down. Although environmental release of radioisotopes has been substantially less than that of Chernobyl, many evacuation areas remain off-limits. Decontamination activities, such as scraping and burying topsoil, are widespread, even in areas where evacuation orders were never issued.

The Fukushima Health Management Survey was developed to address health risks - real or imagined - in a meaningful way. It includes 5 components: (1) a Basic Survey to estimate the external radiation exposure of anyone in Fukushima Prefecture March 11 - July 11, 2011; (2) a Thyroid Ultrasound Examination (TUE) program for anyone in Fukushima who was 18 years old or younger at the time of the accident; (3) a Comprehensive Health Check and (4) a Mental Health and Lifestyle Survey for people from designated evacuation areas; and (5) a Pregnancy and Birth Survey for women who gave birth in Fukushima on or after March 11, 2011, or who received Maternal and Child Health Handbooks in Fukushima since August 1, 2010.

Although no fatalities have been directly linked to radiation effects, significant morbidity and mortality can be attributed to the triple disaster of an earthquake, tsunami, and nuclear crisis. Survey data, correctly interpreted and communicated, can guide personal and community initiatives to build a healthier future.

Crisis Standards of Care: Lessons from the Recent Ebola Outbreak in Africa. Lewis Rubinson, MD

Lessons learned from a doctors experience in Liberia and how these could apply to the medical surge following an IND.

Exhibitor's Information Page

Neumedicines

RITN Corporate Fact Sheet

Developing a proprietary Interleukin-12 (aka NM-IL-12 or HemaMax) as an effective, frontline antidote to the hematopoietic syndrome of acute radiation syndrome (HSARS), and for oncology and other indications

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Date of Incorporation: June 2003
Headquarters: Pasadena, CA
Targets: Hematopoietic syndrome of acute radiation syndrome (HSARS), oncology, surgical site infections

Capital invested to date: $70 million
Clinical trials: Three entering Phase II in Autumn 2015, and a fourth entering Phase III
Estimated date of first product sales: July 2017

Likely to Become the New Front-Line Antidote to Hematopoietic Syndrome of Acute Radiation Syndrome

A protein known as "The Master Regulator of the Immune System," Interleukin-12, stimulates the innate and adaptive arms of the immune system, and regenerates all components of blood. The first application is as a front-line antidote to hematopoietic syndrome of acute radiation syndrome (HSARS). The company has three clinical programs entering Phase II Autumn 2015, plus the HSARS program entering Phase III. The disease targets create eligibility for Emergency Use Authorization for HSARS and early, conditional approvals in the oncology indications.

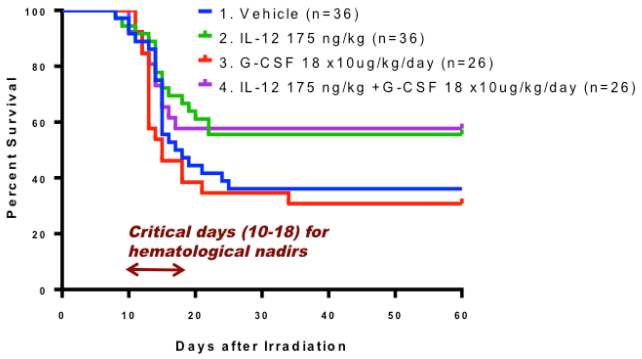
Repopulating Critical Cell Populations Following Lethal Radiation Exposure

NM-IL-12 has a key operational advantage in a disaster scenario in that a single dose administered without supportive care, no antibiotics, fluids or blood products, is sufficient to get victims to definite care. Phase 2, GLP blinded efficacy studies in rhesus monkeys have shown that the drug has a potent ability to stimulate the body to regenerate bone marrow following lethal-dose radiation exposure, which provides the mechanism of action leading to its increased survival potential.[1]

Key Operational Advantages Compared to Standard-of-Care

The only currently available pharmacologic agent to treat patients in the immediate aftermath of a nuclear event, G-CSF, requires daily dosing with full supportive care including transfusions, and an intensive antibiotic regimen. Hence, it needs be administered in a hospital ICU-like environment and is impractical or impossible to administer at disaster sites by first-responders. **By contrast with G-CSF, NM-IL-12 provides a survival benefit and recovery of all major blood cell counts with administration of only a single subcutaneous injection in the complete absence of antibiotics, fluids and blood products.**

Another Phase 2, GLP blinded efficacy study in rhesus monkeys compared the survival benefit of a single dose of NM-IL-12 with 18 daily doses of G-CSF, both regimens without supportive care, where monkeys were exposed to high-dose radiation -- similar to what a human victim of a nuclear disaster would experience -- G-CSF did not provide any survival benefit compared to placebo, whereas NM-IL-12 increased survival.[2] NM-IL-12-treated monkeys also had attenuated nadirs for both neutrophils and platelets with early recovery of cell counts.



Nonhuman Primate Survival Following Lethal Radiation: NM-IL-12, but not G-CSF, Increased Survival

Safety Established Over Two Decades of Science

Neumedicines' research has established safety in 203 healthy human volunteers across three studies, in addition to the lack of toxicity established in non-human primate studies. A previous formulation of IL-12 has been well-tolerated in some 1,400 patients in cumulative published studies.

What Matters Most For Frontline Medical Countermeasures (MCMs) for HSARS

The morbidity and mortality of a "dirty bomb" in a major city would be horrific. Possibly hundreds of thousands or more people would face death within weeks from opportunistic infections and hemorrhage, if not given an effective hematopoietic regenerating agent, **likely within the first 48 hours following exposure.** We owe it to ourselves to be prepared with the only pharmaceutical agent, known to date, that could be effective in treating large numbers of victims at the frontline with a single subcutaneous injection.

Note: The content is solely the responsibility of the authors and does not represent the official views of the Biomedical Advanced Research Development Authority. All work fully funded by HHS-BARDA under contract Nos. HHSO10020110037C and HHSO1002008000060C

[1] Gluzman-Poltorak et al.. *J.Hem & Onc.*2014, 7:31

[2] Gluzman-Poltorak et al. *American Journal of Hematology*, 2014