CMCR RITN

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RADIATION INJURY TREATMENT NETWORK

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A CMCR & RITN Workshop:

Mitigation and Treatment of Radiation Damage

Centers for Medical Countermeaures against Radiation &

the Radiation Injury Treatment Network

July 31 - August 2, 2013

Tremont Plaza Hotel
222 Saint Paul Place
Baltimore, MD 21202

Mitigation and Treatment of Radiation Damage Workshop

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Program Overview

The tremendous environmental, social, and medical cost of a large-scale release of nuclear or radiological material as a result of deliberate attack or natural disaster has led to several programs aimed at improving national and local preparedness.

The Radiation Injury Treatment Network (RITN) and the Centers for Medical Countermeasures against Radiation (CMCR) are convening a three-day workshop on the Mitigation and Treatment of Radiation Damage from July 31st to August 2nd, 2013 that will cover topics such as patient assessment, biomarkers and biodosimetry, suitability of animal models, small molecules, growth factors, and cells as mitigators, as well as their mechanisms of action in radiation-damaged tissues, late effects of acute and prolonged exposure, survivorship issues, and future developments. The workshop will be held at the historic Tremont Plaza Hotel.

The meeting will provide an open forum for invited and plenary speakers and discussants to assess progress on issues related to radiation injury, mitigation and treatment. Various radiation scenarios will be presented along with novel approaches at multiple stages of development.

Educational Objectives

1) Assess progress on issues related to radiation injury, mitigation and treatment
2) Describe various radiation scenarios
3) Discuss novel approaches at multiple stages in development

Target Audience

Physicians, nurses 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.

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 providers, the approver (MCW) or ANCC/ACCME of any commercial products discussed.

Verification of Participation and Continuing Education

Continuing Education Credits are available for participants who attend the sessions **and complete and submit the online evaluation**. Attendees will receive an email following the Workshop to with a link to the evaluation. Certificates of Attendance will be mailed/emailed to attendees following the meeting

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.

  The Medical College of Wisconsin designates this live educational activity for a maximum of 15 *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 15.0 contact hours may be claimed for this educational activity.

- **Medical Technologists:**
  The NMDP is approved as a provider of continuing education in the clinical laboratory sciences through the ASCLS PACE Program. ASCLS PACE® 6701 Democracy Blvd., Suite 300, Bethesda, MD 20817-1574.

  Up to 15.0 contact hours may be claimed for program **#115-024-13.**

- **Certified Hematopoietic Transplant Coordinators (CHTC)**:
  Up to 15.0 contact hours may be claimed by certified coordinators for participation in this educational activity.

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

Conference Planning Committee

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Financial Disclosures

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Speakers/Panelists:

J. Mark Cline, DVM, PhD, DACVP	Consultant/Advisory Board – Roche, Pfizer, Paloma Pharmaceuticals
Zoya Gluzman-Poltorak, PhD, MBA	Employment – Neumedicines, Inc.
Andrei V. Gudkov, PhD, DSci	Board of Directors, Research Funding, Consultant/Advisory Board, Investment Holder – Cleveland BioLabs, Inc.
Isabel L. Jackson, PhD	Consultant/Advisory Board – Aeolus Pharmaceuticals, Inc.
Thomas J. MacVittie, MS, PhD	Research Funding – BARDA
Paul Okunieff, MD	Board of Directors with GainPep, Inc. and DiaCarta, LLC Research Funding from DiaCarta, LLC
Robert H. Schiestl, PhD	Board of Directors, Investment Holder – RadMit Pharma LLC
Alexander Shakhov, PhD	Employment – Cleveland BioLabs, Inc.
Bob Terbrueggen, PhD	CEO, Investment Holder – DxTerity Diagnostics
David Weinstock, MD	Consultant/Advisory Board – Sanofi and Genzyme
Julian Whitelegge, PhD	Research Funding – Chromologic

All disclosures were reviewed by the Activity Director/Nurse Planner and either determined to be unrelated to the educational assignment or resolved with the speaker/panelist.

The following speakers/planners did not identify any relevant financial relationships:

Lyndsey Aspaas
Christine Barbon
David Brenner
Jason Butler
Cullen Case
Nelson Chao
Benny Chen
John Chute
C. Norman Coleman
John Crapo
Jacob Finkelstein
Joel Greenberger
Chandan Guha
Chrisanne Hall
Richard Hatchett
Mary Horowitz
Amy Huser
Kei Iwamoto
Naduparambil Jacob
Martha Lassiter
Bert Maidment
Diana Marquez-Garban
William McBride
James Palis
Luigi Racioppi
Julie Ryan
Daniel Sosin
Adela Salame-Alfie
Helen Turner
Jacqueline Williams

CMCR & RITN Workshop – Mitigation and Treatment of Radiation Injury

July 31 - August 2, 2013 - *Tremont Plaza Hotel* - Baltimore, MD

WEDNESDAY JULY 31ST

9.00 – 9.05am Welcome and Introduction

Nelson Chao (*Duke University*)

9.05 – 9.45am Keynote Address: Preparedness and Response to Radiation:

Daniel Sosin (*Centers for Disease Control*)

9.45 – 10.30am Possible Radiological Scenarios:

John Crapo (*Oak Ridge Institute for Science and Education*)

10.30 – 10.50am Coffee Break

10.50 – 11.20am Casualty Triage and Distribution:

C. Norman Coleman (*DHHS/ASPR*)

11.20 – 11.50am The Local Response:

Adela Salame-Alfie (*NY State Department of Public Health*)

LUNCH: 11.50am – 12.40pm

12.40 – 1:10pm The RITN Response to Radiological Scenarios:

David Weinstock (*Harvard University*)

1.10 – 1.50pm Emergency Management from the CMCR perspective:

Joel Greenberger (*University of Pittsburgh*)

1.50 – 2.40pm Animal Models of Radiation Damage and Confounders:

Jacqueline Williams (*University of Rochester*) & **Tom MacVittie** (*University of Maryland*)

2.40 – 3.00pm Coffee Break

3.00pm – 4.45pm **Workshop 1**: *Biodosimetry and Biomarkers - Assessing the Need.* **(CME event)**

Short Presentations (15 minutes each) and Panel Discussion (30 minutes):

MODERATOR - **David Brenner** (*Columbia University*)

1. **David Brenner** (*Columbia University*): Why biodosimetry?
2. **Bob Terbrueggen** (*DxTerity Diagnostics Inc.*): High throughput multiplexed gene expression biodosimetry from a drop of blood
3. **Julian Whitelegge** (*University of California – Los Angeles*): Organ-specific Nrf-2 modulated biomarkers of early- and late-effects of radiation exposure in the mouse model
4. **Naduparambil Jacob** (*Ohio State University*): Development of a panel of miRNA biomarkers for radiation dose estimation
5. **Helen Turner** (*Columbia University*): The RABiT: Ultra-high throughput biodosimetry and beyond

5.15pm – 7.30pm *Welcome Reception*

THURSDAY AUGUST 1ST

8.30 – 9.00am The Challenge underlying Radiation Mitigation:

Nelson Chao (*Duke University*)

9.00 – 9.30am Mitigation Strategies:

André Gudkov (*Roswell Park Cancer Center*)

9.30 – 10.00am Coffee Break

10.00 – 11.45am **Workshop 2**: *Small Molecule Radiation Mitigators*: **(CME event)**

Short Presentations (15 minutes each) and Panel Discussion (30 minutes):

MODERATOR - **William McBride** (*University of California – Los Angeles*)

6. **Luigi Racioppi** (*Duke University*): Calcium/Calmodulin dependent kinase kinase 2: a novel target for medical countermeasures in radiation syndrome
7. **Robert Schiestl** (*University of California – Los Angeles*): A novel radiation mitigator
8. **James Palis** (*University of Rochester*): PGE2 mitigates the megakaryocyte lineage following sublethal radiation injury
9. **Paul Okunieff** (*University of Florida*): FGF-P promotes bone marrow recovery after irradiation
10. **William McBride** (*University of California – Los Angeles*): 4-Nitrophenylsulfonamides as mitigators of hematopoietic radiation damage

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LUNCH: 11.45pm – 1.00pm

1.00pm – 2.45pm **Workshop 3**: *Ligand-receptor Pathways Involved in Mitigation*: **(CME event)**

Short Presentations (15 minutes each) and Panel Discussion (30 minutes):

MODERATOR – **John Chute** (*Duke University*)

11. **Christine Barbon** (*Harvard University*): A combination with oral enrofloxacin and rBPI21 markedly increases survival of irradiated animals and provides significant amelioration of acute hematopoietic syndrome
12. **Diana Marquez-Garban** (*University of California – Los Angeles*): Development of estrogen receptor-beta ligands as medical radiation mitigators
13. **Andrei Gudkov** (*Roswell Park Cancer Center*): Randomized, blinded placebo-controlled GLP/GCP study validates efficacy of Toll-like receptor 5 agonist Entolimod (CBLB502) as a mitigator of lethal radiation injury in 179 non-human primates
14. **Alexander Shakov** (*Cleveland Biolabs*): Prevention and mitigation of acute radiation syndrome in mice by synthetic agonists of Toll-like receptor 2 (TLR2) mimicking lipopeptide of mycoplasma
15. **Zoya Gluzman-Poltorak** (*Neumedicines*): Recombinant human interleukin-12 (rHuIL-12) increases survival in mice and non-human primates

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2.45 – 3.15pm Coffee Break

3.15 – 5.00pm **Workshop 4**: *Cell Replacement Approaches for Radiation Mitigation*: **(CME event)**

Short Presentations (15 minutes each) and Panel Discussion (30 minutes):

MODERATOR - **Chandan Guha** (*Albert Einstein College*)

16. **John Chute** (*Duke University*): Radiation Induces Expression of Growth Factor Receptor-Bound Protein 10 (Grb10) Expression in Hematopoietic Stem Cells
17. **Jason Butler** (*Weill Cornell Medical College*): Endothelial cell transplantation for mitigation of life-threatening radiation-induced hematopoietic suppression
18. **Chandan Guha** (*Albert Einstein College*): Macrophage-derived regenerative factors in the mitigation of radiation induced gastrointestinal syndrome
19. **Kei Iwamoto** (*University of California – Los Angeles*): Correction of Radiation-Induced Skin Wound Healing Deficits with Marrow-Derived Mesenchymal Cells
20. **Benny Chen** (*Duke University*): Delayed wound healing after whole body irradiation is reversed by bone marrow transplantation

5.30 – 7.00pm *Poster Session and Reception* *(light refreshments)*

Poster Presentations Include:

P1.1	Bolduc, David	AFRRI	Testing Radiation-Injury Estimation Algorithms using Blood Parameters from a Nonhuman Primate Model: A Pilot Study
P1.2	Dainiak, Nicholas	Yale University	Correlation of nuclear abnormalities in myeloid cells with estimated whole-body dose of radiation received during the Y-12 criticality accident
P1.3	DeBenedetto, Anna	University of Rochester	Individuals With Impaired Skin Barrier Function May Be A Vulnerable Population For Radiation Damage
P1.4	Schaue, Dorthe	UCLA	Autofluorescence as a tool to monitor radiation exposure and mitigation
P1.5	Shaowen Hu	NASA	Modeling the blood cell kinetics following radiation exposure--potential use for dose assessment
P1.6	Vidyasagar, Sadasivan	University of Florida	Anoctamin 1: A potential marker for radiotoxicity
P2.1	Cacalano, Nicholas	UCLA	Screen for radiation mitigators that act through the STAT3 pathway
P2.2	Chen, Benny	Duke University	A novel nanoparticle platelet analogue mitigates radiation-induced thrombocytopenia.
P2.3	Danilova, Nadia	UCLA	Zebrafish model for the evaluation and mechanistic studies of radio-mitigators.
P2.4	Lento, William	Duke University	Loss of beta catenin triggers oxidative stress and impairs hematopoietic stem cell regeneration in vivo
P2.5	Greenberger, Joel	University of Pittsburgh	Delivery of Ionizing Irradiation Mitigator, JP4-039, by Biodegradable Skin Patches
P3.1	Cline, Mark	Wake Forest University	Determination of an optimal subcutaneous dose of MnTnHex-2-PyP5+ in Non-Human Primates
P3.2	Gluzman-Poltorak, Zoya	Neumedicines	Enhanced recovery from radiation-induced neutropenia and thrombocytopenia in rHuIL-12-treated NHPs
P3.3	Medhora, Meetha	Medical College of Wisconsin	Histological marker for delayed radiation injury to the lung
P3.4	Ting, Jenny	Duke University	Inflammation and Radiation-Induced Injury
P3.5	Karsunky, Holger	Cellerant Therapeutics	Development of CLT-008, a novel universal myeloid cell therapeutic for the treatment of neutropenia caused by exposure to radiation
P4.1	Chute, John	Duke University	Bone Marrow Endothelial Cell-Derived Mitigators of Radiation Sickness
P4.2	Quarmyne, Mamle	Duke University	Protein Tyrosine Phosphatase Sigma (PTPS) Regulates Hematopoietic Stem Cell (HSC) Differentiation and PTPS (-) cells are highly enriched for HSCs
P4.3	Greenberger, Joel	University of Pittsburgh	Late irradiation pulmonary fibrosis is ameliorated by the water soluble radiation mitigator MMS350 administered in drinking water.
P5.1	Calvi, Laura	University of Rochester	Long term hematopoietic stem cell dysfunction following low dose sublethal radiation injury
P5.2	Lee, Chang-Lung	Duke University	The tumor suppressor p53 acts during total-body irradiation to promote clonal expansion of thymic lymphomas with dysregulated Notch signaling
P5.3	Lento, William	Duke University	Long-term effects of total body irradiation (TBI) in the hematopoietic compartment of non-human primates (NHP).
P5.4	Mahmood, Javed	University of Toronto	Targeting the renin-angiotensin system combined with an antioxidant mitigates radiation-induced lung damage
P5.5	Jackson, Isabel	University of Maryland	MnTnHex-2-PyP5+ exerts a protective role on irradiated lung tissues through regulation of PTEN signaling

FRIDAY AUGUST 2ND

8.30 – 10.15am **Workshop 5**: *Mitigation and Treatment of Late Effects*: **(CME event)**

Short Presentations (15 minutes each) and Panel Discussion (30 minutes):

MODERATOR - **Jacqueline Williams** (*University of Rochester*)

21. **William McBride** (*University of California – Los Angeles*): Late effects of hematopoietic damage
22. **Julie Ryan** (*University of Rochester*): Combined radiation skin injury is reduced by local administration of tetrahydrocurcumin or IL-12
23. **Isabel Jackson** (*University of Maryland*): Development and refinement of murine model (s) of radiation pneumonitis/ fibrosis to link with non-human primate and human pulmonary responses to radiation
24. **Mark Cline** (*Wake Forest University*): Multisystemic Late Effects of Radiation Injury in Nonhuman Primates
25. **Jacob Finkelstein** (*University of Rochester*): Lung irradiation increased susceptibility to infection with influenza A virus and impaired the ability to complete recovery

10.15 – 10.45am Coffee Break

10.45 – 12.30pm **Identification of the Grand Challenges in Radiation Mitigation and Treatment**

MODERATOR: **William McBride** (*University of California – Los Angeles*)

PANELISTS: **Richard Hatchett** (*DHHS/BARDA*), **Nelson Chao** (*Duke University*), and **Bert Maidment** (*DHHS/NIAID*)

12.30pm Meeting Closes

Novel Radiation mitigators and anticancer drugs

Yelena Rivina and Robert H. Schiestl

Departments of Pathology, Environmental Health and Radiation Oncology,
UCLA Medical School and School of Public Health

The possibility of a radiation disaster from a nuclear detonation or accident has existed for over 50 years and spawned much of the basic research in radiobiology in the 1950-60s. Here we report on the development of two novel radiation countermeasure therapies: Yel002 and CJ010 a Yel001 analog. These small, biologically active, drug-like molecules were uncovered in the DEL high throughput assay reducing radiation-induced cyto- and geno-toxicity in yeast. Radiation-modulating activity was further confirmed in the yeast plate-based DEL Assay: addition of either Yel002 or CJ010 to irradiated cultures reduced cell death and genomic instability. Both reduce radiation induced microhomology mediated recombination to the unirradiated level. Further, Yel002 and CJ010 compounds increase survival to 75% in vivo following an LD100/30 dose of ionizing radiation with the first therapeutic subcutaneous injection administered 24 hours post exposure followed by injections at 48,72,96, and 120 hours. A dose response experiment yielded a DMF of 1.15. Additionally, treatment with Yel001 and Yel002 compounds reduces radiation-induced leukemia from 90% to 50% and 40% respectively. Of note, treatment with either Yel001 or Yel002 reduced spontaneous leukemia rate from 10% to 0%. Treatment with Yel002 following irradiation accelerates the recovery of the hematopoietic cells after sub-lethal exposures. Furthermore, Yel002 reduces radiation-induced senescence in primary human keratinocytes two fold and the spontaneous frequency by 15%. In addition, treatment with Yel002 reduces I131 induced toxicity as well as genotoxicity. Toxicity has not been observed in neither in vitro nor in vivo administrations nor in a two-generation teratogenicity study. In addition, proteomics indicate that Yel002 highly significantly induces the ATM signaling pathway, homologous recombination, nonhomologous end joining, base excision repair, DNA damage binding and chromosome maintenance proteins. It is a novel paradigm for a radiation mitigator and anticancer agent to induce DNA repair.

FGF-P promotes bone marrow recovery after irradiation

P. Okunieff, M. Zhang, S. Swarts
University of Florida

Radiation-induced bone marrow damage can be fatal even at low doses; however, members of the fibroblast growth factor (FGF) family have been shown to protect against such damage. Since FGF-2 is the only growth factor used universally in serum–free media to support the growth of all types of stem cells, we designed and synthesized a peptide analog of FGF-2 (FGF-P) and examined its mitigatory effect on bone marrow syndrome and progenitor cell maturation. C57BL/6 mice were exposed to different single doses of FGF-P (0.25 to 20 mg/kg) 24 hr after total body irradiation (TBI, 7.5 and 7.75 Gy). At low FGF-P doses (≤2 mg/kg), the survival rate was substantially increased; tachyphylaxis occurred at the higher FGF-P doses. Among animals receiving 0.25 to 2 mg/kg, 15/24 vs 0/6 control animals were alive at 30 days ($P < 0.01$). To examine the effects of FGF-P on progenitor maturation, we treated irradiated NIH Swiss mice (3 Gy TBI) with 10 daily doses of FGF-P (5 mg/kg). The blood differential counts were monitored, and the long-term hematopoietic stem cells (LT-HSC) and pro-B and pre-B cells in bone marrow were analyzed.

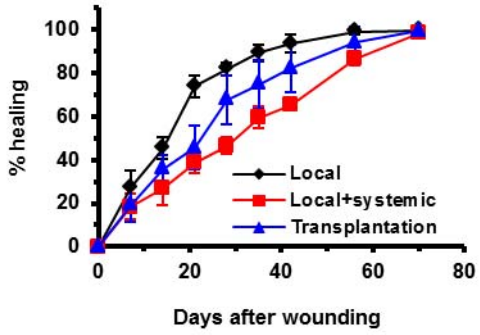
We found the following results: **(1)** FGF-P in culture media stimulated the growth of bone marrow cells harvested from mice exposed to 3 Gy; **(2)** on day 25 after 6 Gy TBI, the number of white blood cells and granulocytes was higher in the FGF-P group; and **(3)** FGF-P treatment *in vivo* increased LT-HSC, pro-B, and pre-B cells in the bone marrow.

These results reveal the underlying mechanism by which FGF-P, given 24 or more hours after a potentially lethal dose of radiation, rescued a significant percentage of the exposed mice. The increase of LT-HSC in bone marrow led to an increase of pro-B and pre-B cells and then white blood cells and granulocytes, thereby enhancing immunity against infection and decreasing mortality.

This study was funded in part by NIH/NIAID 1R43AI098330-01 (Zhang), NIH/NIAID 1RC1AU078519 (Zhang), and NIH/NIAID 5U19AI067733-05 (Okunieff).

Delayed wound healing after whole body irradiation is reversed by bone marrow transplantation. Benny J. Chen, Wei Huang, Divino DeOliveria, Dunhua Zhou, Yiqun Jiao, and Nelson J. Chao. Division of Hematologic Malignancies and Cellular Therapy/BMT, Duke University Medical Center, Durham, NC (This study was funded by a grant from NIAID, AI080525)

Local and systemic radiation can cause dermal lesion directly and delay the healing of surgical wound. In this study, we investigated specifically how whole body radiation affected the healing of surgical wound using two different wound healing models. In the first model, surgical wounds were induced by a 2 mm surgical punch in the ear pinnae of MRL/MpJ mice. Pictures of the wounds were taken and the sizes of the ear punch wounds were quantified by using Photoshop software. Local radiation was delivered by using a special constructed jig. Using this model, we demonstrated that 10 Gy of local radiation significantly delayed the healing of ear punch wounds (28±2.2% vs. 66±2% at day 7 and76±5.6% vs. 96±2.3% at day 28; $P<0.05$). Addition of sublethal whole body irradiation (7 Gy) further delayed the healing of ear punch wounds (16±6.6% at day 7 and 44±8.1% at day 28; $P<0.05$ compared with local irradiation alone). The delay in wound healing could be at least partly reversed by bone marrow transplantation (55±6.7 vs. 44±8.1 at day 28 and 97±3.3 vs. 87±8.2% at day 56, $P<0.05$). In the second model, full thickness surgical wounds were induced on the back of dorsal skin in C57BL/6 mice. Similar effect of whole body irradiation on the speed of wound healing was observed. Again, bone marrow transplantation significantly facilitated the speed of wound closure in this full thickness cutaneous wound model. Taken together, the data from two different models demonstrate that whole body irradiation affects the speed of wound healing and bone marrow transplantation is able to reverse this negative effect.



Combined radiation skin injury is reduced by local administration of tetrahydrocurcumin or IL-12

Julie L. Ryan, PhD, MPH[1,2], Doug Milano-Johnson[1], Scott Gerber, PhD[3], Alice P. Pentland, MD[1], Jacqueline P. Williams, PhD[2], Edith M. Lord, PhD[3]
Departments of [1]Dermatology, [2]Radiation Oncology, [3]Microbiology & Immunology, University of Rochester Medical Center, Rochester, NY

Background: Combined radiation skin injury results in increased transepidermal water loss, delayed healing, and altered inflammatory and antioxidant response. We examined the ability of topical tetrahydrocurcumin (TH-curcumin) or intradermal IL-12 to reduce the severity of combined radiation skin injury.

Methods: Hairless C57BL6 mice (N=18) were subjected to 6 Gy TBI (Cs-137) + concurrent 7.5 mm diameter 40 Gy β burn (Sr-90). Mice were split into three groups: a) untreated; b) topically administered 10% TH-curcumin for seven days starting 48 hours post-radiation; or c) intradermally injected IL-12 (100 ng) at 48 hours post-radiation. Clinical effects of the combined injury were characterized by skin toxicity scores, transepidermal water loss (TEWL), and burn healing image analyses. Skin and blood were harvested at 4, 7, 14, 21, and 60 days post-radiation. Real-time RTPCR assessed alterations in inflammatory and antioxidant responses in the skin. Whole blood counts were analyzed by FACS.

Results: TBI+β resulted in severe skin toxicity (skin score = 3.3) and high TEWL (27.8 g/hm^2). TH-curcumin and IL-12 significantly reduced TEWL (15.6 g/hm^2 and 15.1 g/hm^2) and skin toxicity (2.4 and 2.6) ($p<0.04$). Repeated measures ANOVA showed that both agents reduced the burn size over time ($p\leq0.003$). TH-curcumin and IL-12 altered mRNA expression at the TBI+β site through up-regulation of IL-10, IL-4, and TSLP and down-regulation of iNOS and SOD3 ($p\leq0.05$). No differences in whole blood cell counts confirmed that both TH-curcumin and IL-12 were localized to the skin.

Conclusions: Topical TH-curcumin or intradermal IL-12 reduced the severity of combined radiation injury. These data suggest that anti-inflammatory and Th2 mechanisms, as well as balancing antioxidant responses, may be important in mitigation of radiation skin injury. Further research is required to determine the exact mechanism these two agents.

Multisystemic Late Effects of Radiation Injury in Nonhuman Primates

Cline JM[a], Dugan G[a], Lees C[a], Willey J[b], Bourland D[b], Hanbury D[a], Register TC[a], MacVittie T[c], Chao NJ[d]

[a]Department of Pathology, Section on Comparative Medicine and [b]Department of Radiation Oncology, Wake Forest School of Medicine, Winston-Salem, NC; [c]Department of Radiation Oncology, University of Maryland, School of Medicine, Baltimore, MD; and [d]Division of Hematologic Malignancies and Cellular Therapy, Duke University Medical Center, Durham, NC

Introduction/Methods: The major burden of radiation injury among survivors lies in long-term effects on multiple organ systems. We present here the clinical and pathologic long-term adverse effects of single dose whole body exposure at 6.5 to 8.4 Gy in 34 male rhesus macaques exposed at 2.5-11 years of age and observed for 2 to 7 years after exposure. Radiation was administered by linear accelerator at 60 cGy/min in two opposed fields. Observations include clinical examinations, imaging (CT and MRI scans), hematology, clinical chemistry, and necropsy.

Results: Findings to date include the anticipated effects of immunologic impairment, testicular atrophy, cataracts, mild azotemia, and a higher incidence of malignant neoplasms. We have also observed adverse effects that are somewhat surprising for the doses given, including myocardial fibrosis, pulmonary fibrosis, osteopenia, and diabetes. Immunologic impairment consisted of marked atrophy of lymphoid organs (lymph nodes, spleen, thymus), impaired antibody response to pneumococcus vaccine, persistent reductions in peripheral T, B, NK and macrophage cell counts, and oral/esophageal candidiasis. Myocardial fibrosis was identified in 6/11 irradiated animals dying over the 7-year period. Pulmonary fibrosis was seen in doses as low as 7.2 Gy, at 3 years post-irradiation, and incident pulmonary lesions have been identified by CT. Bone mineral density was lowest (25% below controls at the femoral neck, $p<0.05$) in animals irradiated after puberty. Diabetes was defined by hemoglobin A1c >6%, was seen in 10/34 animals, was highly correlated with body weight and irradiation status ($p<0.0001$); islet amyloidosis was found in two diabetic animals at necropsy.

Conclusions: Observations of this unique cohort indicate (1) that long-term time-by-dose interactions occur, leading to disease manifestations at doses lower than would be anticipated from acute or intermediate-term studies; and (2) that multiple organ systems are impaired, including endocrine, bone and cardiovascular injury.

Supported by the NIH/NIAID through the Radiation Countermeasures Center of Research Excellence (U19 AI67798) Drs. Nelson Chao (PI), Mark Cline (Primate Core Leader)

Modeling the blood cell kinetics following radiation exposure--potential use for dose assessment

Shaowen Hu[1] and Francis A. Cucinotta[2]

[1]*Universities Space Research Association, Division of Space Life Sciences, Houston, TX 77058*

[2]*NASA, Lyndon B. Johnson Space Center, Houston, TX 77058,USA*

Peripheral blood cell depression is well known as a robust and high throughput indicator to assess the extent of radiation induced injury. In this study we apply a set of biomathematical models of hemotopoiesis to analyze the granulocyte and lymphocyte changes in victims exposed to high dose radiation. The coarse-grained architecture of cellular replication and production and implicit cellular regulation mechanisms used in this model make it straightforward to incorporate various radiation conditions. Model simulations with reported absorbed doses as inputs are shown to qualitatively and quantitatively describe a wide range of accidental data in vastly different scenarios. In addition, the absolute lymphocyte counts and the depletion rate constants calculated by this model show good correlation with some widely recognized dose assessment methods such as the Guskova's and Goan's formulas. This demonstrates the potential to use these models as alternative tools for the assessment of radiation injury in the case of large-scale radiation disaster. Algorithms have been developed to estimate the absorbed dose based on the clinical hematological data after radiation exposure, and have been implemented in a software package ARRBOD, which can be run online or on a Windows computer. This work is supported by NASA Space Radiation Risk Assessment Project.

A novel nanoparticle platelet analogue mitigates radiation-induced thrombocytopenia.

Benny J. Chen, Anthony Sung, Divino Deoliveira, Yiqun Jiao, Dunhua Zhou, and Nelson J. Chao. Division of Hematologic Malignancies and Cellular Therapy/BMT, Duke University Medical Center, Durham, NC (This study was funded by a pilot grant from NIAID, U19 AI067798)

Bleeding resulting from thrombocytopenia is a life-threatening condition after radiation injury. Current treatment requires transfusion of allogeneic platelets. We tested the effects of a novel platelet substitute composed of polymerized human albumin nanospheres coated with human fibrinogen (Fibrinoplate-S) on radiation-induced thrombocytopenia. We first studied the effect of Fibrinoplate-S on bleeding time after irradiation. BALB/c mice were lethally irradiated (7.5 Gy) and treated with three doses of Fibrinoplate-S (8 mg/kg, i.v.) at 24 hours, 5 days, and 10 days after irradiation. The bleeding time (in seconds) was significantly shortened after treatment with Fibrinoplate-S when compared with the saline control (44.8±20.4 vs. 69.9±30.8 at day +5, 63.6±24.6 vs. 139.9±55.9 at day +10, 67.2±7.3 vs. 145±43.9 at day +15, $P<0.05$ at all timepoints). To test for a survival advantage, BALB/c mice were irradiated with 7.25 Gy and then treated with Fibrinoplate-S. As shown in Fig. 1, Fibrinoplate-S rescued 15 out of 20 mice (75%) while only 7 out of 20 mice (35%) in the saline control group survived more than 50 days after irradiation ($P<0.05$). To further determine whether Fibrinoplate-S mediates its radioprotective effects through bridging the thrombocytopenic phase, a second animal model was used. In this model, BALB/c mice were first sublethally irradiated (7 Gy) and then administered with platelet-depleting anti-CD41 antibody. As shown in Fig. 2, only 5% (1 of 20) of the sublethally irradiated mice injected with anti-CD41 antibody survived more than 100 days in the saline control group. By contrast, 55 % of the mice treated with Fibrinoplate-S survived ($P<0.05$).The survival in the Fibrinoplate-S-treated group was close to that in the sublethally irradiated mice without receiving platelet-depleting anti-CD41 antibody (55%% vs. 70%). These data demonstrate that Fibrinoplate-S is able to shorten bleeding time and improve survival through bridging thrombocytopenic phase after total body irradiation.

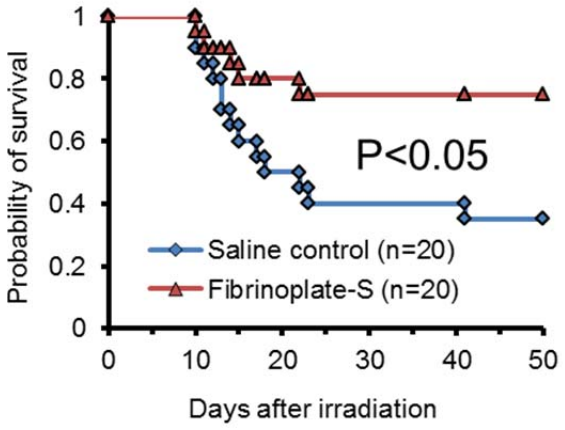


Fig. 1.

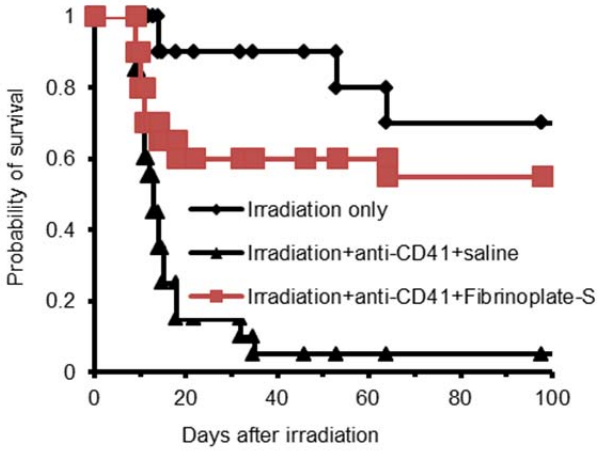


Fig. 2

Zebrafish model for the evaluation and mechanistic studies of radio-mitigators

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We are developing zebrafish as an alternative cheaper model for the study of radioprotective drugs. Hundreds of embryos/larva can be irradiated in one Petri dish. To treat embryos with drugs, most compounds can be simply added to fish water. Effects of drugs can be evaluated in live zebrafish embryos that are transparent during early stages. Blood cells are visible in embryos even with a simple microscope. In addition, many transgenic lines with expression of fluorescent markers in various blood lineages are available in zebrafish so that different blood cells can be traced in live embryos. Similar to mammals, hematopoietic organs are the most sensitive targets in zebrafish. In adults, head kidney, which is bone marrow analog in zebrafish, can be excised and analyzed for cells of various lineages.

Several laboratories at the UCLA are involved in the identification of compounds that can mitigate radiation damage. Several compounds have been discovered using cellular systems and murine models. They include compounds 360 and 512 from the lab of William McBride, glycyrrhizic acid (GA) from Genhong Cheng lab, and Yel002 from Robert Schiestl lab.

To demonstrate the feasibility of zebrafish for the development of radioprotective drugs, we tested these compounds in irradiated zebrafish. We found that all these compounds have radioprotective effects in zebrafish. The effect of these compounds and their combinations on zebrafish survival, blood lineages, and inflammation will be presented.

Acknowledgments

This work was supported by a grant from UCLA Center for Biological Radiation Mitigators.

Delivery of Ionizing Irradiation Mitigator, JP4-039, by Biodegradable Skin Patches

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A highly effective mitochondrial targeted GS-nitroxide, JP4-039, has been demonstrated to mitigate total body irradiation damage when delivered intravenously up to 72 h after the LD 50/30 dose of total body irradiation to C57BL/6NTac mice. We now demonstrate topical/transdermal delivery by biodegradable micro-needle skin patches. Pharmacokinetics of I.V. drug delivery were compared with skin patch delivery using pharmacokinetics measurements of a fluorochrome labeled drug analog, JP4-039-BODIPY. JP4-039-BODIPY was itself an effective radiation mitigator when delivered I.V. 24 h after the LD 50/30 dose of total body irradiation. Pharmacokinetics of 10 mg/kg of JP4-039 delivered either I.V. or by skin patch was similar with respect to plasma clearance within 1 h, and lung, intestine, liver, and kidney clearance within 2 h. Administration of JP4-039 by biodegradable skin patch compared to I.V. at 24 h after the LD 50/30 dose of total body irradiation resulted in significant improvement in survival. Transdermal/biodegradable skin patch delivery of a potent and safe radiation mitigator should facilitate quantifiable and convenient administration both in the setting of mass casualties for radiation counter terrorism and also in clinical normal tissue radiation protection during fractionated radiotherapy.

Center for Medical Countermeasures Against Radiation, U19-A1068021

Determination of an optimal subcutaneous dose of MnTnHex-2-PyP5+ in Non-Human Primates

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Introduction: Radiation-induced pulmonary injury causes substantial morbidity and mortality in accidentally and therapeutically exposed individuals. We seek to develop a medical countermeasure to mitigate radiation induced pulmonary fibrosis for which currently there is no treatment. MnTnHex-2-PyP5+ (hexyl) is a potent lipophilic metalloporphyrin-based SOD mimetic that accumulates in mitochondria and crosses the blood brain barrier. It has been first investigated in rodent studies. This compound has demonstrated a beneficial effect in pulmonary radioprotection at lower doses (0.05 mg/kg) in rats and also in monkeys when administered 2 hours post irradiation. We have first determined what is the single and maximum tolerated dose (MTD) in mice as a base for the non-human primate studies. The non-human primate studies provide unique and necessary data that cannot be obtained by other means and are essential for forwarding drug into clinic. This dose escalation study was used to determine the maximum tolerated dose in rhesus macaques.

Methods: Single dose study - Macaques received a single dose of hexyl (0.125 -0.5 mg/kg) subcutaneously and were observed for any signs of toxicity. Once toxicity was noted the dose of hexyl was decreased 50%. A second animal was injected subcutaneously at the lower dose and observed for signs of toxicity. PK samples were collected at 15 min, 30, 1hr, 4hr, 12, 24 hr. Long term multiple dose - Three macaques received twice daily doses of hexyl (0.125 mg/kg) SQ for a period of 3 months and were observed for any signs of toxicity.

Results: For the single dose MTD signs of toxicity observed were severe lethargy, prolonged recovery from sedation, vomiting and hypotension. The dosage of hexyl was decreased twice by 50% before reaching a dosage with tolerable side effects (0.125 mg/kg). After 4 months of twice daily SQ administration of 0.125 mg/kg hexyl-treated animals were humanely euthanized. Histologic findings revealed pigment accumulation in Kupffer cells (3/3), and mild fibrosis and pigment deposition in the skin (macrophages) which is presumed to be drug accumulation. Other findings included a mild membranous glomerulopathy (2/3) which is considered a background change. Hypertrophy, zona fasciculata (2/3) was also noted and considered a possible stress effect. The tests showed mild degenerative changes in the seminiferous tubules (2/3) which may be seasonal, although a drug effect could not be ruled out.

Conclusion: The final dose of drug was two and a half-fold higher than the previous dose that already showed efficacy. We have demonstrated no evidence of toxicity from hexyl at the single or multiple subcutaneous doses of 0.125 mg/kg.

Supported by the NIH/NIAID through the Radiation Countermeasures Center of Research Excellence (U19 AI67798) Drs. Nelson Chao (PI), Mark Cline (Primate Core Leader)

Histological marker for delayed radiation injury to the lung

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Introduction: Pulmonary fibrosis is a 'late effect' of irradiation that can severely impair lung function. Fibrosis is difficult to measure biochemically since the marker, collagen, is also abundantly present in large pulmonary airways and blood vessels. Histological measurements are often semi-quantitative unless the fibrosis is abundant. Robust fibrosis does not develop for years after a single dose of irradiation to the whole thorax. An animal model to reliably and consistently detect late effects is essential to pursue the FDA animal rule and to develop countermeasures for mitigation.

Aim: Our goal is to develop sensitive markers in rodents to facilitate the development of countermeasures that can mitigate late effects in the lung.

Experimental procedures: Rats were treated with a single fraction of X-irradiation to the thorax ranging from 10-15 Gy. Lungs were harvested at intervals from 3 months up to 1 year. Hematoxylin and eosin sections were prepared and slides examined for markers of injury. Lung injury was also graded by standard tests such as breathing rate, collagen content, vascular injury, inflammatory cell infiltration and animal body weight.

Summary of results: We observed characteristic radiation-associated lesions that were rich in giant cells and macrophages containing cholesterol clefts in lungs of irradiated rats. These lesions were first observed after resolution of pneumonitis (~12 weeks), beginning at 21 weeks after thoracic irradiation. The number of cholesterol clefts increased with time. Lesions were associated with several indices of deterioration in lung structure and function.

Conclusions: We propose that alveolar lesions with cholesterol clefts may be used as a histological marker of the severity of late effects of radiation to the lungs and to study mitigation in rats. Similar lesions have been reported in the lungs of one strain of irradiated mice and in patients following radiotherapy.

Funding: NIH/NIAID RC-1 AI 81294, agreement U19 AI67734 and the Department of Radiation Oncology (MCW).

We thank Merck Inc. for providing enalapril.

DEVELOPMENT OF CLT-008, A NOVEL UNIVERSAL MYELOID CELL THERAPEUTIC FOR THE TREATMENT OF NEUTROPENIA CAUSED BY EXPOSURE TO RADIATION

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Cellerant has developed a novel universal cellular therapeutic for the treatment of the hematopoietic subsyndrome of the Acute Radiation Syndrome (ARS). CLT-008, human Myeloid Progenitor Cells (MPC), derived *ex vivo* from human adult hematopoietic stem cells has the ability to generate functional neutrophils *in vitro* and *in vivo*. We previously reported that in pre-clinical *in vivo* studies in mice using an animal analog product MPCs prevent fungal and bacterial infection, provide protection from lethal radiation and enable engraftment of low doses of stem cells. We have demonstrated that mouse MPC can be administered five to seven days after exposure to lethal doses of radiation (9 Gy and above) with significant survival benefit. The function of MPCs is not MHC restricted and no matching was necessary. CLT-008 (human myeloid progenitors) is being developed as an off-the-self product for the treatment of ARS under the Food and Drug Administration's Animal Rule guidance. Efficacy for approval will be demonstrated in two animal models and the safety will be demonstrated in human clinical trials. We have developed a scalable culture system for the human product using animal product-free medium and a defined cytokine to generate myeloid progenitors that are significantly depleted of long term reconstituting HSCs and lymphoid cells. Further, we have demonstrated that cryopreserved MPC maintain their colony formation potential and produce mature neutrophils when exposed to G-CSF in vitro. These neutrophils are indistinguishable by phenotype from peripheral blood neutrophils, respond to physiologic stimuli, release reactive oxygen species and possess phagocytotic activity. Using a mouse xenograft model we also have shown the potential of human MPCs to generate neutrophils *in vivo.* This human product CLT-008 is currently in two Phase 1/2 clinical trials: (a) patients undergoing cord blood transplantation after chemotherapy and radiation for the treatment of hematological malignancies and (b) patients receiving high-dose chemotherapy for the treatment of Acute Myeloid Leukemia. We have dosed over fifty patients to date. CLT-008 offers a novel approach to mitigate conditions of severe neutropenia and potentially provide life-saving therapy to victims that have been exposed to radiation.

This work was supported by funding from NIAID/NIH SBIR grant and CBMS (US Department of Defense). The advanced development of CLT-008 for ARS is currently being pursued under a contract with BARDA (US Department of Health and Human Services).

Late irradiation pulmonary fibrosis is ameliorated by the water soluble radiation mitigator MMS350 administered in drinking water.

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The irradiated C57Bl/6 murine lung displays an acute inflammatory phase (days 1to 21), followed by a latent period (days 21 to 125) and late organizing alveoitis/fibrosis (after day 125) We determined whether mice continuously treated with a water soluble small molecule radiation mitigator suffered less pulmonary fibrosis. C57BL/6NHsd mice were irradiated to 20 Gy to the pulmonary cavity and placed continuously on drinking water containing 400 uM MMS350 developed as a 2nd generation analog of dimethyl sulfoxide (DMSO) either before irradiation or 80 days after irradiation. Mice consumed an average of 463 ug of drug per day based on levels of water consumption. Mice were followed for changes in gene expression, percent of the lung displaying fibrosis, and migration of luciferase positive bone marrow stromal cells into the lungs. Histopathology revealed a significant decrease ($p < 0.0001$) in pulmonary fibrosis at day 200 measured by Optimus Imaging System in mice maintained on MMS-350 compared to irradiated control mice. There was decreased collagen by scoring of Masson's trichrome stained positive areas and decreased CD45+ inflammatory cells per 20 high powered fields scored per lung in MMS-350 treated mice compared to irradiated controls. No fibrosis or increased collagen was detected in control, acute or latent phase irradiated lung tissue and immunostaining for CD45 showed low numbers of CD45+ cells. There was also decreased migration of I.P. injected clonal cell lines of luciferase positive bone marrow stromal cells at day 150 into lungs of mice administered MMS350 compared to irradiated control mice. Mice drinking MMS350 had decreased lung expression of genes associated with pulmonary fibrosis including: MnSOD, TGF-B, Nrf2, NfkB, IGFbp7 and TLR4 during the late phase. Thus, administration of MMS350 in drinking water significantly decreases pulmonary fibrosis, collagen deposition, and accumulation of CD45+ inflammatory cells in lungs of 20 Gy thoracic irradiated C57BL/6NHsd mice. The water solubility and ease of administration of MMS-350 in drinking water makes long-term administration practical. Further investigations should determine whether this small molecule radiation mitigator may show efficacy in radiation counterterrorism and/or in clinical radiotherapy patients.

Center for Medical Countermeasures Against Radiation, U19-A1068021

Preparing for Irradiated Casualties after a Radiological/Nuclear Incident

Authors: Cullen Case Jr.[1], David Weinstock, M.D.[2], Nelson Chao, M.D.[3], John Chute, M.D.[3], Daniel Weisdorf, M.D.[4], Robert Krawisz[5], Julie Wilhauk[6], Dennis Confer, M.D.[1]
[1]National Marrow Donor Program, [2]Dana-Farber Cancer Institute, [3]Duke University Medical Center, [4]University of Minnesota Cancer Center, [5]American Society for Blood and Marrow Transplantation, [6]University of Kansas Hospital

WHAT IS THE RADIATION INJURY TREATMENT NETWORK (RITN)?

RITN is a voluntary consortium focused on preparing for and responding to a large incident that results in casualties with acute radiation syndrome. RITN was established through a collaboration between the National Marrow Donor Program and the American Society for Blood and Marrow Transplantation. RITN includes:

- 41 academic medical centers with expertise in managing patients with bone marrow toxicity, including hematopoietic stem cell transplantation
  a. 28 of these 41 are National Disaster Medical System (NDMS) centers
- Seven blood donor centers to facilitate blood collection and distribution
- Seven umbilical cord blood banks to distribute cord blood units

WHAT IS ACUTE RADIATION SYNDROME (ARS)?

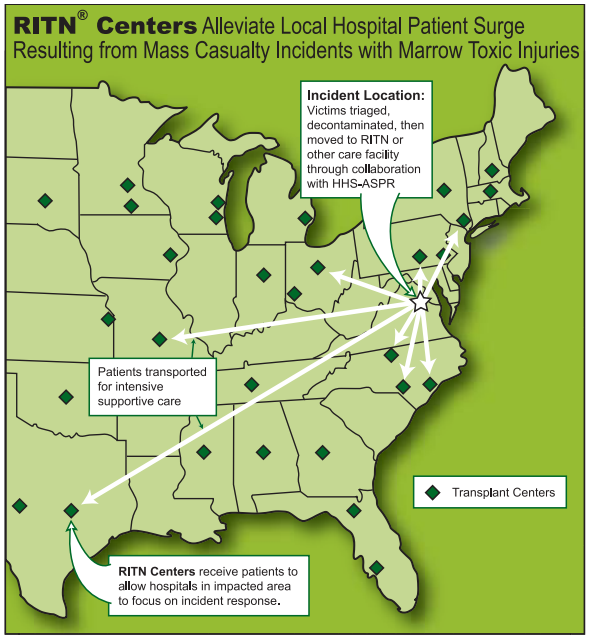
Acute radiation syndrome results from exposure to significant amounts of Ionizing Radiation (>2 Gy) and includes:

- Hematologic toxicity – bone marrow suppression manifested as leucopenia, anemia and thrombocytopenia
- Gastrointestinal toxicity – mucositis, nausea, vomiting and diarrhea
- Cutaneous toxicity – partial and full-thickness burns
- Neurovascular toxicity – autonomic instability, cardiovascular collapse

Note: Exposure to some chemicals (e.g. mustard agent) can cause a similar syndrome

PREPARATION ACTIVITIES

- Development of admission and treatment guidelines
- All participating centers have an emergency operations plan
- Centers integrate with hospital and local emergency planners
- Centers conduct an annual disaster response tabletop exercise
- Education of health care professionals:
  a. Basic Radiation Training (over 2300 trained since 2006)
  b. Grand Rounds education of medical staff
  c. Radiation Emergency Assistance Center and Training Site (REAC/TS) (110 since 2008)
- Data collection elements are incorporated into the standard NMDP Data Collection Protocol
- Emergency communications equipment distributed to all centers
  a. Government Emergency Telecommunications Service calling cards
  b. Satellite telephones



ADDITIONAL RESOURCES

1) National Security Staff Interagency Policy Coordination Subcommittee for Preparedness & Response to Radiological and Nuclear Threats (2010), Planning Guidance for Response to a Nuclear Detonation 2nd Edition, Washington, D.C., Government Printing Office.

2) Department of Health and Human Services-Assistant Secretary for Preparedness and Response, Radiological Dispersal Device Playbook, http://www.phe.gov/Preparedness/planning/playbooks/rdd/Pages/default.aspx, accessed 2/25/2011

3) Joel Ross, Cullen Case, Nelson Chao, et al. Radiation Injury Treatment Network (RITN): Healthcare professionals preparing for a mass casualty radiological or nuclear incident. Int. J. Radiat. Biol., Vol. 87, No. 5, PrePub Feb 2011

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6) Fliedner TM, Chao NJ, Case C Jr, et al. Stem Cells, Multi-organ Failure in Radiation Emergency Medical Preparedness: A US/European Consultation Workshop. Stem Cells, pre-publication.

7) Weinstock DM, Case C Jr, Bader JL, et al. Radiological and nuclear events: contingency planning for hematologist/oncologists. Blood, June 15, 2008;111 (12):5440–5445.

8) D. M. Weinstock, C. Case Jr, and D. L. Confer. Response: Radiologic and nuclear events. Blood, June 15, 2008; 111(12): 5758 – 5759.

PREPARATION ACTIVITIES continued

- Participation in national/international exercises and events:
  a. Top Officials IV (TOPOFF) (2007) – DHS Exercise
  b. Pinnacle07 (2007) – DHHS-ASPR Exercise
  c. ConvEx-3 (2008) – IAEA Exercise
  d. Republican National Convention (2008)
  e. Democratic National Convention (2008)
  f. National Level Exercise (NLE) 2010
- Memoranda of Understanding with key organizations:
  a. Department of Health and Human Services Assistant Secretary for Preparedness and Response (DHHS-ASPR)
  b. American Society for Blood and Marrow Transplantation (ASBMT)
  c. AABB Disasters Taskforce
  d. New England Center for Emergency Preparedness (NECEP)
- Partnerships with other key organizations:
  a. World Health Organization – Radiation Emergency Medical Preparedness and Assistance Network (WHO-REMPAN)
  b. European Group for Blood and Marrow Transplantation – Nuclear Accident Committee (EBMT-NAC)
  c. Radiation Emergency Assistance Center and Training Site (REAC/TS)

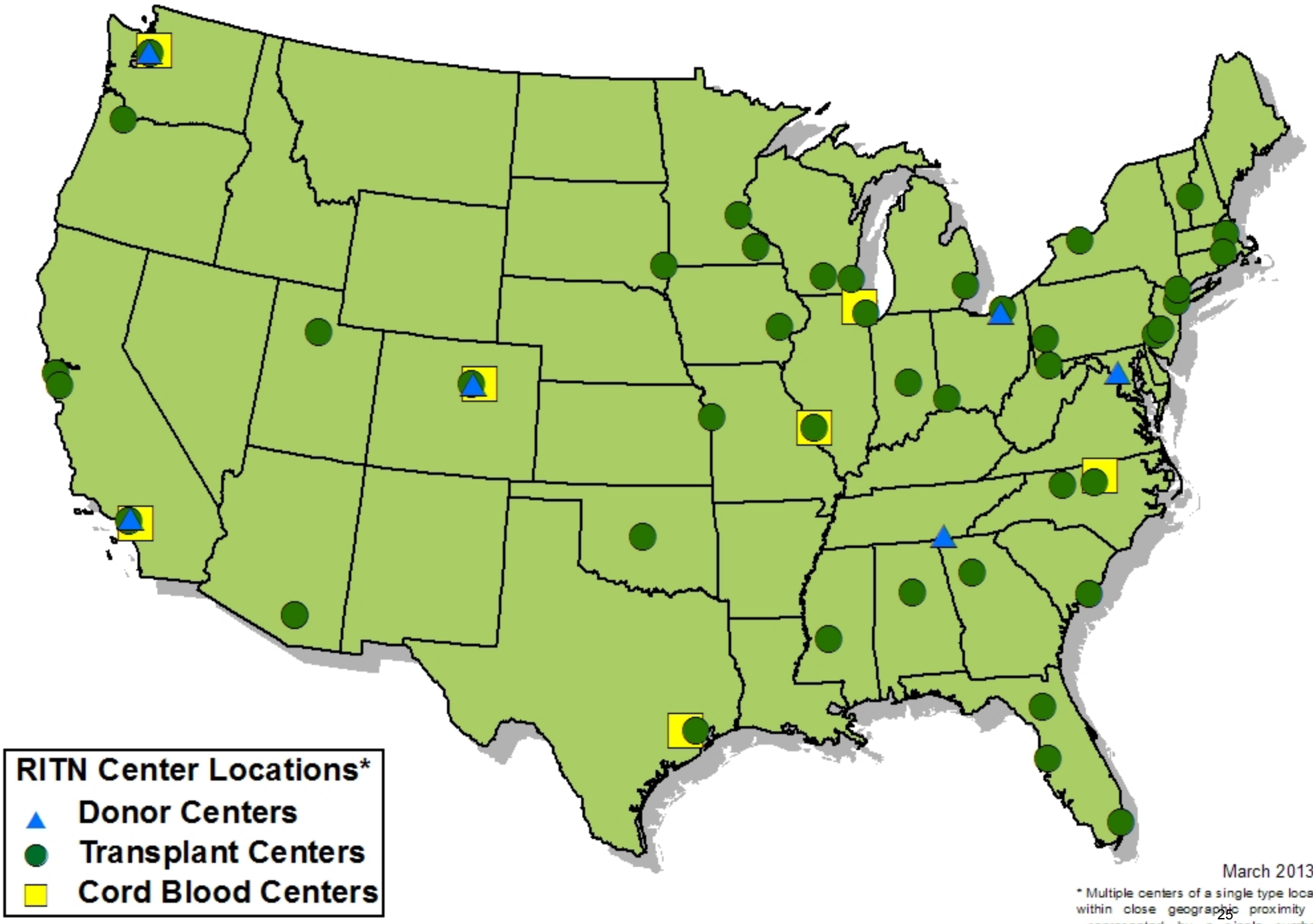
WHAT CAN BE EXPECTED FROM RITN CENTERS?

- Accept patient transfers to their institutions from the disaster area through established NDMS distribution processes
- Provide intensive supportive care for casualties with marrow toxic injuries
- Provide treatment expertise to practitioners caring for victims at other locations
- Travel to other hospitals or treatment locations to provide medical expertise
- Provide data on victims treated at their treatment facility
- Facilitate marrow transplantation for those casualties who require hematopoietic stem cell transplantation

ONGOING EFFORTS

- Strengthen relationship with NDMS to facilitate selective transfer of casualties with ARS
- Establish guidelines for management of pediatric casualties with ARS
- Support planning of outpatient and inpatient capabilities at non-RITN centers
- Organize scientific efforts around the development of novel radiation mitigators
- Education of non-physician hospital staff

National Marrow Donor Program, ATTN: Radiation Injury Treatment Network, 3001 Broadway St. N.E., Suite 100, Minneapolis, MN 55413 | www.RITN.net | RITN@nmdp.org | (612) 884-8276
This project has been supported by funding from the National Marrow Donor Program and the Department of the Navy, Office of Naval Research Grant #N00014-08-1-0204 to the National Marrow Donor Program.


RITN Center Locations*
Donor Centers
Transplant Centers
Cord Blood Centers
March 2013
* Multiple centers of a single type located within close geographic proximity are represented by a single symbol.

Radiation Injury Treatment Network

Transplant Centers			
AL - University of Alabama at Birmingham	P/A	NDMS	HPP
AZ - University Medical Center	P/A	NDMS	HPP
CA - UCSF Medical Center	P/A		
CA - City of Hope National Medical Center	P/A	NDMS	HPP
CA - Stanford Hospital and Clinics	P/A	NDMS	HPP
CO - Presbyterian/St. Lukes Medical Center		NDMS	HPP
FL - H. Lee Moffitt Cancer Center	P/A	NDMS	
FL - Shands Hospital at the University of Florida	P/A		HPP
FL - University of Miami		NDMS	HPP
GA - Northside Hospital			HPP
IA - University of Iowa Hospitals and Clinics	P/A	NDMS	HPP
IL - Rush University Medical Center			
IN - St. Francis Hospital and Health Centers		NDMS	HPP
KS - University of Kansas Medical Center		NDMS	HPP
MA - Children's Hospital of Boston	Ped	NDMS	HPP
MA - Dana Farber/Partners Cancer Care	P/A		HPP
MA - Massachusetts General Hospital		NDMS	HPP
MI - Barbara AnnKarmanos Cancer Center			
MN - Mayo Clinic Rochester	P/A	NDMS	HPP
MN - University of Minnesota BMT Program	P/A	NDMS	
MO - Barnes-Jewish Hospital at Washington			HPP
MO - The Children's Mercy Hospital	Ped	NDMS	HPP
MS - University of Mississippi Medical Center	P/A	NDMS	HPP
NC - UNC Hospitals	P/A	NDMS	HPP
NC - Wake Forest Univ Baptist Medical Center		NDMS	HPP
NC - Duke University Medical Center	P/A	NDMS	HPP
NH - Dartmouth-Hitchcock Medical Center			
NY - Strong Memorial Hospital	P/A	NDMS	
NY - Memorial Sloan-Kettering Cancer Center	P/A		HPP
NY - Mount Sinai Hospital	P/A	NDMS	HPP
NY - Westchester Medical Center		NDMS	HPP
OH - Cincinnati Children's Hospital Medical Center	Ped		
OH - Cleveland Clinic Foundation		NDMS	HPP
OH - University Hospitals of Case Medical Center		NDMS	HPP
OK - Oklahoma Univ. Medical Center & Childrens Hospital	P/A	NDMS	

Transplant Centers			
OR - Oregon Health & Science University	P/A	NDMS	HPP
PA - Children's Hospital of Philadelphia	Ped	NDMS	HPP
PA - Temple University		NDMS	HPP
PA - University of Pennsylvania Medical Center		NDMS	HPP
PA - Western Pennsylvania Cancer Institute		NDMS	
RI - Roger Williams Medical Center		NDMS	HPP
SC - Medical University of South Carolina		NDMS	HPP
SD - Avera McKennan Transplant Institute			HPP
TX - M.D. Anderson Cancer Center	P/A		HPP
TX - Texas Children's Hospital	Ped	NDMS	HPP
UT - LDS Hospital		NDMS	
UT - Primary Children's Medical Center	Ped	NDMS	HPP
UT - University of Utah	P/A	NDMS	HPP
WA - Seattle Cancer Care Alliance	P/A		
WV - West Virginia University Hospitals		NDMS	HPP
WI - Children's Hosp of WI & Midwest Children's CC	Ped	NDMS	HPP
WI - Froedtert Memorial Lutheran Hospital		NDMS	
WI - Univ. of Wisconsin at Madison	P/A	NDMS	HPP

Donor Centers

CA - City of Hope National Medical Center
CO - Colorado Marrow Donor Program
MD - C.W. Bill Young Marrow Donor Center
MI - NMDP operated donor center
TN - Blood Assurance
WA - Puget Sound Blood Center

Cord Blood Banks

CA - StemCyte International Cord Blood Center
CO - University of Colorado
IL - ITxM Cord Blood Services
MO - St. Louis Cord Blood Bank
NC - Carolinas Cord Blood Bank
TX - MD Anderson
WA - Puget Sound Blood Center

Ped = Pediatric patient only facility
P/A = Pediatric and adult capable facility
NDMS = National Disaster Medical System Center
HPP = Hospital Preparedness Program
If no capability is annotaed the facility is adult only

As of 12 Mar 2013

TC	**54**
DC	**6**
CBB	**7**
Total	**67**
Total NDMS Centers	**39**
% TCs that are NDMS	**72%**
Total HPP Centers	**39**
% TCs that are HPP	**72%**

http://www.remm.nlm.gov

What are the goals of this site?

- Provide guidance for health care providers, *primarily physicians*, about clinical diagnosis and treatment of radiation injury during radiological and nuclear emergencies
- Provide just-in-time, evidence-based, usable information with sufficient background and context to make complex issues understandable to those *without* formal radiation medicine expertise
- Provide web-based information that is also downloadable in advance, so that it would be available during an emergency if the internet is not accessible

Who produced this site?

- REMM was produced by the Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response, Office of Planning and Emergency Operations, in cooperation with the National Library of Medicine, Division of Specialized Information Services, with subject matter experts from the National Cancer Institute, the Centers for Disease Control and Prevention, and many US and international consultants.
- RITN consulted on the creation of several key pages, including the template for orders. http://www.remm.nlm.gov/adultorderform.htm

Can I download REMM to my mobile device and laptop?

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- Mobile device? Yes! http://www.remm.nlm.gov/downloadmremm.htm

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- Library of multimedia http://www.remm.nlm.gov/imagegallery.htm