Overview of the NIAID Radiation and Nuclear Countermeasures Program (RNCP)

Andrea L. DiCarlo, PhD
Director, NIAID RNCP

NIAID

NIAID RNCP Background

NIH Strategic Plan and Research Agenda for Medical Countermeasures Against Radiological and Nuclear Threats

Established in 2004, to accelerate development of medical countermeasures (MCMs) and biodosimetry devices for use during a radiation public health emergency

Mission

- Support early through advanced development of MCMs and biodosimetry
- Fund research via grants, cooperative agreements, contracts, Inter-agency agreements

Research Priorities

- Products to mitigate/treat injury when administered >24 hours post-irradiation
- Drugs to remove radionuclides (inhaled, ingested, absorbed radioactivity) from the body
- Biodosimetry tools and biomarkers for triage and guide medical management

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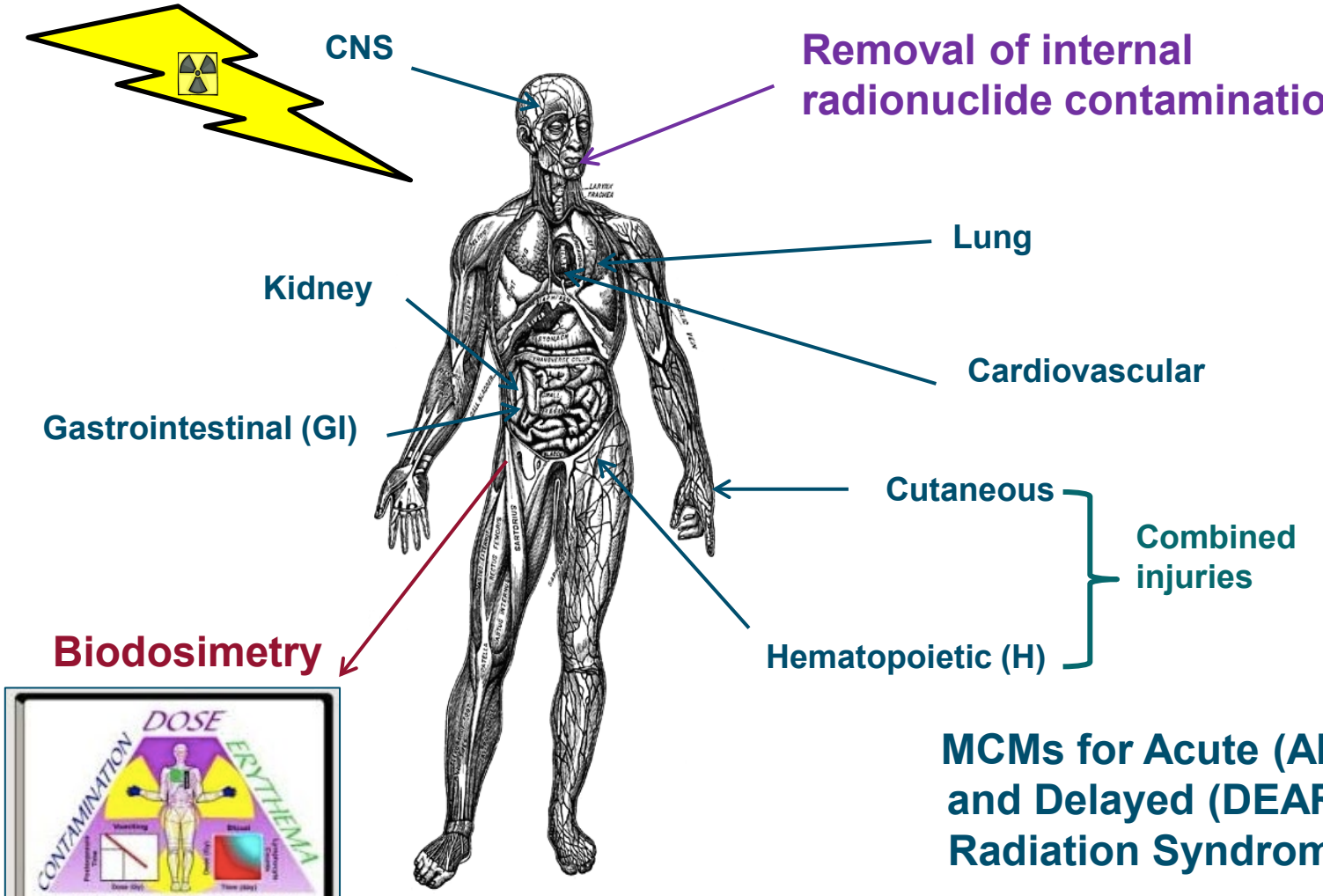
Possible Scenarios and Tissue Targets

- Detonation of a nuclear bomb or improvised nuclear device
- Nuclear power plant accident or attack
- Dirty bomb or other dispersal device
- Hidden radiation-emitting source
- Radionuclide release in air, water, food supply



MCMs for Acute (ARS) and Delayed (DEARE) Radiation Syndromes

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RNCP MCM Product Evaluations

Area Addressed	# Studies
Hematopoietic-ARS	>475
Gastrointestinal-ARS	96
Lung DEARE	80
Skin, cardiovascular, CNS, kidney, combined injuries	<120
Radionuclide decorporation	12
Biodosimetry	65

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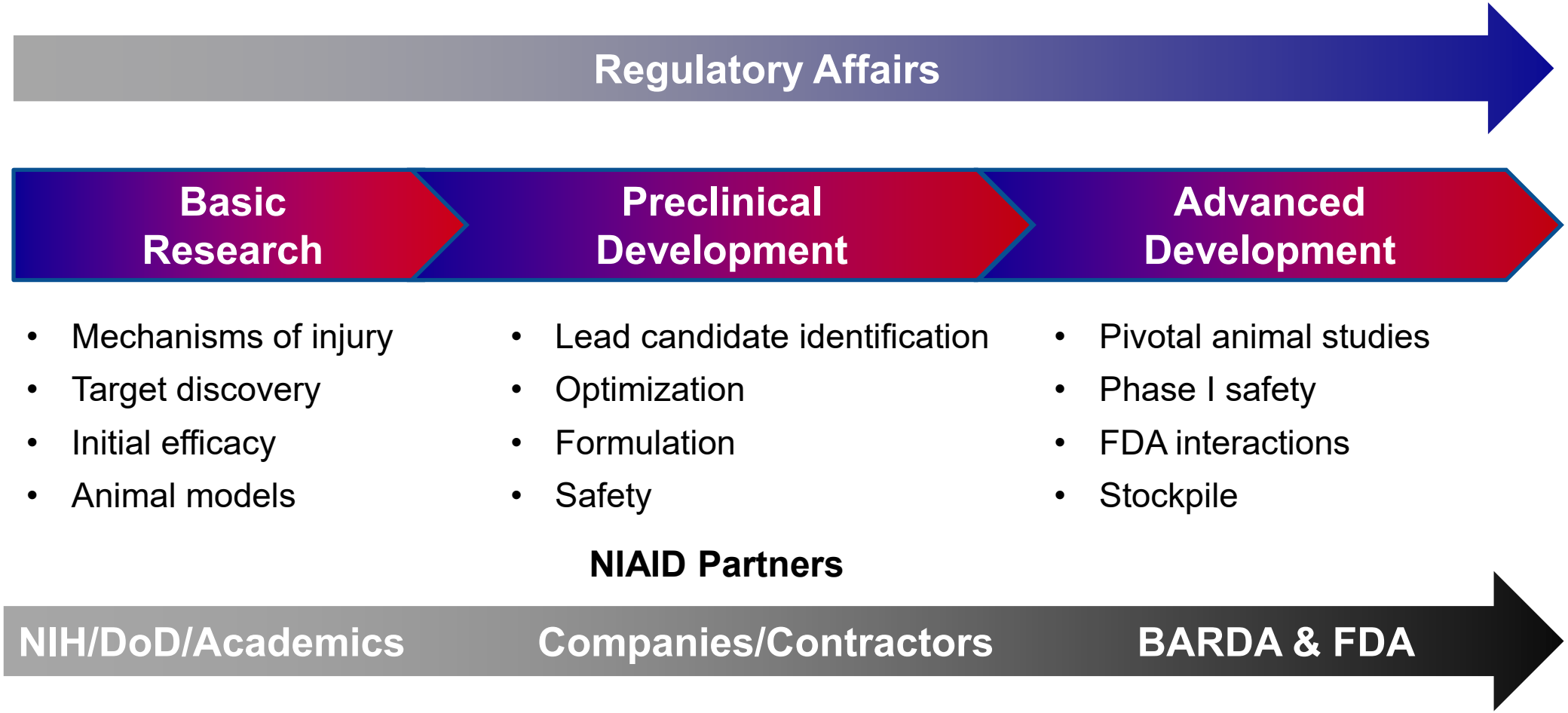
RNCP Radiation Research Continuum



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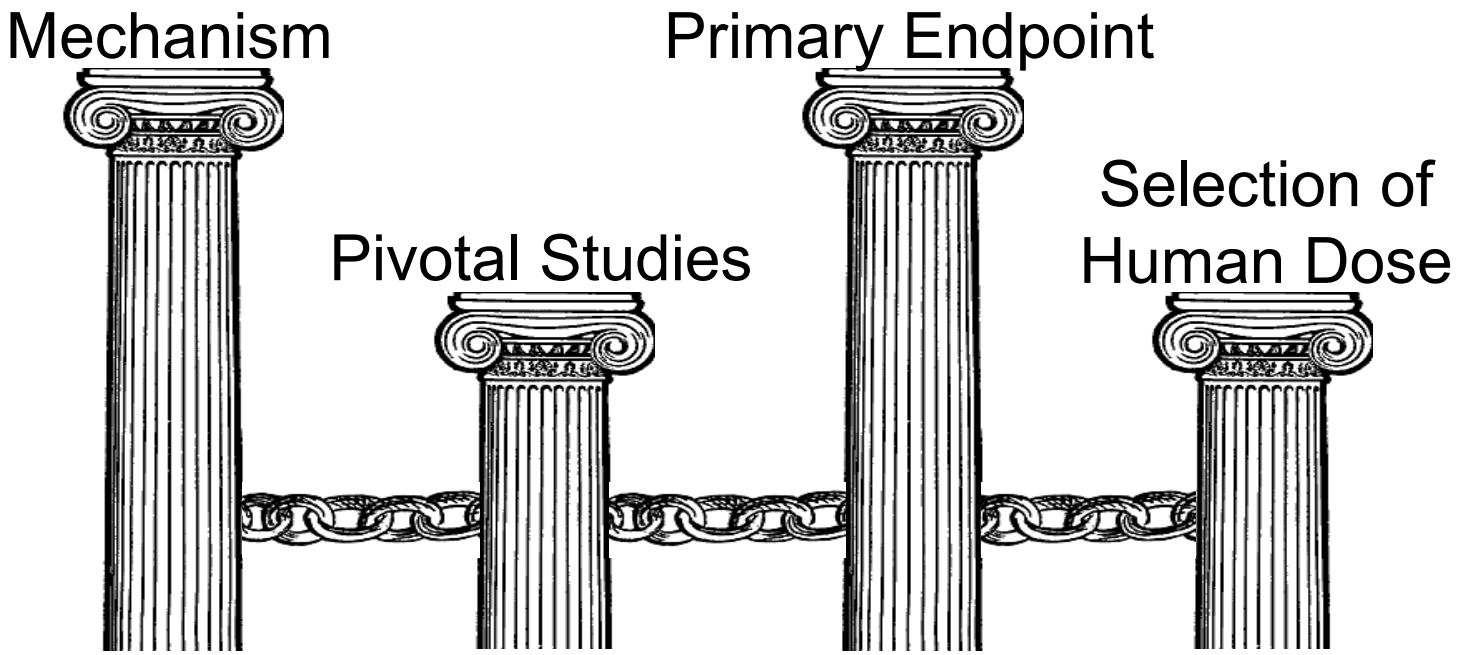
U.S. Food and Drug Administration (FDA) Animal Rule to License Radiation MCMs

21 CFR 314.600-650 drugs; 21 CFR 601.90-95 biologics

- When clinical trials are *not* ethical or feasible (e.g., lethal doses of radiation)
- Four key points to address



Clipart courtesy FCIT: http://etc.usf.edu/clipart

- Post-marketing requirements in event of use
- Biodosimetry devices do not use the Animal Rule

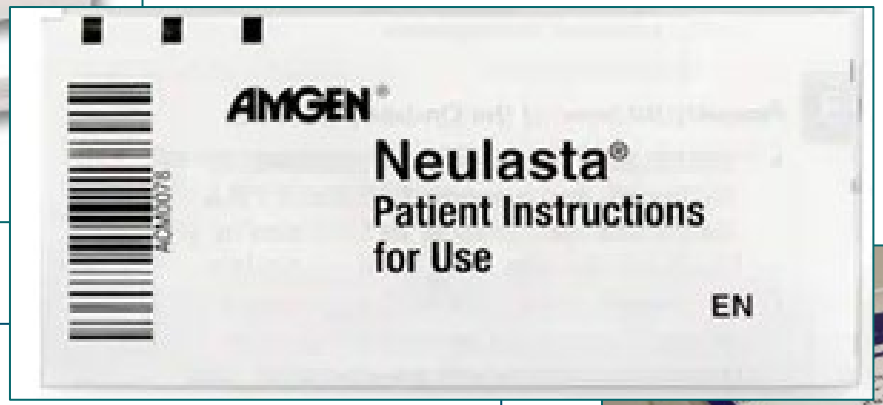
Bone Marrow MCMs

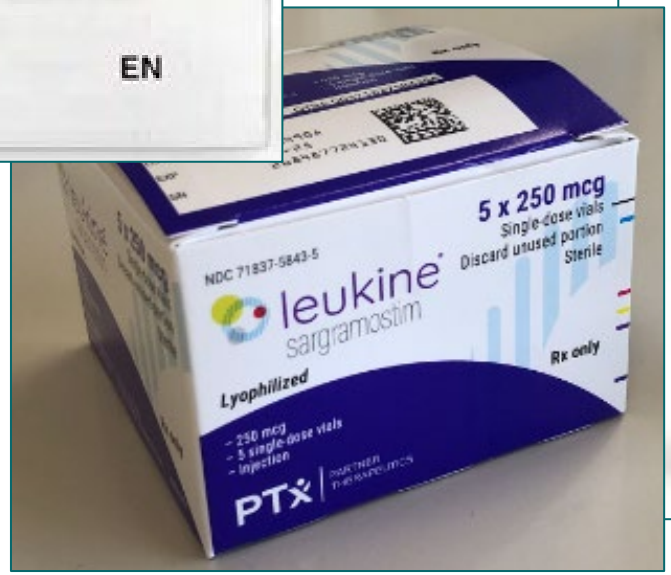
RADIATION RESEARCH
0033-7587/11 $15.00

DOI: 10.1667/RROL01.1

Medical Countermeasures for Platelet Regeneration after Radiation ExposureReport of a Workshop and Guided Discussion Sponsored by the National Institute of Allergy and Infectious Diseases, Bethesda, MD, March 22–23, 2010

Andrea L. DiCarlo,[a,1] Mortimer Poncz,[b] David R. Cassatt,[a] Jui R. Shah,[a] Christine W. Czarniecki[a] and Bert W. Maidment[a]





RADIATION RESEARCH **192**, 99–120 (2019)
0033-7587/19 $15.00

DOI: 10.1667/RR15363.1

WORKSHOP REPORT

Use of Growth Factors and Other Cytokines for Treatment of Injuries During a Radiation Public Health Emergency

Andrea L. DiCarlo,[a,1] Zulmarie Perez Horta,[a] Jennifer T. Aldrich,[b] Ann A. Jakubowski,[b,c] William K. Skinner[d] and Cullen M. Case, Jr.[b]

Cellular Therapies as Bone Marrow MCMs

- Stem (Fred Hutchinson)
  - MHC-mismatched umbilical cord blood
  - Delayed MHC-mismatched adult
- Placental
  - Pluristem
- Progenitor
  - Cellerant Therapeutics
    - Myeloid and megakaryocytes
  - Athersys, Inc.
    - Multi-Stem
  - Fred Hutchinson
    - Off-the-shelf, expanded myeloid
- Platelets
  - Platelet Biogenesis
    - Microfluid human platelet bioreactor

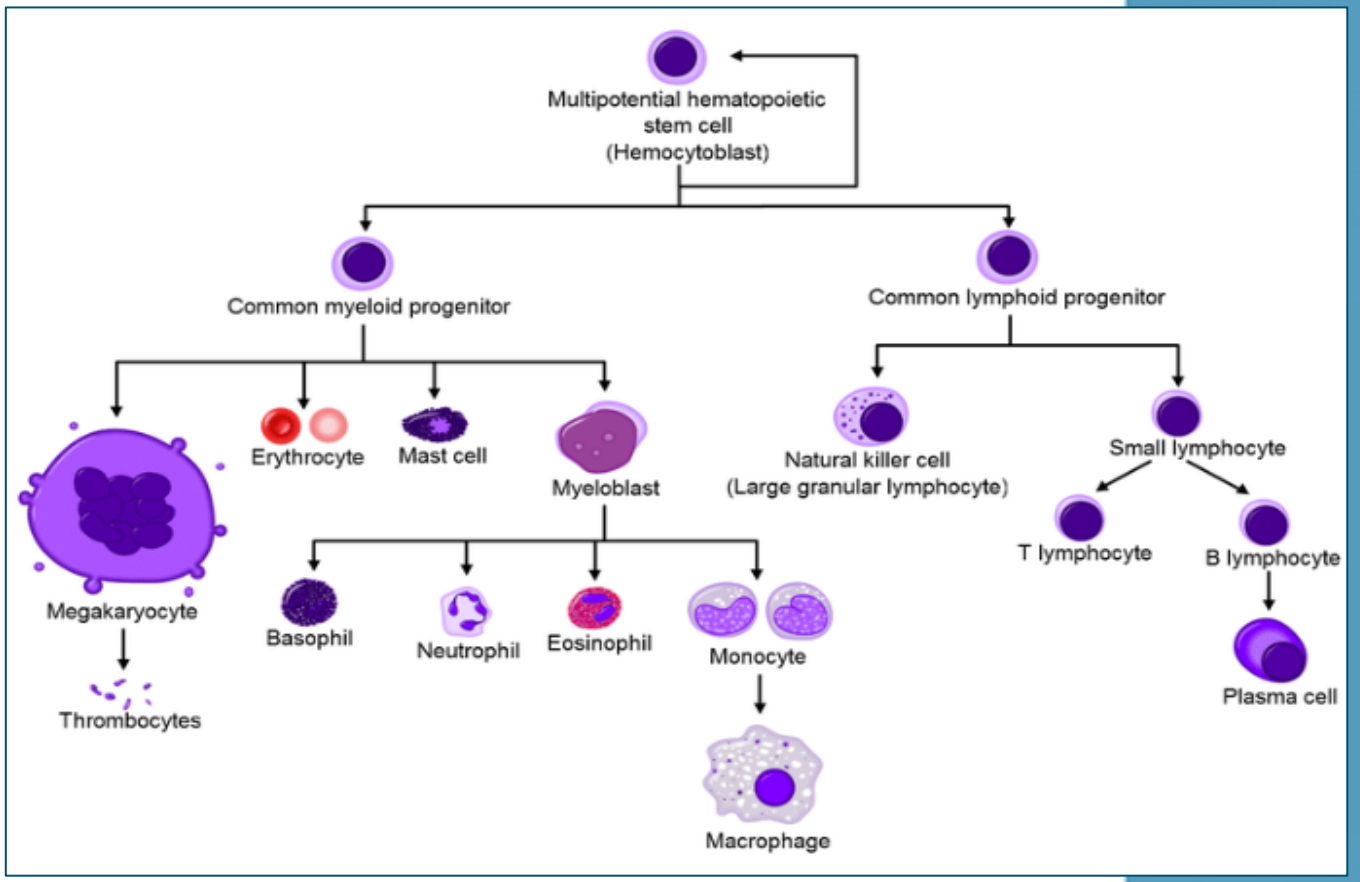
RADIATION RESEARCH **188**, 000–000 (2017)
0033-7587/17 $15.00

DOI: 10.1667/RR14810.1

WORKSHOP REPORT

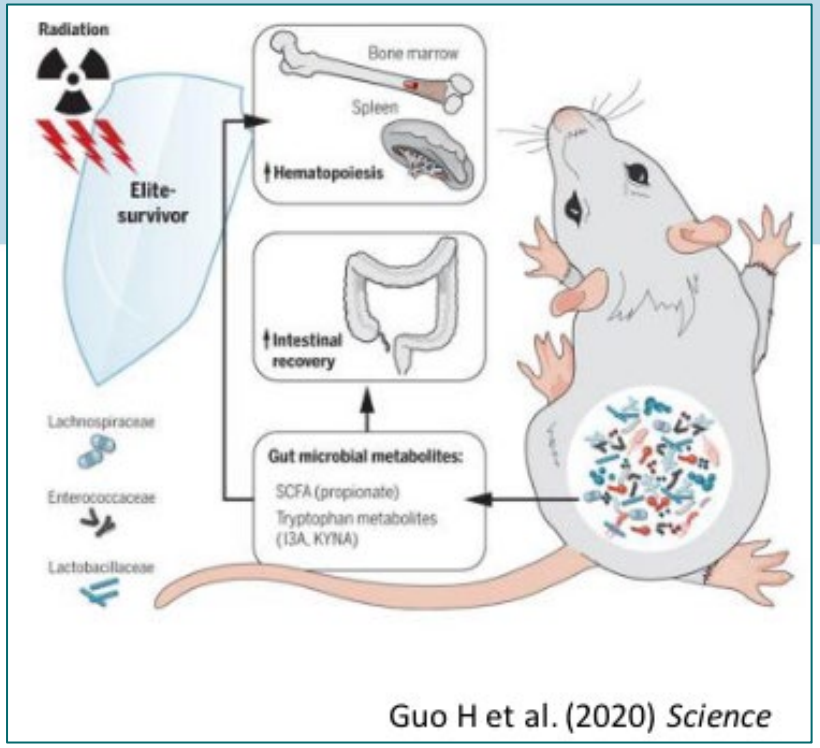
Cellular Therapies for Treatment of Radiation Injury: Report from a NIH/NIAID and IRSN Workshop

Andrea L. DiCarlo,[a,1] Radia Tamarat,[b] Carmen I. Rios,[a] Marc Benderitter,[b] Christine W. Czarniecki,[c] Theresa C. Allio,[d,2] Francesca Macchiarini,[e] Bert W. Maidment[f,3] and Jean-Rene Jourdain[b]

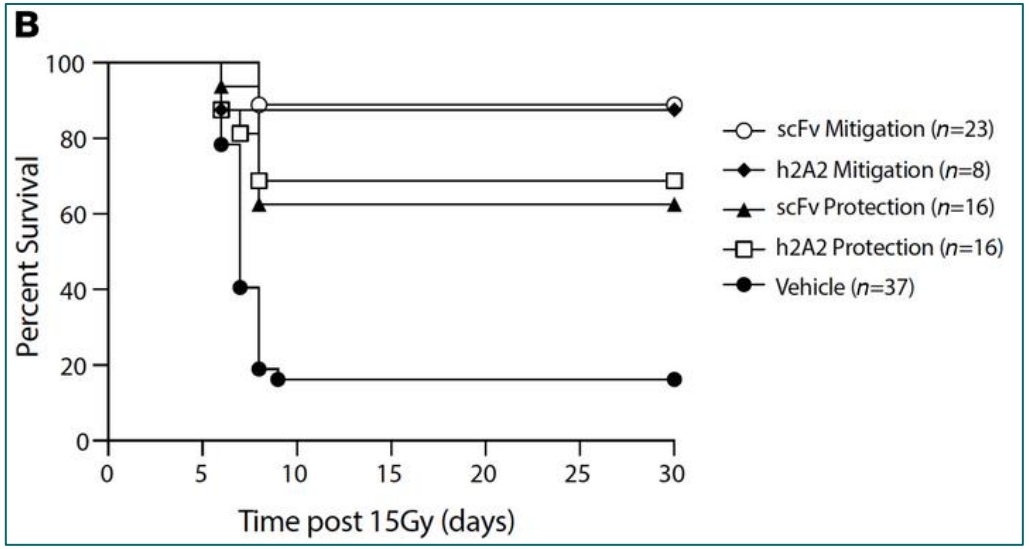


Gastrointestinal (GI) Tract MCMs

- Cytokines/cytokine blockers
- Immunomodulators
- Cellular therapies
  - Mesenchymal (MSC)
  - Bone marrow / progenitors
- Steroids/hormones
  - Beclomethasone dipropionate
  - Ghrelin
- Microbiome-focused
- Endothelium/vascular-focused
- Growth factors (KGF, FGF)
- Anti-apoptotics/anti-inflammatories
  Anti-microbials/anti-oxidants



Guo H et al. (2020) *Science*



Rotolo JA, et al. JCI Insight. 2021 Apr 22;6(8):e145380.

Hollingsworth et al. Acute Radiation Syndrome and the Microbiome: Impact and Review. Front Pharmacol. 2021.

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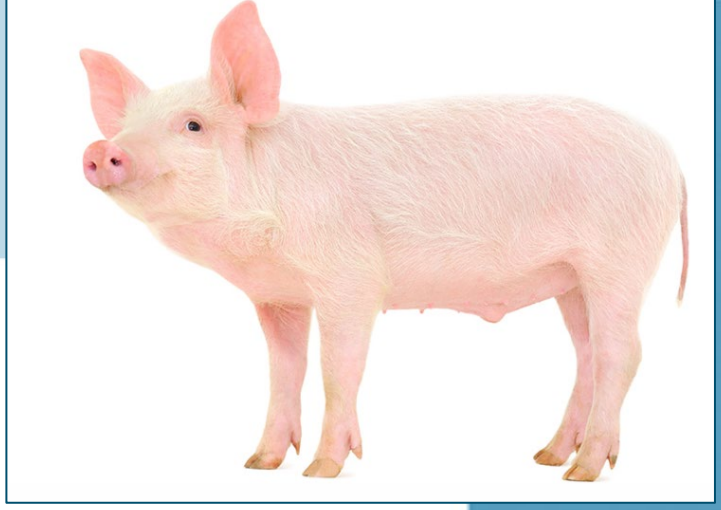
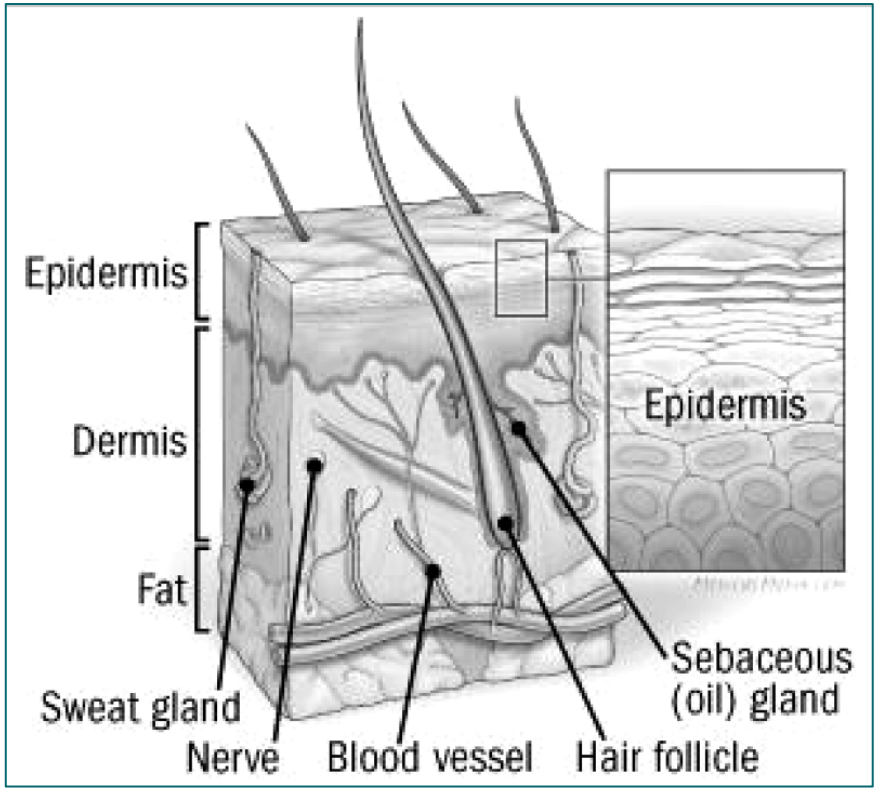
Skin Radiation Injury Models



- Efficacy testing
  - Mouse / Rat
  - Guinea pig / Göttingen minipig / Yorkshire pig
  - Human *ex vivo* skin
- Radiation
  - Localized to skin (gamma, x-ray, beta)
  - Radiation combined injuries (RCI)
- Endpoints
  - Survival / Healing time / % healing
  - Histopathology
  - Limb shortening
  - Barrier function
  - Wound tensile strength
  - Novel methods
    - Infra-red
    - Other imaging



Skin MCMs

MCM	Site (mechanism)	M
Granexin Gel	AFRRI (IAA)/Xequel (contract)	Minipig – x-ray
TP508	UTMB Galveston (SBIR)	Mouse TBI† + wound
Nor Leu 3-A(1-7)‡	US Biotest (grant)	Guinea Pig & Mouse RCI (thermal)
Antibiotics (cipro, gentamicin)	Multiple (IAA)	IR alone / RCI (burn or wound)
Mesenchymal cells (MSCs)	UCLA (grant)	Mouse RCI (wound)
Curcumin	Univ. of Rochester (grant)	Mouse IR alone
Celecoxib (NSAID)	Univ. of Rochester (grant)	Mouse RCI (wound)
Timolol (beta blocker)	UC Davis (grant)	Ex vivo human – RCI (burn)
Esculentoside-A	Univ. of Rochester (grant)	Mouse IR alone
G-CSF	AFRRI (IAA)	RCI (wound)
Ghrelin	AFRRI (IAA)	RCI (burn)
CPG-ODN	Brigham and Women's (grant)	Mouse IR & RCI (burn)
Ex-RAD	AFRRI (IAA)	Mouse IR & RCI (wound)
Phytocannabinoid	AFRRI (IAA)	RCI (wound); Minipig plan

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Radiation Combined Injuries (RCI)

- Radiation combined with burn, blast, trauma, bleeding, sepsis, fracture, chemical exposure
- Radiation exposure in animal models worsens development and progression of other injuries
- In Hiroshima and Nagasaki, 60-70% of victims had thermal burns plus radiation exposure
- 115 Chernobyl victims developed ARS; 49% also had radiation burns

Medical Countermeasures for Radiation Combined Injury: Radiation with Burn, Blast, Trauma and/or Sepsis. Report of an NIAID Workshop, March 26–27, 2007

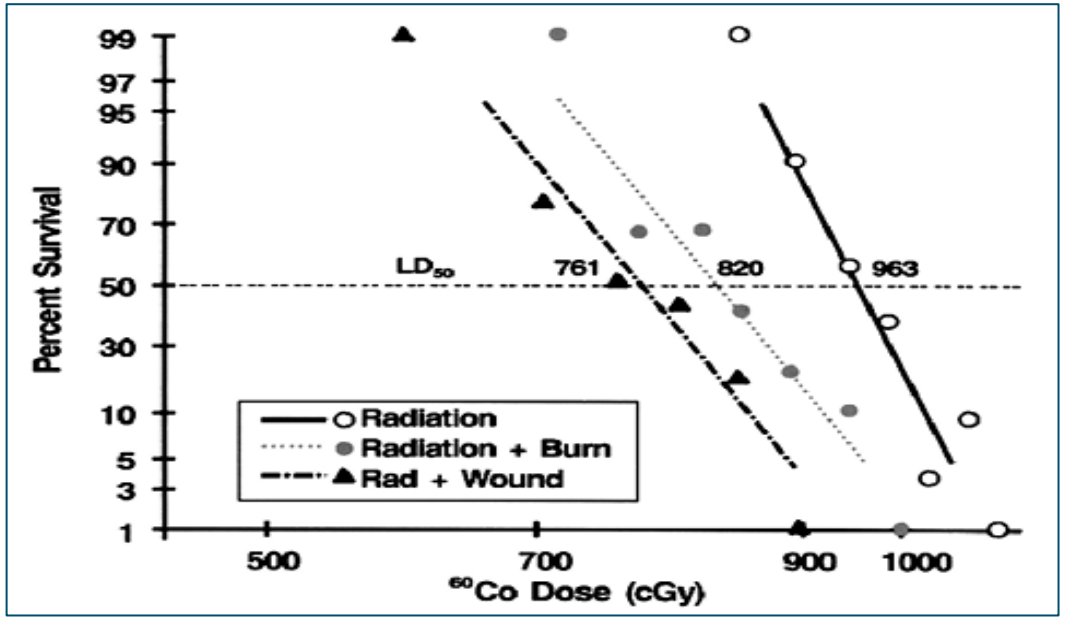
Andrea L. DiCarlo, Richard J. Hatchett, Joseph M. Kaminski, G. David Ledney, Terry C. Pellmar, Paul Okunieff, Narayani Ramakrishnan

Author Affiliations +

Radiation Research, 169(6):712-721 (2008). https://doi.org/10.1667/RR1295.1

Severity (grade)	No. of patients	Percentage skin involvement in patients			
		50	11–49	1–10	Total
IV	20	9	10	1	20
III	21	3	15	3	21
II	43	1	9	2	12
I	31	0	1	2	3
Total	115	13	35	8	56

Note. Table provided by A. Shapiro, FDA, Silver Spring, MD. Originally published in UNSCEAR 1988 Report (*10*).



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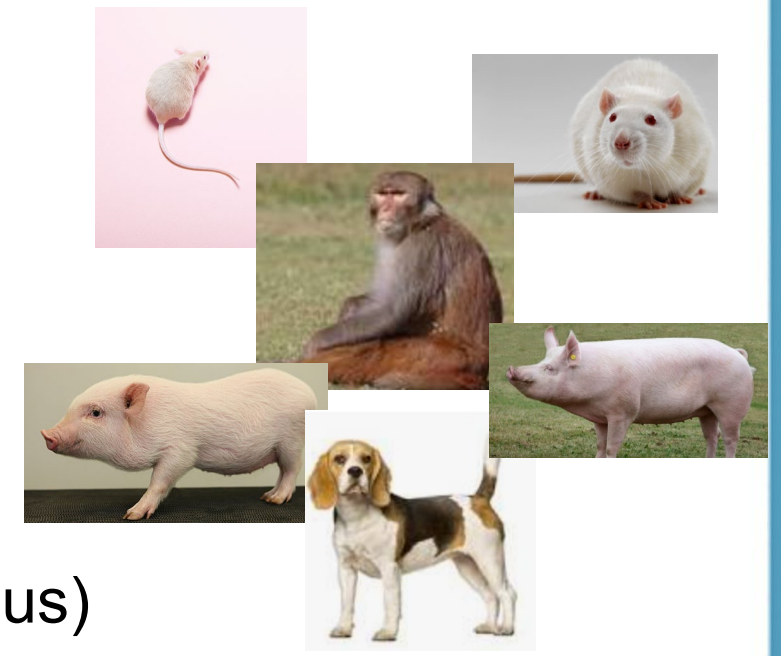
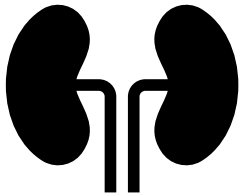
DEARE Laboratory Animal Models

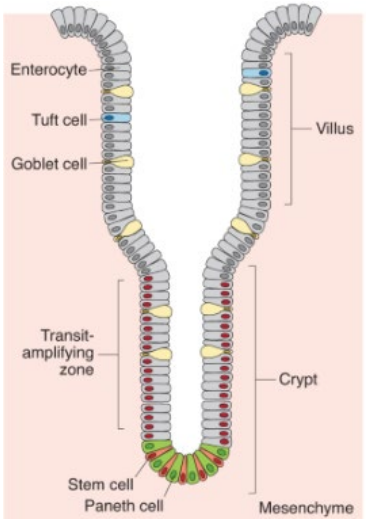
- Small and large
  - Mouse
  - Rat
  - Minipig
  - Pig
  - Dog
  - Nonhuman primate (NHP; rhesus and cynomolgus)
- Lung/kidney – partial-body irradiation (PBI)
- Cardiovascular –Total-body irradiation (TBI)
- Cutaneous – focused, high dose irradiation our rad + trauma
- Delayed heme and GI – TBI or PBI

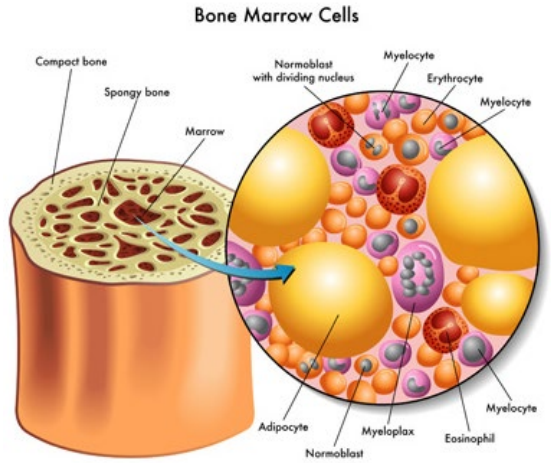


DEARE MCM Approaches

- Lung
  - Anti-fibrotics (anti-TGFß (IPW-5371, etc.)
  - Anti-apoptotics (BIO300, LGM2605)
  - Immune modulators (TLR agonists; homspera)
  - Angiotensin converting enzyme (ACE) inhibitors/receptor blockers
  - Surfactants (KL4)
  - Mucociliary clearance
- Kidney
  - ACE inhibitors/receptor blockers
- Cardiovascular
- Delayed GI/Heme
  - Growth factors







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Lung-Targeted MCMs

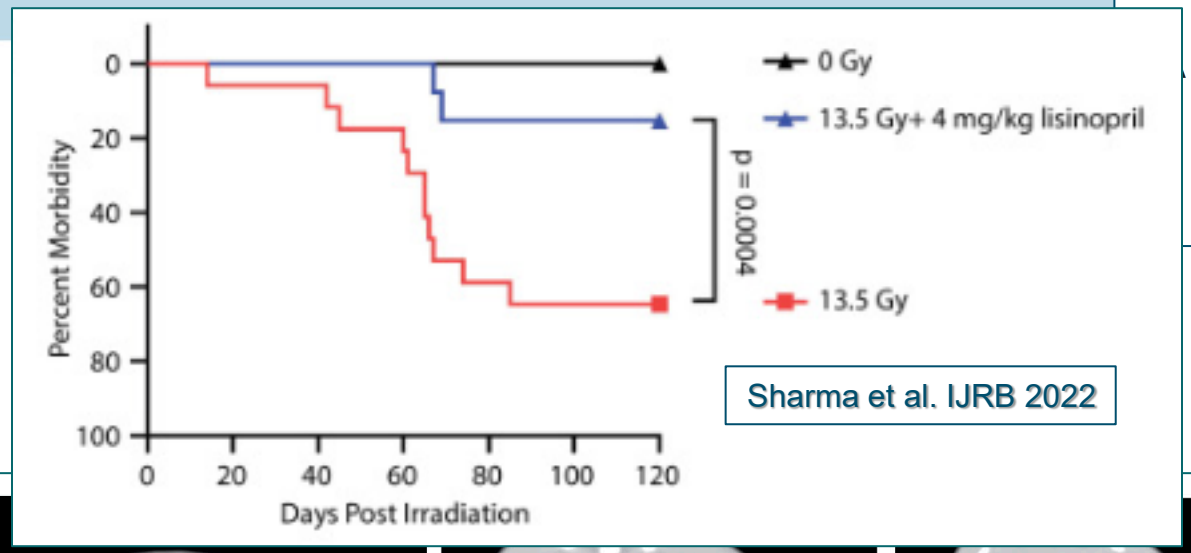
RADIATION RESEARCH **197**, 415–433 (2022)
0033-7587/22 $15.00

DOI: 10.1667/RADE-21-00127.1

MEETING REPORT

Trans-Agency Workshop on the Pathophysiology of Radiation-Induced Lung Injury

David R. Cassatt,[a,1] Alex Gorovets,[c] Banu Karimi-Shah,[c] Rosemary Roberts,[c] Paul W. Price,[b] Merriline M. Satyamitra,[a] Nushin Todd,[c] Sue-Jane Wang[c] and Libero Marzella[c]



Sharma et al. IJRB 2022

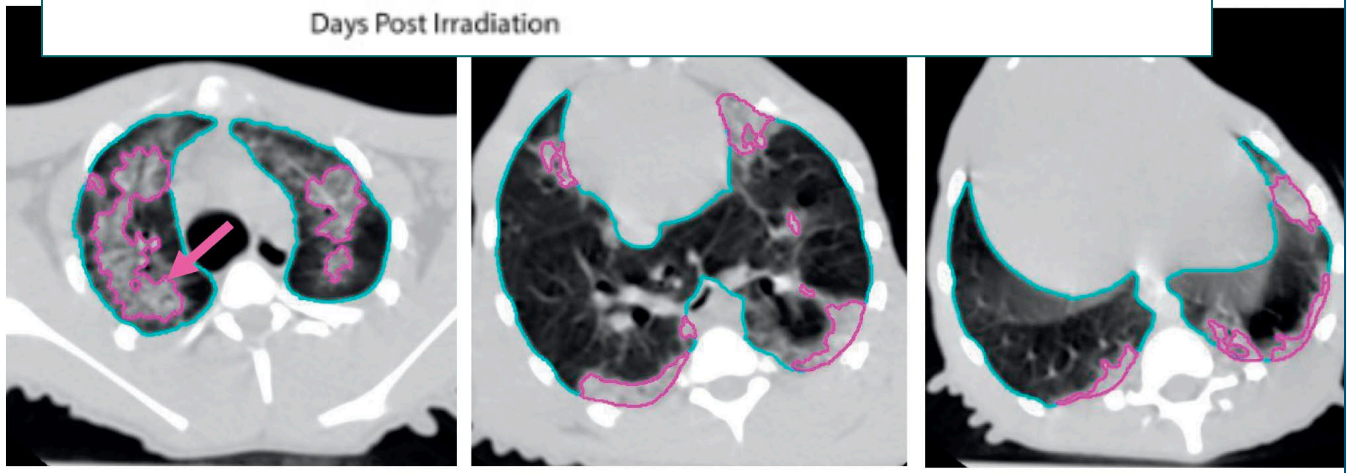
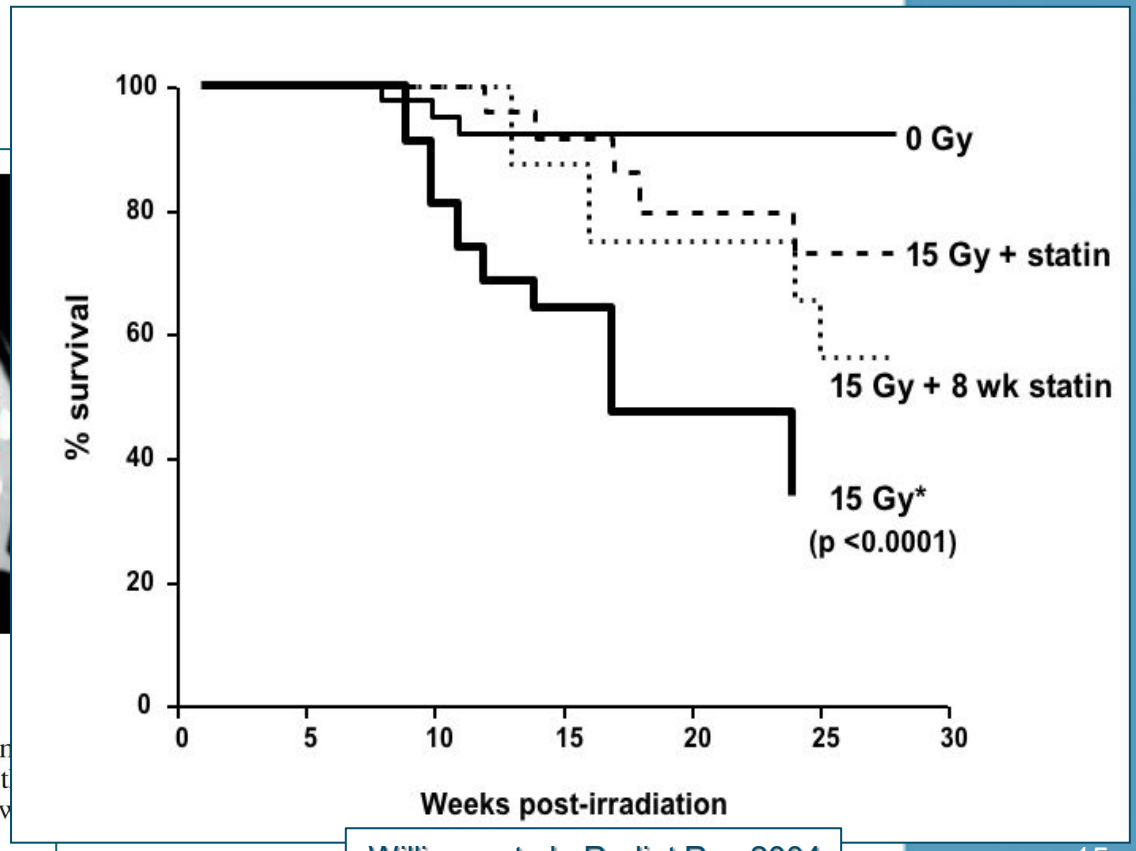


FIG. 2. Radiographs from rhesus macaques that received 11.5 Gy PBI with 5% of bone marrow sparin
Radiographs were taken 120 days postirradiation. Lungs show evidence of damage. These scans allow for t
determination of total lung volume (blue outline) and percentage with lung damage (red outlines and arrov
This figure was presented at the meeting.

MacVittie et al., Health Phys 2015



Williams et al., Radiat Res 2004

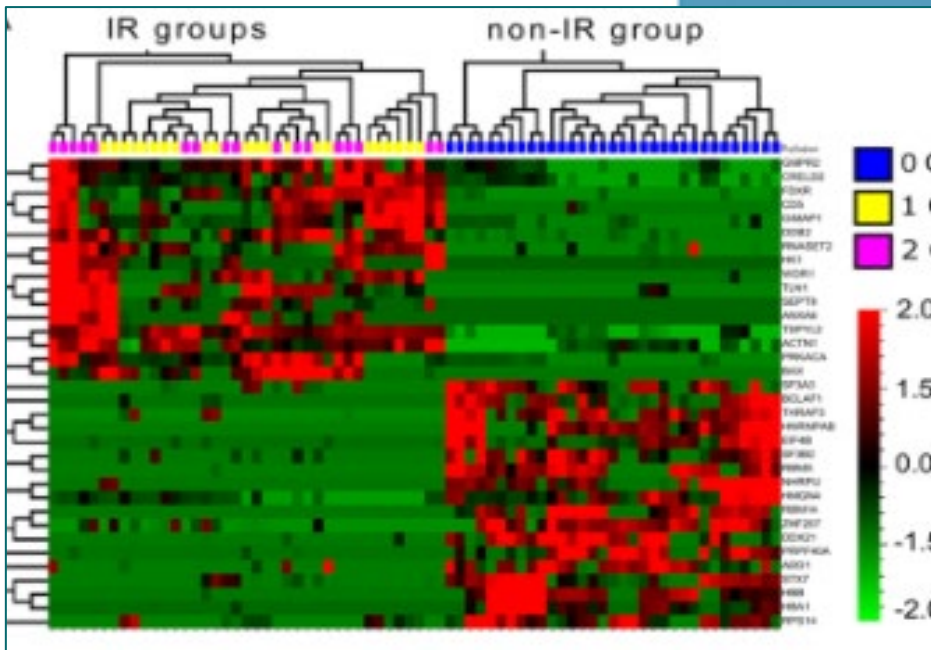
Biodosimetry

- Assess radiation exposure to triage & guide medical management
- Ideally rapid, inexpensive, non-invasive, radiation-specific
- Biomarkers to track MCM efficacy
- Biomarkers to bridge MCM PK/PD from animal models to humans
- Cytogenetics and “-omics”

> Radiat Res. 2022 May 1;197(5):514-532. doi: 10.1667/RADE-21-00157.1.

Development of Biomarkers for Radiation Biodosimetry and Medical Countermeasures Research: Current Status, Utility, and Regulatory Pathways

Merriline M Satyamitra [1], Andrea L DiCarlo [1], Brynn A Hollingsworth [1], Thomas A Winters [1], Lanyn P Taliaferro [1]

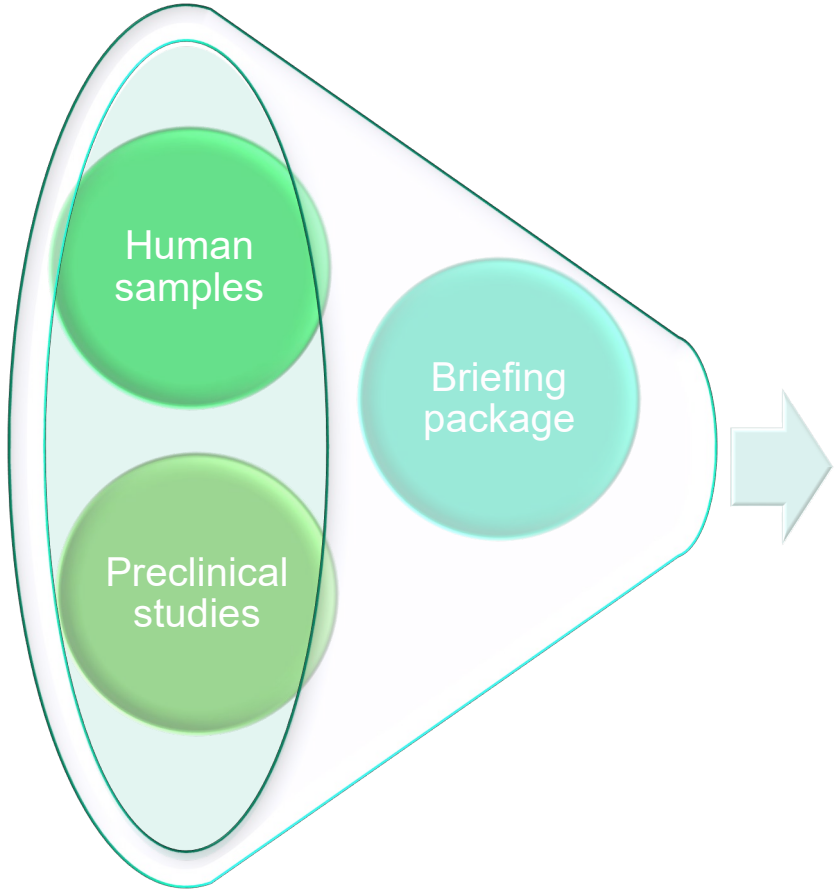


Current RNCP Biodosimetry Portfolio

Early stage
- NCI/AFRRI/FDA [6]
- CMCRC pilots [25]

Mid stage
- CMCRC [3]
- U01s [7]
- SBIR Phase I [1]; Phase II [1]

Advanced stage
- Chromologic, LLC
- Mesoscale Diagnostics



Biomarkers of DEARE

- Predictive biodosimetry
  - Early biomarkers predict late effects
  - Allows best use of scarce resources & guides physicians
  - Consortium awarded 2012
  - Current biodosimetry U01 awardees (2019-2024)
  - NCI/FDA IAA funding

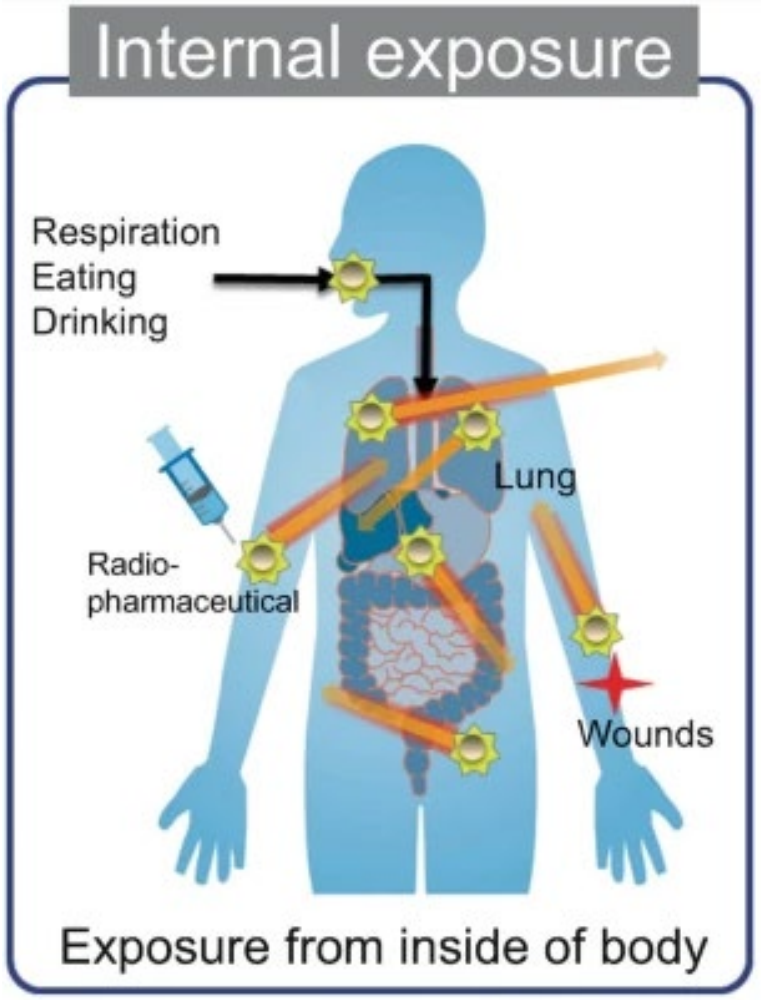
- Irradiated NHP study (4 Gy)
  - Acute samples distributed to 12 labs in 2018
  - Survivors to Wake Forest survivor colony for late follow-up
  - Study for 2023 under consideration (different Gy level)

Radionuclide Decorporation & Blocking

Radiat Res. Author manuscript; available in PMC 2021 Aug 21.
PMCID: PMC8379839
Published in final edited form as:
NIHMSID: NIHMS1731820
Radiat Res. 2008 Oct; 170(4): 540–548.
PMID: 19024661
doi: 10.1667/rr1485.1

Medical Countermeasures against Nuclear Threats: Radionuclide Decorporation Agents

David R. Cassatt,[1] Joseph M. Kaminski, Richard J. Hatchett, Andrea L. DiCarlo, Jessica M. Benjamin, and Bert W. Maidment



- Chelators bind isotopes and allow for excretion
- Licensed products in the U.S.
  - Prussian blue (cesium; oral)
  - Potassium iodide (iodine; KI; oral)
  - Ca- and Zn-DTPA (plutonium, americium, uranium)
    - Only intravenous forms of DTPA are available
- Chelators developed by the RNCP
  - 4 oral DTPA formulations
    - Better for mass casualty use
  - 1 novel oral agent (HOPO)
    - Superior to DTPA
      - Higher-affinity radionuclide binding
      - Broader binding range (also binds neptunium)

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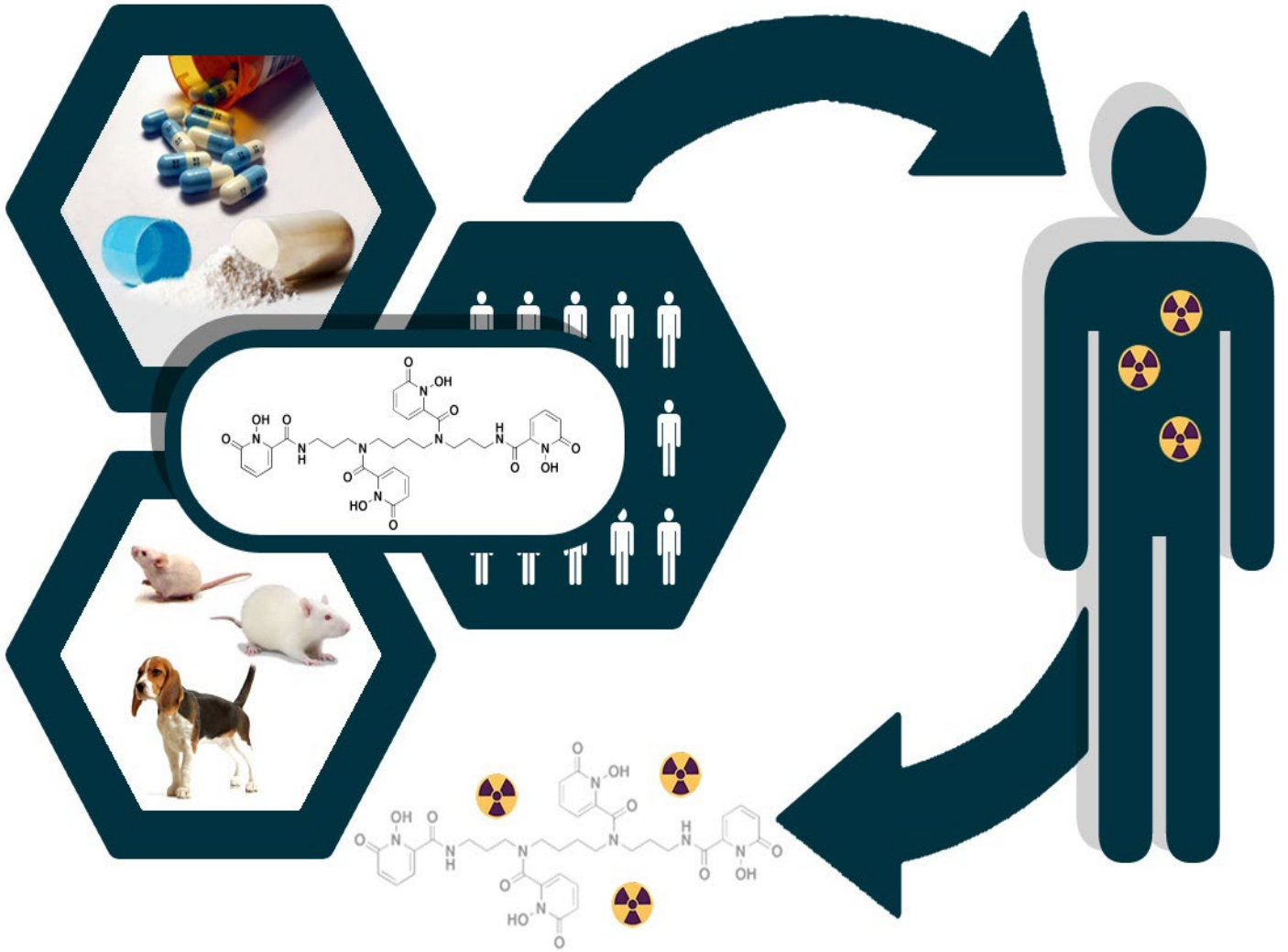
Hashimoto et al. Forest Radioecology in Fukushima. 2022

HOPO-14-1 Clinical Trial Now Recruiting (18-65 years old)

- Currently available therapy for radionuclide internal contamination is suboptimal
- Pharmacological and toxicological data support the clinical development of HOPO 14-1 for decorporation of radionuclides
- Study of Single Oral Doses of HOPO 14-1 Evaluating Safety, Tolerability, Pharmacokinetics
- ClinicalTrials.gov Identifier: NCT05628961
  - Seven cohorts (six healthy volunteers each)
  - Single ascending doses (mg) of HOPO
    - 100, 200, 500, 1200, 2500, 5000, 7500



NIAID Leads the Way in Preclinical Radiation Dosimetry Harmonization

- MCM efficacy is determined at specified levels of tissue damage, radiation response curves are very sensitive to dose
- Studies with different radiation sources must be comparable
- Achieving +/- 5% of intended dose is considered acceptable
- Accuracy/reproducibility is best maintained and expanded across the RNCP portfolio through a centralized contract
- Interest from other U.S. government agencies

Prior Dosimetry Efforts

- **2005-2015**
  - Radiation Core - Product Development at UMD
- **2011 meeting (NIAID, NIST, NCI)**
  - "Importance of Dosimetry Standardization in Radiobiology"
- **CMCRC dosimetry core (UCLA)**
  - 3D anatomical phantoms
  - Calculations to correct for heterogeneity
- **Dosimetry meetings 2016 & 2019**
  - Government, academia, industry expertise
- **UCLA expanded**
  - Evaluate non-CMCRC sites

Volume 118 (2013) http://dx.doi.org/10.6028/jres.118.021
Journal of Research of the National Institute of Standards and Technology

The Importance of Dosimetry Standardization in Radiobiology

Marc Desrosiers[1], Larry DeWerd[2], James Deye[3], Patricia Lindsay[4], Mark K. Murphy[5], Michael Mitch[1], Francesca Macchiarini[6], Strahinja Stojadinovic[7], and Helen Stone[3]

RADIATION RESEARCH **195**, 480–496 (2021)
0033-7587/21 $15.00

DOI: 10.1667/RADE-20-00213.1

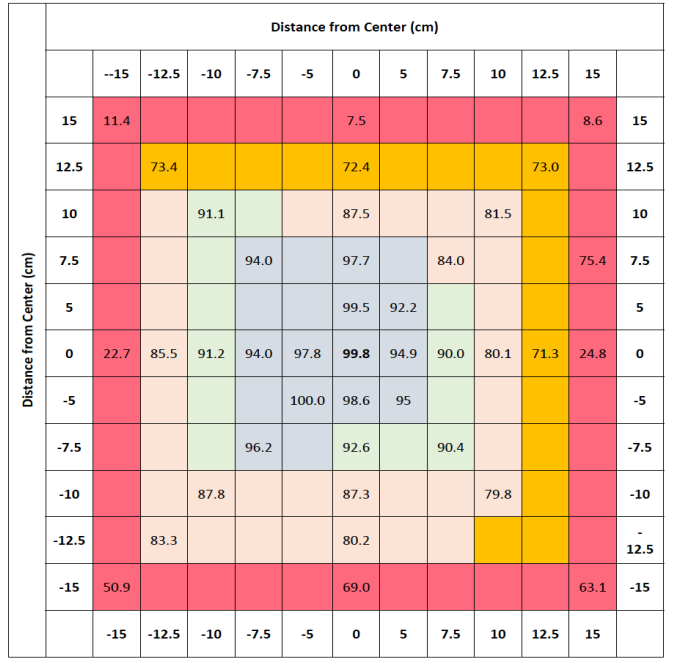
MEETING REPORT

Neutron Radiobiology and Dosimetry

Daniela L. Stricklin,[a] Jama VanHorne-Sealy,[b] Carmen I. Rios,[c] Lisa A. Scott Carnell[d] and Lanyn P. Taliaferro[c,1]

Dosimetry Contract 2020-2025

- Dr. Larry DeWerd, University of Wisconsin
- Amer. Assoc. Phys. Med, Accredited Dosimetry Calibration Laboratory Program
- 30+ irradiators evaluated (sites added continuously)
- TLD dosimetry & field mapping
- Mouse, rat, mini-pig, nonhuman primate phantoms

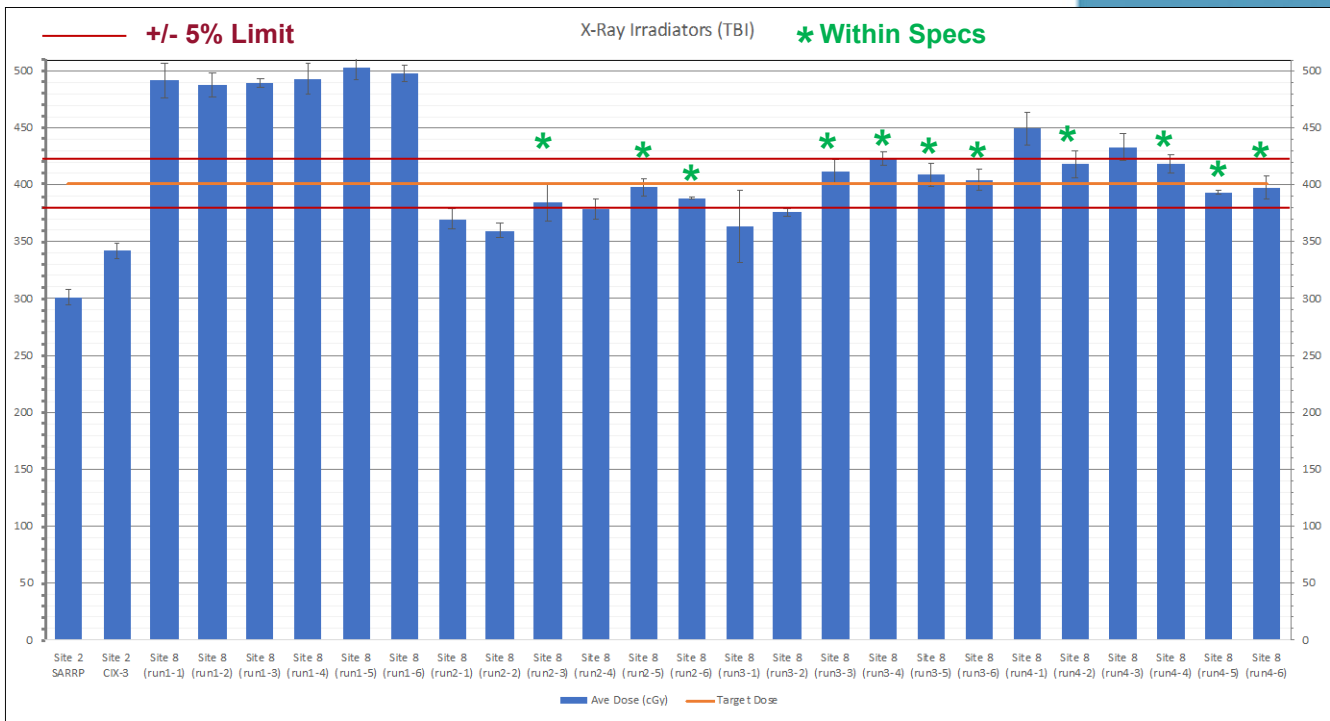


X-Ray Irradiators

Precision X-Rad 320	6	320 kVp
Xstrahl CIX3	3	320 kVp
Pantak X-Rad 320	1	320 kVp
Xstrahl SARRP	4	225 kVp
Xstrahl XENX	1	225 kVp
Rad Source Tech RS2000	1	160 kVp
Elekta Infinity LINAC	1	4 MV
Total to Date	17	

Gamma-Ray Irradiators

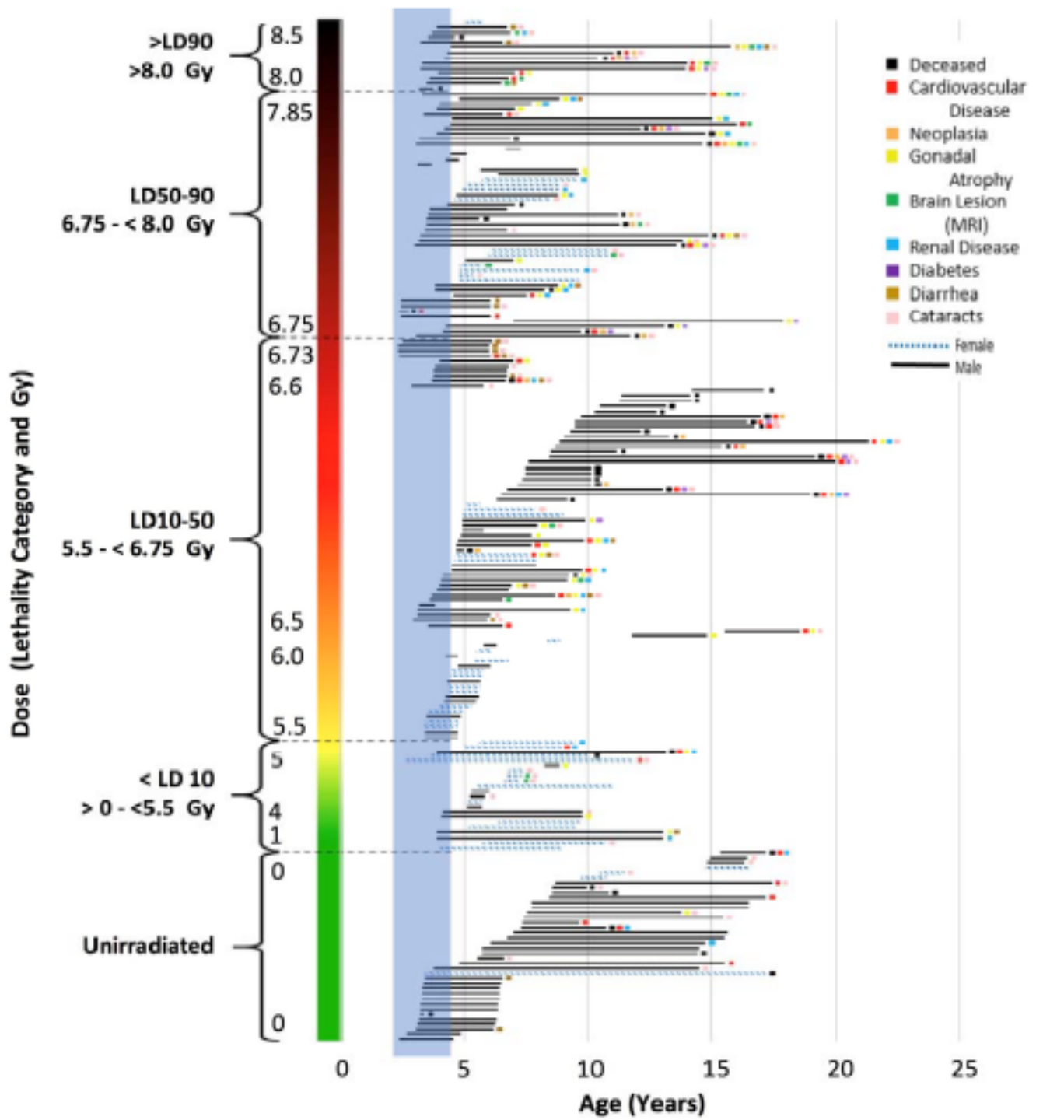
JL Shepherd Mark 1 (Cs-137)	10	662 kV
GammaCell 40 (Cs-137)	1	662 kV
Custom (Co-60)	1	1.2 MV
Total to Date	12	



Nonhuman Primate Radiation Survivor Colony (NHP RSC)

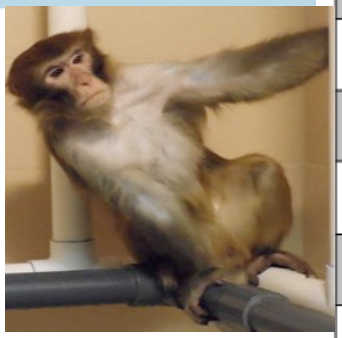
- Established 2007 – PI: Mark Cline
- >215 NHPs current census
- >300 total animals housed (always adding)
- North American diet
- Age-matched, unirradiated controls
- NHP survivors up to 16 years post-exposure
  - 1.1 – 8.5 Gy total body
  - Whole thorax
  - PBI-BM5%
  - MCMs
- Routine assessments/sampling
- Data/samples available by request
- Discover late biomarkers; correlate early biomarkers with late morbidities

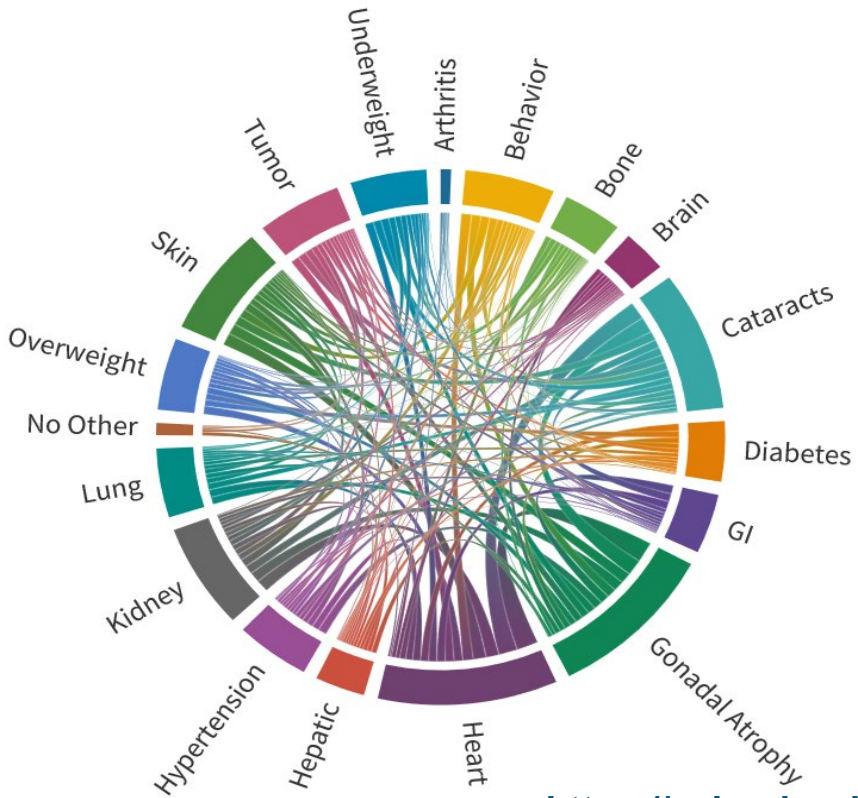
Wake Forest School of Medicine



Nonhuman Primate Radiation Survivor Colony (NHP RSC)

- Chord plot: Disease co-morbidities in 185 irradiated male and female rhesus monkeys in the NHP RSC.
- Nearly all animals have multiple organ systems affected.





Routine Diagnostics

System	Procedure	Frequency
Cardiovascular	MRI Cardiac	Subset; once, may repeat
Nervous	MRI Brain	Once for all then q 3yrs
Cardiovascular	Pulse-wave Velocity	Annually
Urinary/Hepatic	Abdominal ultrasound	Annually
General	TB Test/CBC/Chem	3x/year
General	Blood: Bank	3x/year
Metabolic	DEXA	Annually
Metabolic	Anthropometrics	Annually
General / Respiratory	CT Scan Whole Body Bronchoalveolar Lavage	Annually
Cardiovascular	Echocardiography/EKG Lipids/A1c	2x/year
Gastrointestinal Hematopoietic	GI Endoscopy/Bone Marrow Aspirate/Urine Collection 8 hour	Annually
Ophthalmic General	Eye Exams Physical Exams	Annually
Endocrine	Blood: Hormones	Annually
Immune	Flow Cytometry	Annually
Nervous	Cognitive Testing	Rotating Subset
Urinary	Urine Collection (monthly)	Monthly if sedated

https://school.wakehealth.edu/research/labs/j-mark-cline-lab/radiation-late-effects-cohort

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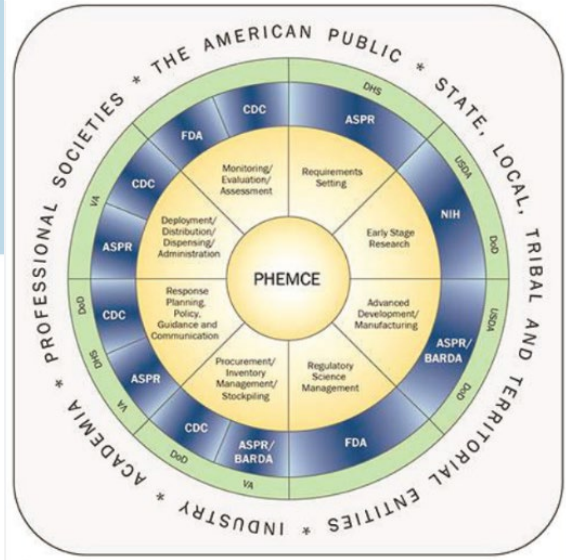
RNCP Extensive and Repeated Engagements with Other Government Agencies

- Public Health Emergency Medical Countermeasures Enterprise (PHEMCE)
  - Scientific Conferences
  - Publications
    - Meeting Reports / Commentaries
    - Agency Overviews
  - Co-Fund Awards
  - Project Coordination Teams
  - Working Groups



U.S. FOOD & DRUG ADMINISTRATION

ASPR ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE

DEPARTMENT OF DEFENSE · UNITED STATES OF AMERICA

NIH NATIONAL CANCER INSTITUTE

NASA

NIH National Center for Advancing Translational Sciences

NIH National Institute on Aging

BIOMEDICAL ADVANCED RESEARCH AND DEVELOPMENT AUTHORITY · BARDA

CDC Centers for Disease Control and Prevention

NIH National Institute of Allergy and Infectious Diseases

NIST NATIONAL INSTITUTE OF STANDARDS AND TECHNOLOGY U.S. DEPARTMENT OF COMMERCE

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RNCP Staff Accomplishments

- 36 Scientific meetings hosted (2005-2023)
- 57 Team publications
- 58 Funding opportunities

Study logistics that can impact medical countermeasure efficacy testing in mouse models of radiation injury

Andrea L. DiCarlo, Zulmarie Perez Horta, Carmen I. Rios, Merriline M. Satyamitra, Lanyn P. Taliaferro & David R. Cassatt

RADIATION RESEARCH 195, 1–24 (2021)
0033-7587/21 $15.00

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REVIEW

Commonalities Between COVID-19 and Radiation Injury

Carmen I. Rios,[1] David R. Cassatt, Brynn A. Hollingsworth, Merriline M. Satyamitra, Yeabsera S. Tadesse, Lanyn P. Taliaferro, Thomas A. Winters and Andrea L. DiCarlo

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Acute Radiation Syndrome and the Microbiome: Impact and Review

*Brynn A. Hollingsworth, David R. Cassatt, Andrea L. DiCarlo, Carmen I. Rios, Merriline M. Satyamitra, Thomas A. Winters and Lanyn P. Taliaferro**

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metabolites

Review

Metabolomics in Radiation Biodosimetry: Current Approaches and Advances

Merriline M. Satyamitra [1,*], David R. Cassatt [1], Brynn A. Hollingsworth [1], Paul W. Price [2], Carmen I. Rios [1], Lanyn P. Taliaferro [1], Thomas A. Winters [1] and Andrea L. DiCarlo [1]

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Thank You for Your Attention!

Olivia Carmen | Lanyn | Andie | Tom | David | Merriline

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