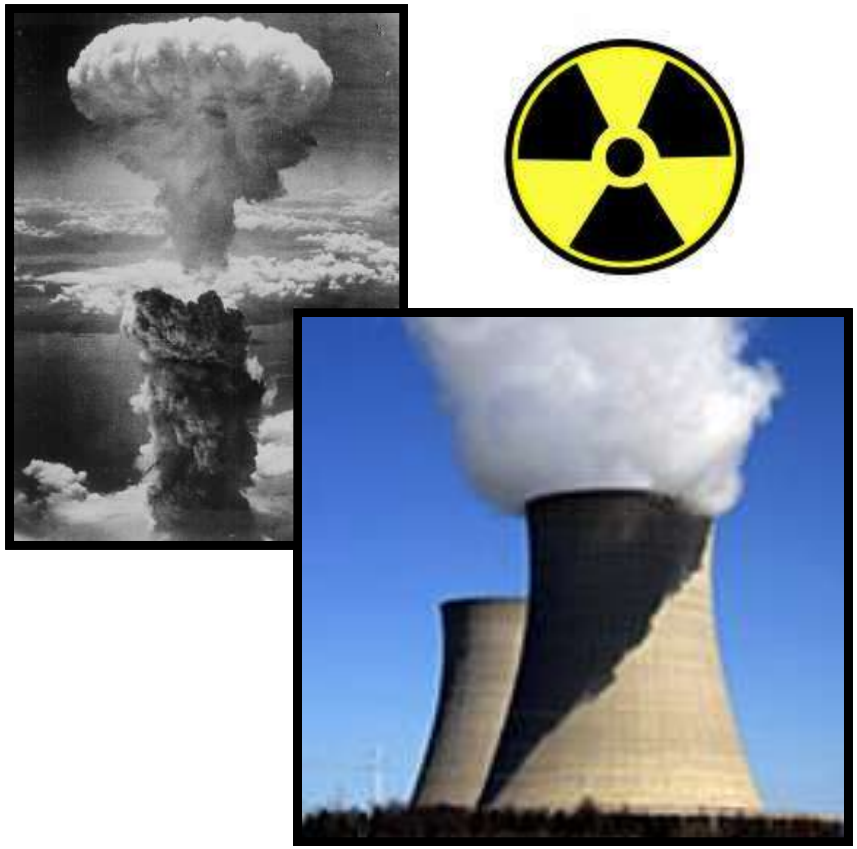
Radiation Dose Is More Than A Number
Workshop 15-16 September 2011

Bert W. Maidment, Ph.D.
Associate Director, Radiation/Nuclear Countermeasures Program
Division of Allergy, Immunology, and Transplantation
National Institute of Allergy and Infectious Diseases
National Institutes of Health

15 September, 2011

Types of Radiation Exposure

- Radiological terrorist events
  - RDD (Dirty Bombs)
  - RED
  - Food or Water Contamination
- Nuclear detonation
- Accident
  - Power Plant Release
  - Sealed radiological sources



NIAID Radiation/Nuclear Medical Countermeasures Development Program

- **HHS assigned NIH/NIAID with the responsibility to identify, characterize and develop new medical countermeasure products against radiological and nuclear attacks that may cause a public health emergency.**
- **Research priority areas of the program are to develop:**
  - **Drugs to treat or mitigate radiation injury**
  - **Drugs to remove radioactive materials from the body**
  - **Biodosimetry tools to determine levels of radiation exposure received by an individual**

Radiation Countermeasure Mission Space

- ARS/DEARE
  - Hematopoietic ARS:
    - Neutropenia
    - Thrombocytopenia
    - Anemia
    - Lymphopenia
  - GI ARS
  - CNS Injury
  - Cutaneous Injury
  - Lung Injury
  - Kidney Injury
  - Combined Radiation Injury
- Biodosimetry Methods and Devices
- Radionuclide Threats
  - Am-241
  - Co-60
  - Cs-137
  - I-131
  - Ir-192
  - Po-210
  - Pu-238/239
  - Sr-90
  - U-235
- Late Effects
  - Carcinogenesis
  - Cardiovascular Disease
  - Cataractogenesis

NIH Strategic Plan and Research Agenda for Medical Countermeasures Against Chemical Threats

05.2005

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

Department of Health and Human Services
National Institutes of Health
National Institute of Allergy and Infectious Diseases
NIH Publication No. 05-5608

Components of NIH Strategic Plan and Research Agenda

- Basic & Translational Research
- Radiation Biodosimetry
- Focused Product Development
- Infrastructure for Research & Product Development

NIAID's Radiation/Nuclear Medical Countermeasures Program

Build Infrastructure and Research Capacity

Basic Research and Discovery

ARS Treatments and Radionuclide Decorporation Agents Development

NIAID

Biodosimetry

Product Development Support Services

Radiation/Nuclear Medical Countermeasure Program Goals

- Support R&D on mechanisms of radiation injury and protection/mitigation
- Identify new radiation medical countermeasures
- Facilitate candidate medical countermeasures product development under the Animal Rule (21 CFR 314 and 601)
- Obtain licensure for radiation emergencies
- Increase the number of safe and effective radiation medical countermeasures available for Strategic National Stockpile procurement

Radiation/Nuclear Medical Countermeasure Development Programs

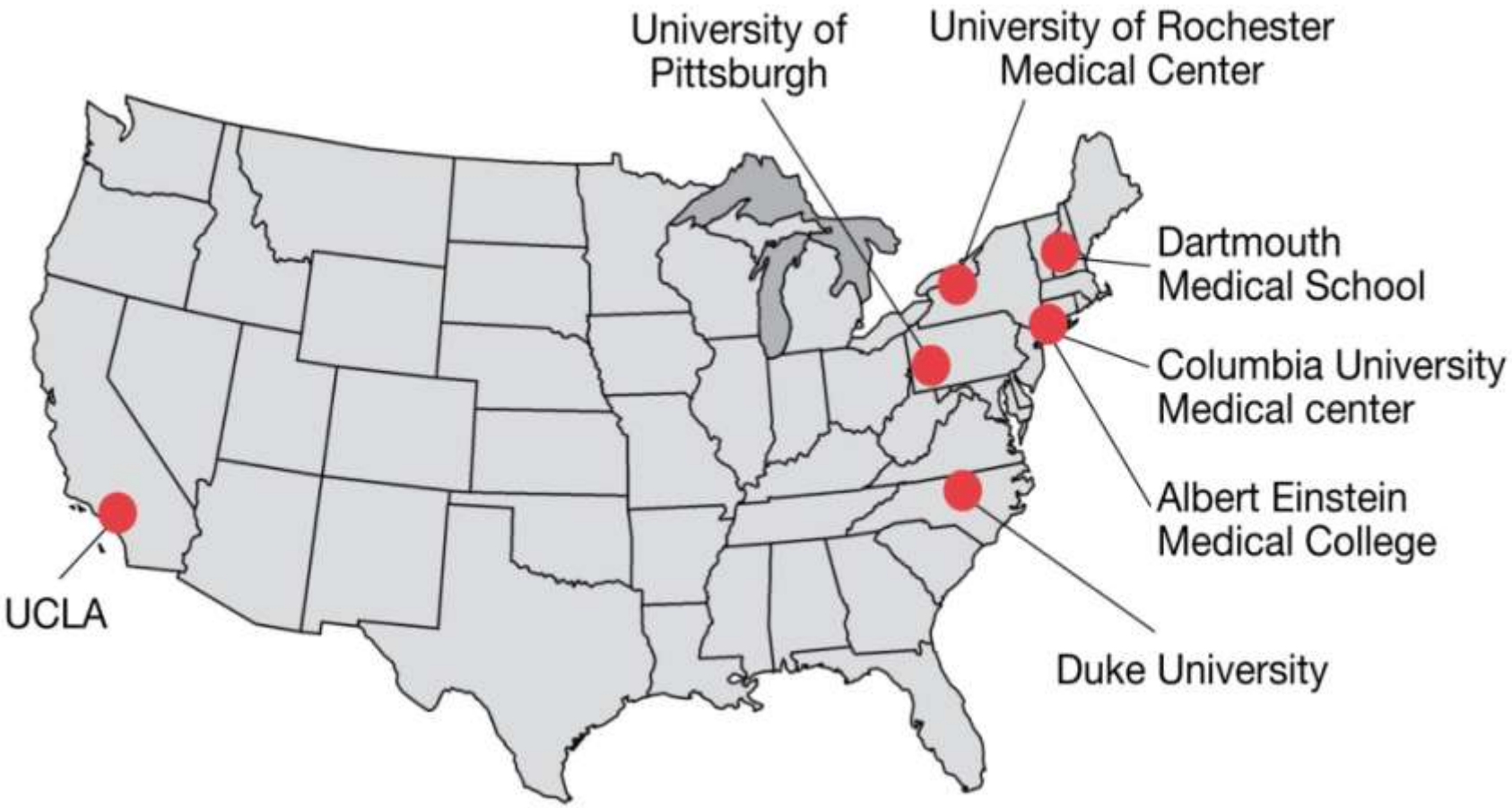
- **Cooperative Agreements**
  - Centers for Medical Countermeasures against Radiation
- **Specific Tissue Injury Grants**
  - Immune reconstitution
  - Oral Decorporation Agents
  - Mechanisms, Diagnostics, and Medical Countermeasures (MCMs)
  - Gastrointestinal MCMs
  - Lung MCMs
  - Skin MCMs
  - Combined Injury MCMs
- **SBIR**
  - Medical Countermeasure Development
  - NIAID Omnibus
- **Contracts**
  - Oral Forms of DTPA (2)
  - RERF
  - Product Development Support Services
- **Inter/intra Agency Agreements**
  - NCI
  - NIA
  - NIDDK
  - NIH RAID
  - AFRRI
- **Company Collaborations**
  - Contacts and presentations
  - Candidate efficacy screen
  - Candidate Optimization
  - Candidate Development
- **International Collaborations**
  - Global Health Security Initiative
  - REMPAN/WHO
  - International Symposia

Centers for Medical Countermeasures Against Radiation (CMCRs) 2010-2014

- 7 Centers awarded, 5-year cooperative agreements
- Awardees

- Columbia University	D. Brenner
- Albert Einstein	C. Guha
- University of Rochester	J. Williams
- Dartmouth University	H. Swartz
- Duke University	N. Chao
- UCLA	W. McBride
- University of Pittsburgh	J. Greenberger

Centers for Medical Countermeasures against Radiation – 2010-2014



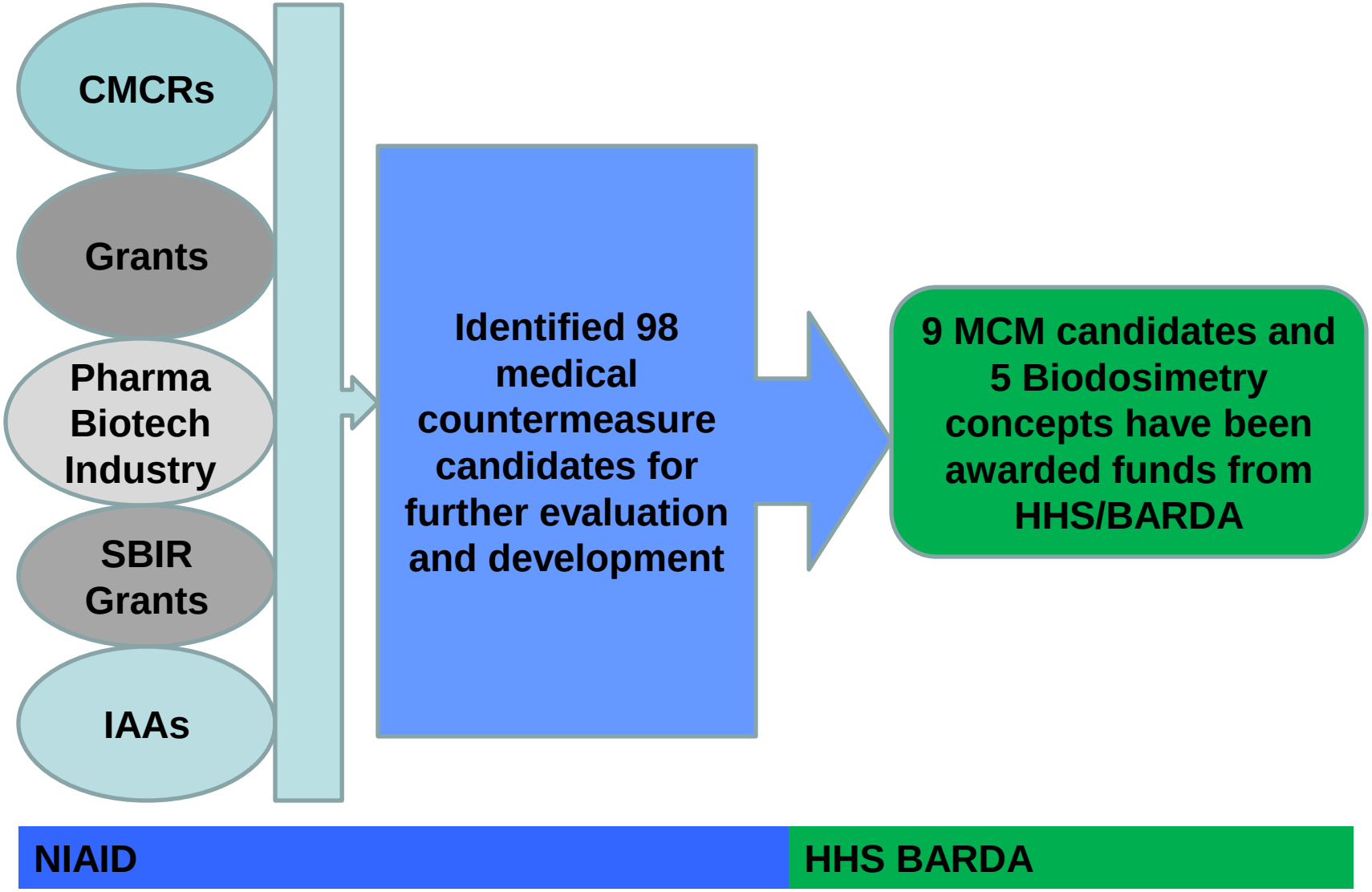
MCM Tissue Specific Injury Mitigation Grant Programs:

- **Investigator-initiated awards (R01s); 11 grants through *FY2012***
- **Radiation Combined Injury (R21/R33s); 11 grants through *FY2012***
- **Thrombocytopenia; 7 grants through *FY2010***
- **Lung Radiation Injury; 9 grants through *FY2010***
- **Cutaneous Radiation Injury; 4 grants through *FY2010***
- **RC2 GO Grants; 5 GI and 1 Decorporation Agent through *FY2010***

Product Development Support Services Contractor Capabilities

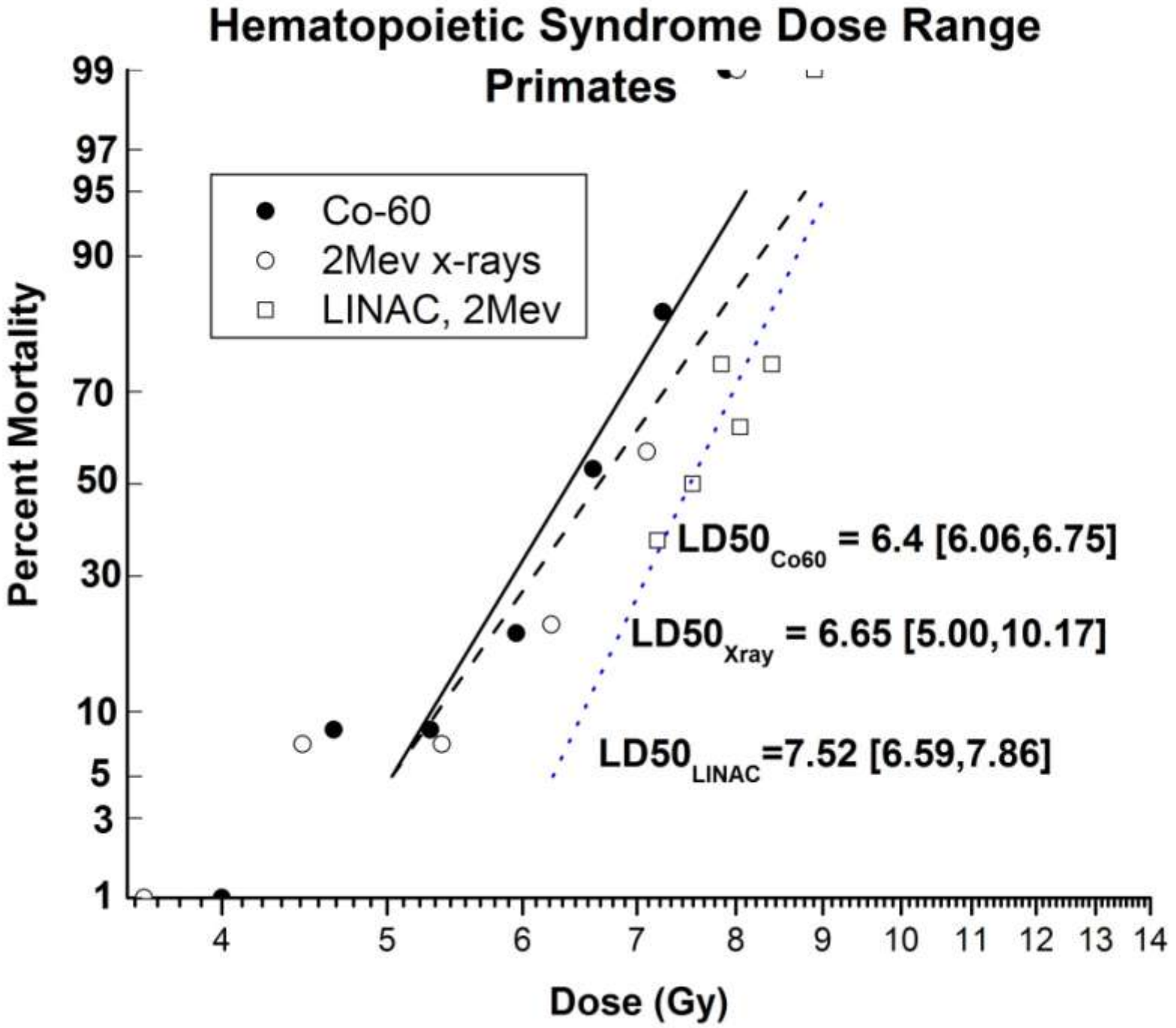
- Evaluate efficacy of candidate countermeasures
  - Acute Radiation Syndrome
    - Rodent hematological and gastrointestinal models
    - NHP hematological models
    - Developing canine hematological model (Thrombocytopenia)
    - Developing NHP gastrointestinal model
  - Radionuclide Decorporation Agents
- cGMP manufacturing support and stability studies
- GLP toxicology and safety pharmacology studies
- GLP pivotal animal efficacy studies (Animal Rule)
  - NHP and rodent models for efficacy in ARS
- Phase I clinical safety and pharmacokinetic studies
- FDA submission support for p-IND

Medical Countermeasure Candidates Identified To Date

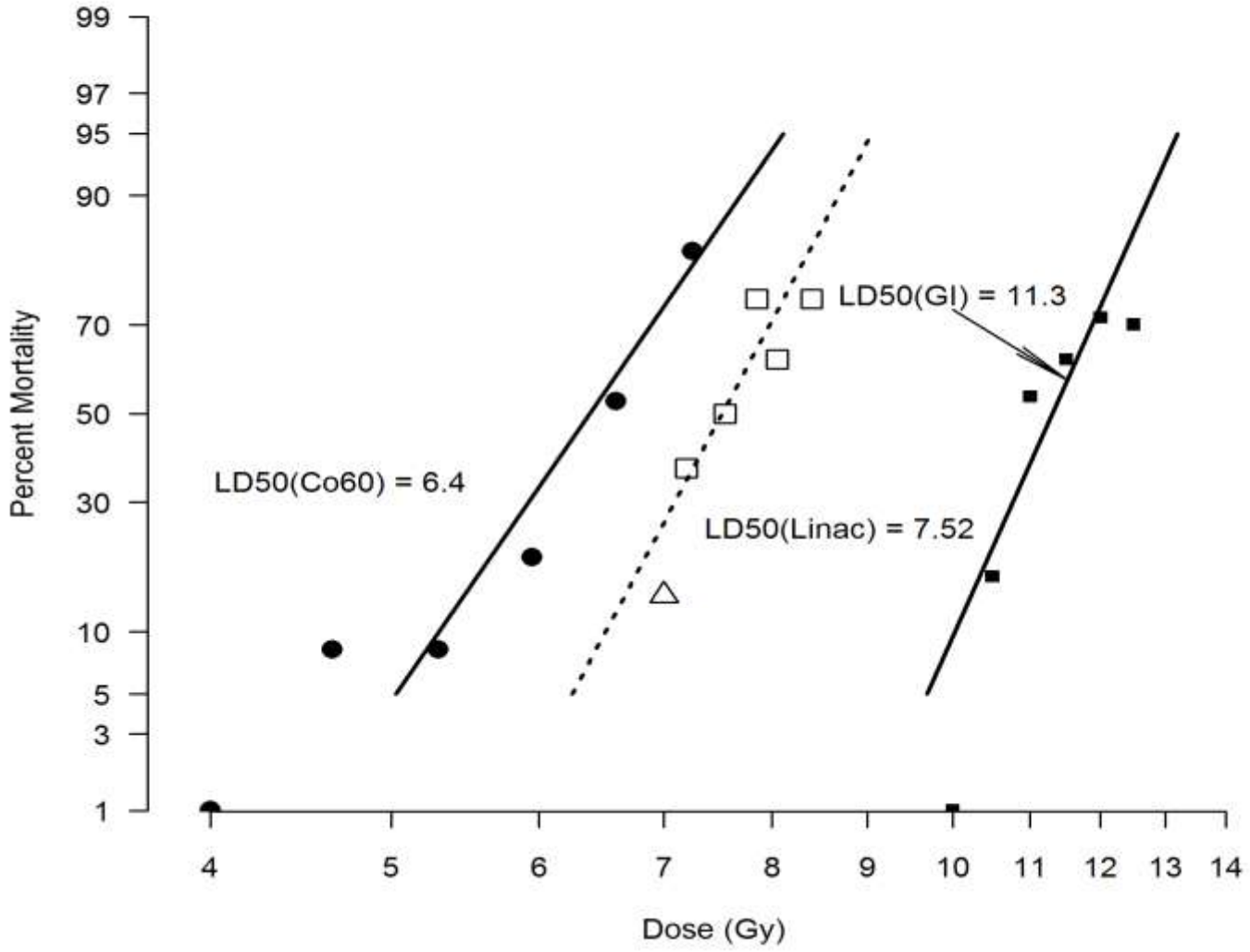


Radiation/Nuclear Medical Countermeasures

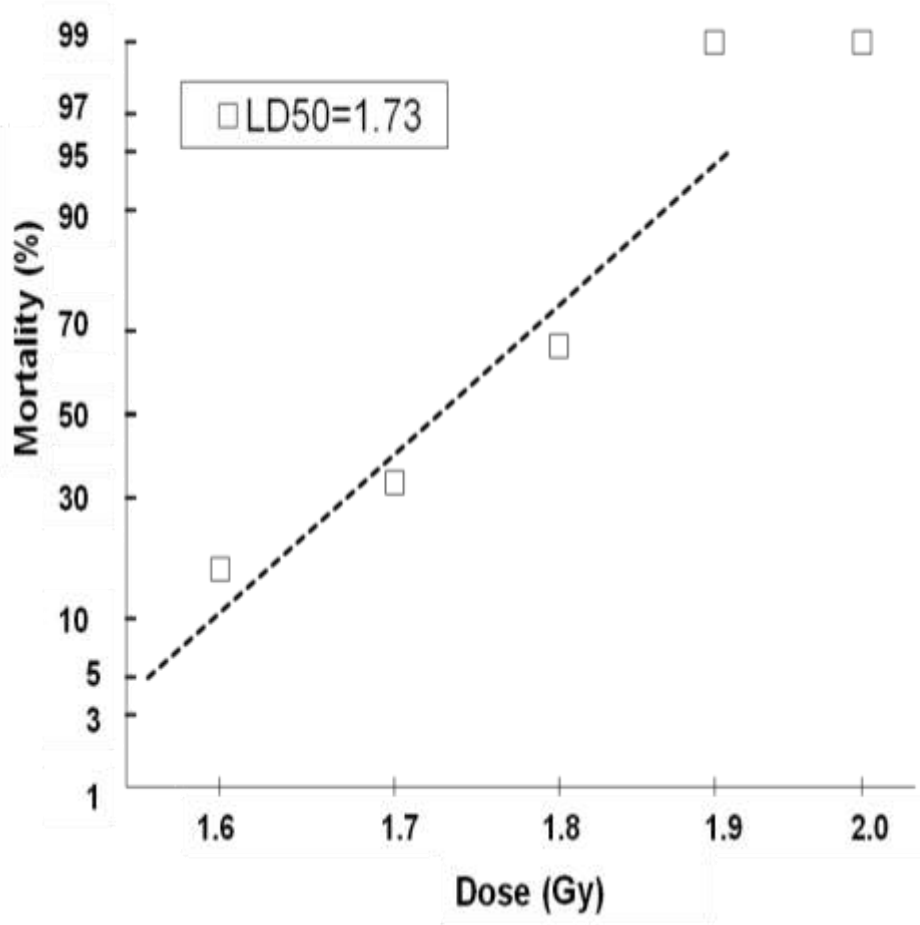
- **Mechanisms of Action**
  - — **Anti-oxidants**
  - — **Anti-inflammatories**
  - — **Anti-apoptotics**
  - — **Growth factors and cytokines**
  - — **Cell-based therapies**
  - — **Others**
- **Radionuclides**
  - — **Blocking agents**
  - — **Decorporation agents**
  - — **Enhancement of mucociliary clearance**


Hematopoietic Syndrome Dose Range
Primates
Percent Mortality
99
97
95
90
70
50
30
10
5
3
1
Co-60
2Mev x-rays
LINAC, 2Mev
LD50Co60 = 6.4 [6.06,6.75]
LD50Xray = 6.65 [5.00,10.17]
LD50LINAC=7.52 [6.59,7.86]
4
5
6
7
8
9
10
11
12
13
14
Dose (Gy)

Lethal Dose Response Curves for Hematopoietic and Gastrointestinal Acute Radiation Syndrome in NHPs



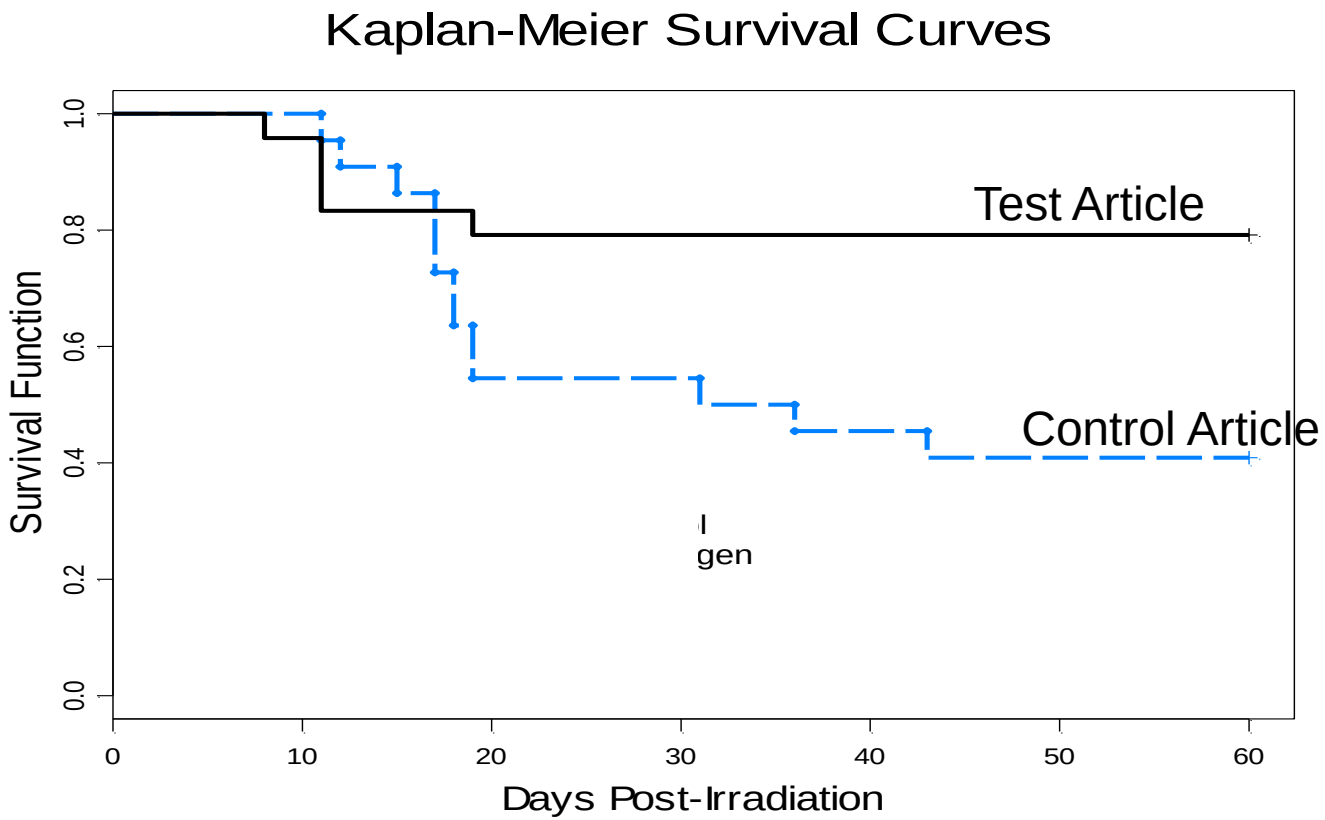
LD50/30 of Mini-pigs Exposed to 1.6 – 2 Gy Co-60 Radiation



	Gy	LCL	UCL
LD5	1.56	1.31	1.64
LD10	1.59	1.38	1.67
LD15	1.62	1.43	1.68
LD20	1.64	1.47	1.70
LD25	1.65	1.50	1.71
LD30	1.67	1.53	1.73
LD35	1.68	1.56	1.74
LD40	1.70	1.59	1.76
LD45	1.71	1.61	1.77
LD50	1.73	1.64	1.80
LD55	1.74	1.66	1.81
LD60	1.75	1.68	1.83
LD65	1.76	1.70	1.86
LD70	1.78	1.71	1.89
LD75	1.79	1.73	1.93
LD80	1.81	1.75	1.97
LD85	1.83	1.77	2.02
LD90	1.86	1.79	2.09
LD95	1.90	1.82	2.20

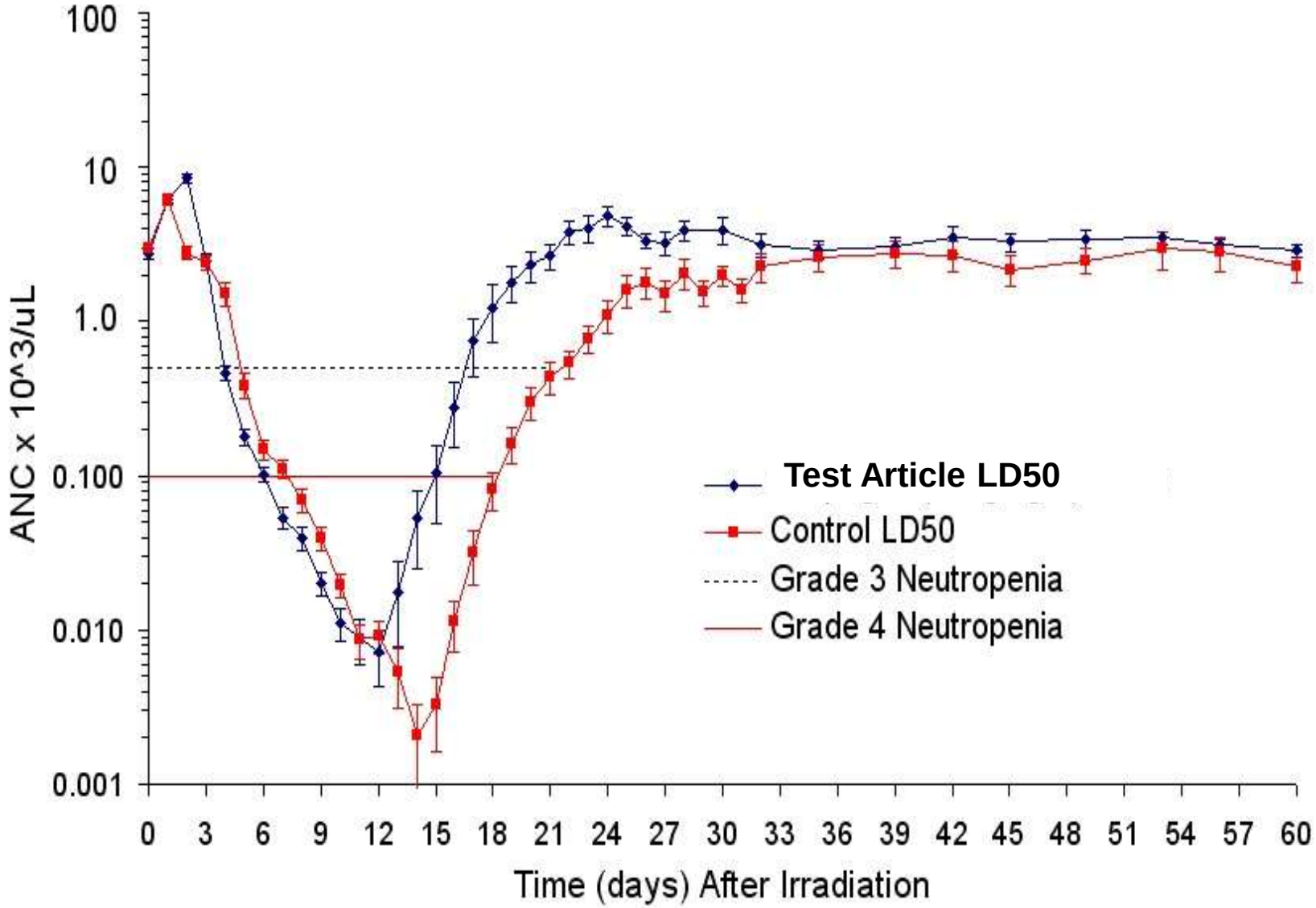
95% confidence intervals

Hematopoietic Medical Countermeasure GLP Non-Pivotal Efficacy Study in NHPs

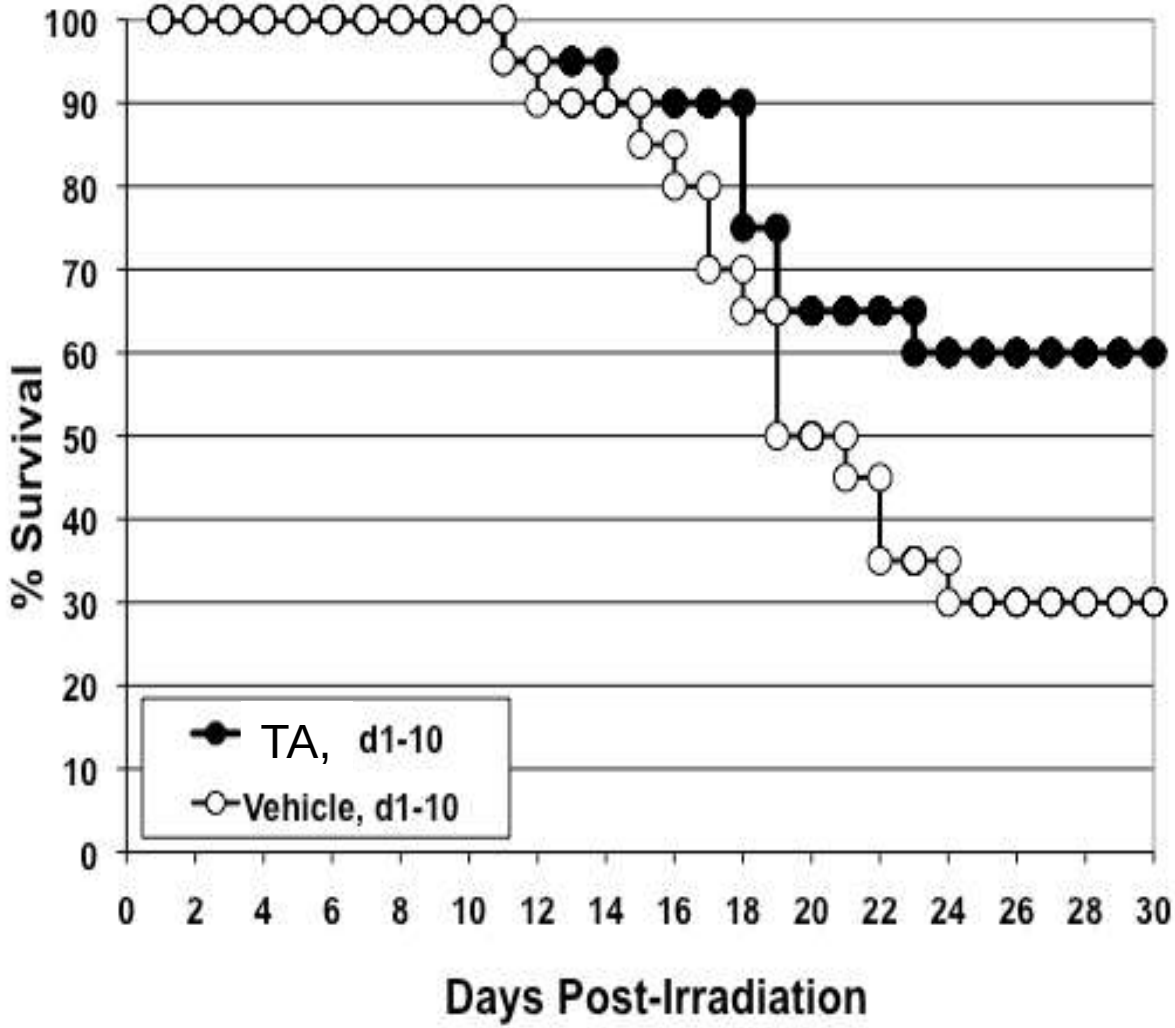


- Administered daily starting 24 hours after lethal irradiation ($LD_{50/30}$)
- Increased survival (80%) vs. control (41%) (p=.004)
- Accelerated neutrophil recovery

Neutrophil Recovery in NHPs



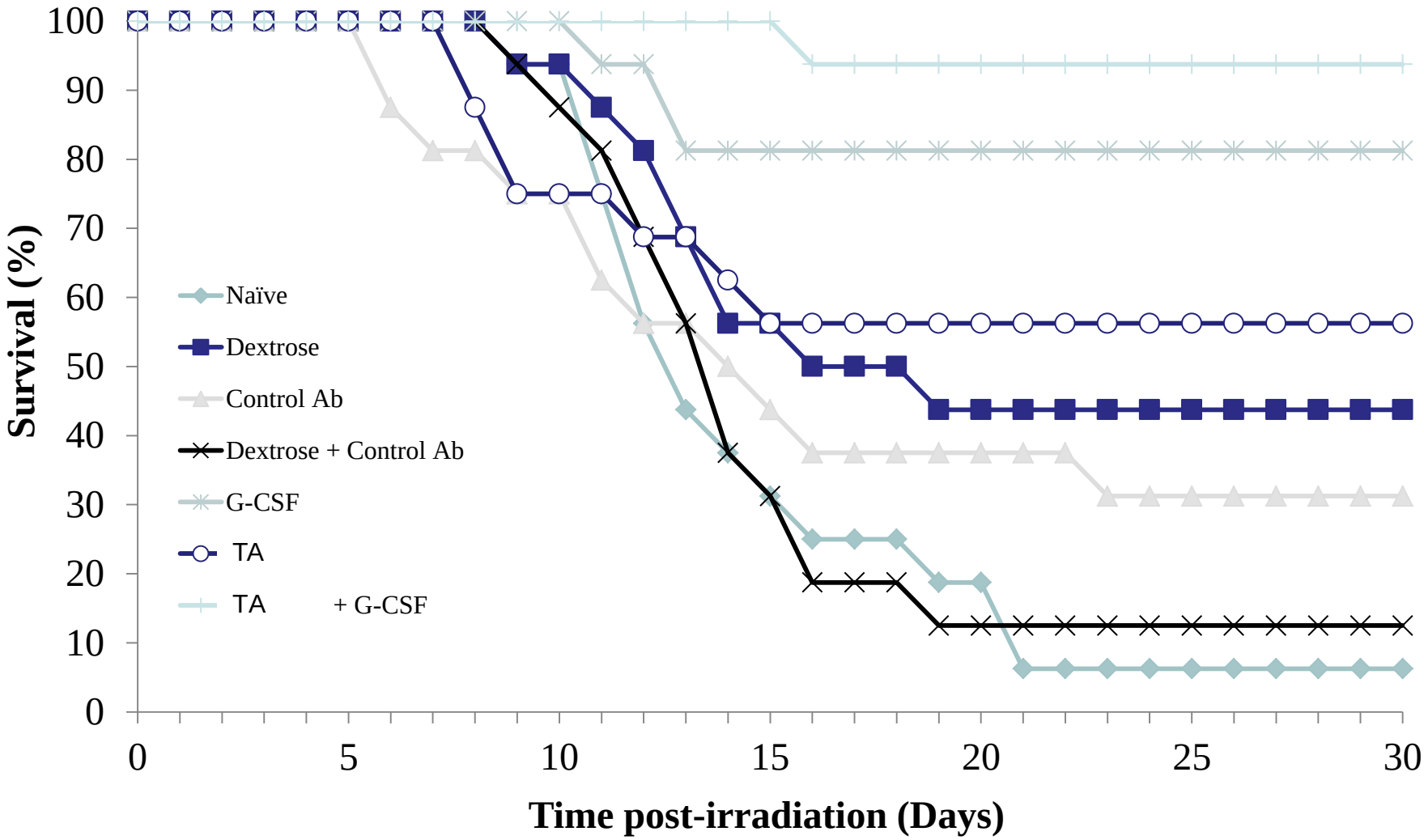
Hematopoietic Acute Radiation Syndrome MCM Candidate (TPO)



30% increase in survival in mice after 7.9 Gy

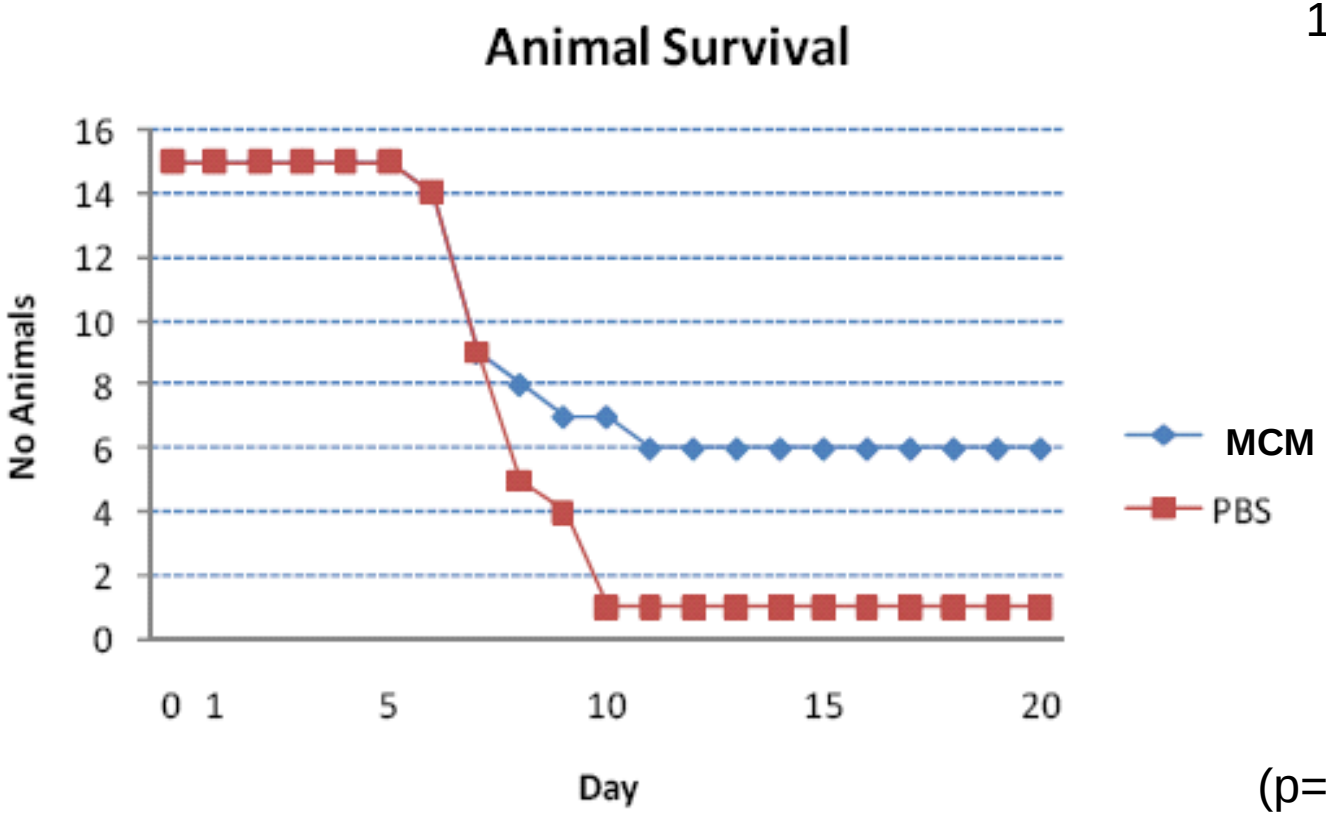
Combination with G-CSF and MCM

1 mg/kg MCM (+12 h, sc) and three once-daily doses of 0.34 mg/kg G-CSF (+6 to +48 h, sc)



Evaluation of Candidate MCM in GI-ARS Rodent Screen after 15 Gy

1500 cGy



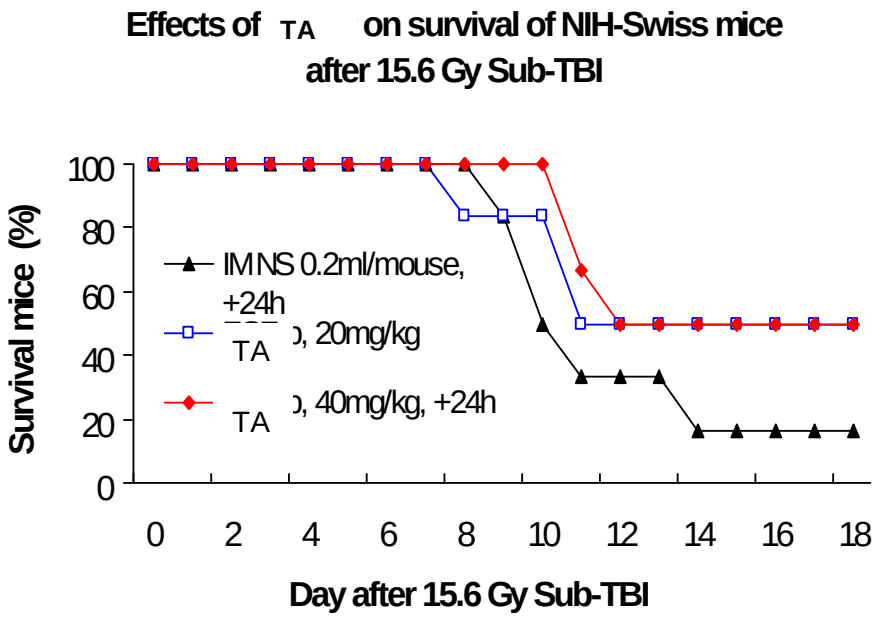
(p=0.04)

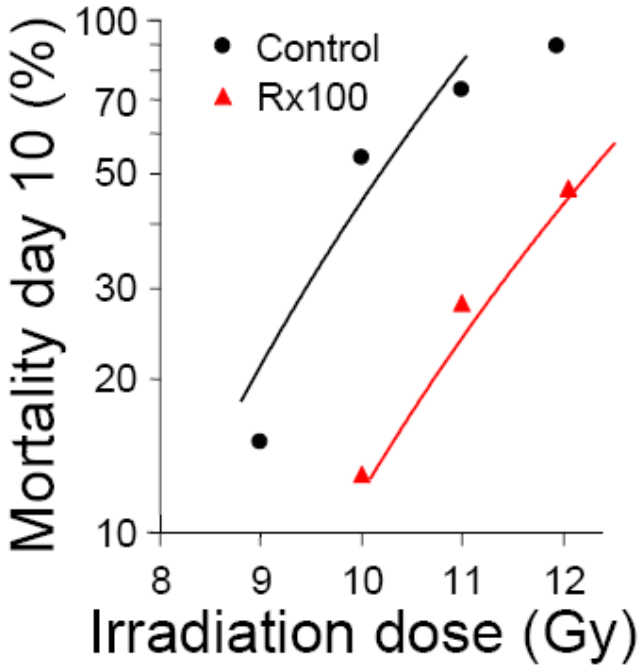
NIAID: EpiStem Ltd.

RC1 - GI Medical Countermeasures

TA mitigates GI death

at +24 hours after IR





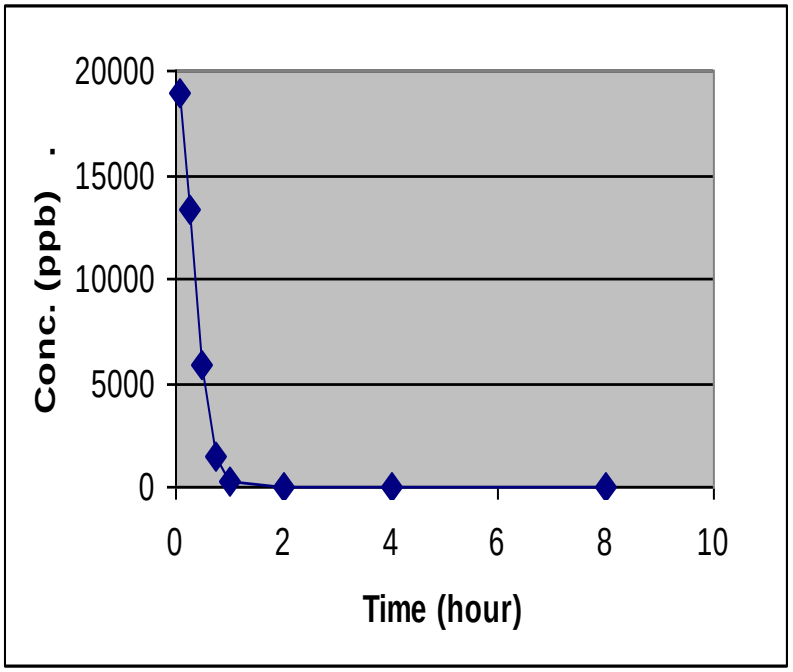
Rx100 shows a DMF of 1.2 when given +26 hours after IR

Radionuclide Medical Countermeasures Development Programs

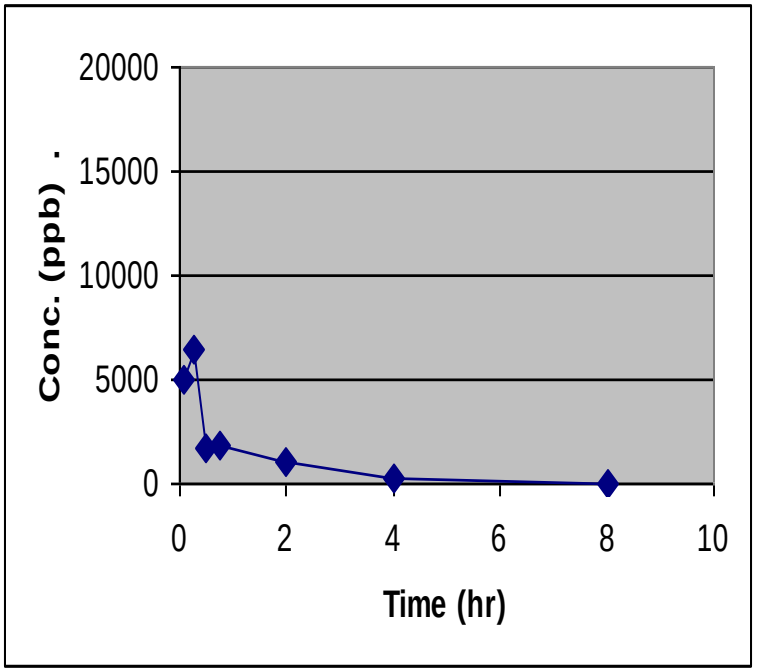
- **Background**
  - Oral administration for mass casualty use
  - Enhanced decorporation efficacy
  - Increase range of radionuclides
- **Contract and Grant Programs**
  - Oral Form of Diethylenetriaminepentaacetate (DTPA)
  - Oral Radionuclide Decorporation Agents

Pro-Drug -- Plasma Levels of DTPA

IV Administration of DTPA
5 mg



Oral Administration of Pro-drug DTPA
7 mg (equivalent dose)



Biodosimetry Program

- **Technical Requirements of a Biodosimetry Architecture**
  - — Capability for rapid screening of large populations
  - — Sufficiently accurate to guide clinical decision-making
  - — Sufficiently flexible to address different needs for different types of radiation exposures
- **Medical / Operational Impact**
  - — Identification of patients requiring urgent medical assessment/triage
  - — Optimization of resource allocation
  - — Reassurance for anxious individuals
  - — Improved risk assessment for delayed or late effects of radiation exposure
  - — Identify specific tissue/organ injuries
  - — Monitoring of therapy (bioassays)

Biodosimetry Architecture

Immediate Triage
Biomarkers of exposure
POC dosimetry

Hematology
N/L ratio
qRT-PCR

EPR
OSL

Significant Exposure

Insignificant Exposure

γH2AX
Micronuclei

Dose Estimation
High-throughput biodosimetry

Risk Assessment
Cytogenetics
Other markers of cancer risk

Dicentrics
Micronuclei

Optimize MCM utilization

Contamination
Committed dose calculation
Decorporation monitoring

Bioassay

Predictive Biodosimetry
Genomics
Proteomics
Metabolomics

Bridging the Radiation/Nuclear Medical Countermeasure "Animal Rule Pathway"

Discovery, Research, and, Development

Licensure and Procurement

Government, Academia, Corporate Partnerships

Food and Drug Administration – CDER, CBER, and CDRH

National Institute of Allergy and Infectious Diseases

HHS/Biomedical Advanced Research and Development Authority

NIAID Radiation/Nuclear Medical Countermeasures Development Program Team

- **Bert Maidment, Ph.D.,** Associate Director for Product Development
- **Narayani Ramakrishnan, Ph.D.,** Program Officer
- **Andrea DiCarlo, Ph.D.,** Program Officer
- **David Cassatt, Ph.D.,** Program Officer
- **Mai-Kim Norman,** Health Specialist
- **Francesca Macchiarini,** Program Officer
- **Erika Davies, Ph.D.,** AAAS Research Fellow
- **Christine Czarniecki, Ph.D.,** Chief, Regulatory Affairs
- **Jui Shah, Ph.D.,** Senior Regulatory Affairs Officer
- **Lawrence Prograis, M.D.,** Special Programs and Bioethics

Radiation/Nuclear Medical Countermeasures Product Development Program

- **Bert W. Maidment, PhD**
  Associate Director, Radiation/Nuclear Countermeasures Program
  NIH/NIAID/DAIT
  6610 Rockledge Drive, Room 5321
  301-594-0641 (Voice)
  maidmentb@niaid.nih.gov

- http://www3.niaid.nih.gov/research/topics/radnuc/