

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. 05-5008



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



Biodosimetry

NIAID



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
- AFRRRI

■ Company Collaborations

- Contacts and presentations
- Candidate efficacy screen
- Candidate Optimization
- Candidate Development

■ International Collaborations

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

■ **7 Centers awarded, 5-year cooperative agreements**

■ **Awardees**

- **Columbia University**
- **Albert Einstein**
- **University of Rochester**
- **Dartmouth University**
- **Duke University**
- **UCLA**
- **University of Pittsburgh**

D. Brenner

C. Guha

J. Williams

H. Swartz

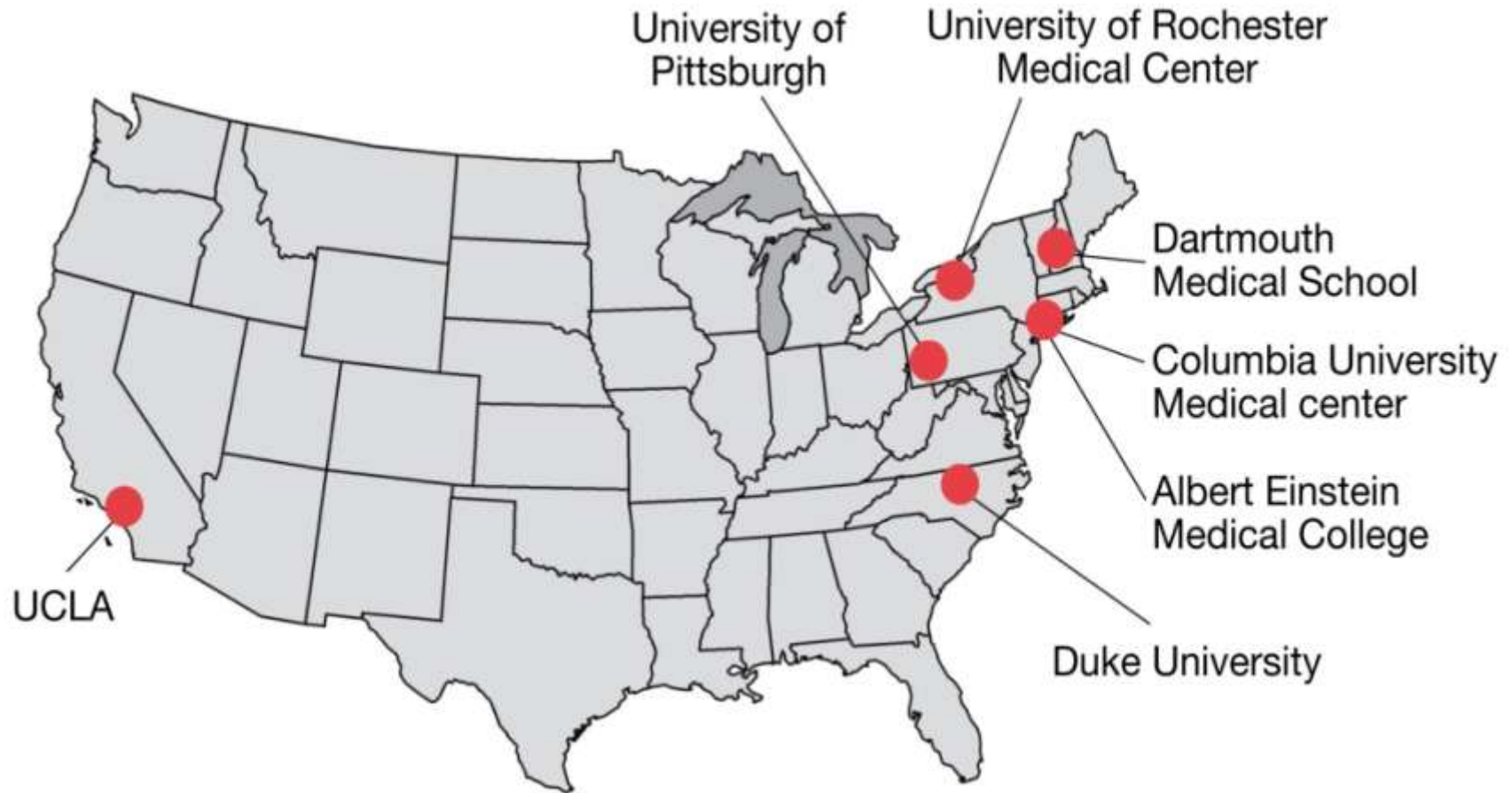
N. Chao

W. McBride

J. Greenberger



Centers for Medical Countermeasures against Radiation – 2010-2014



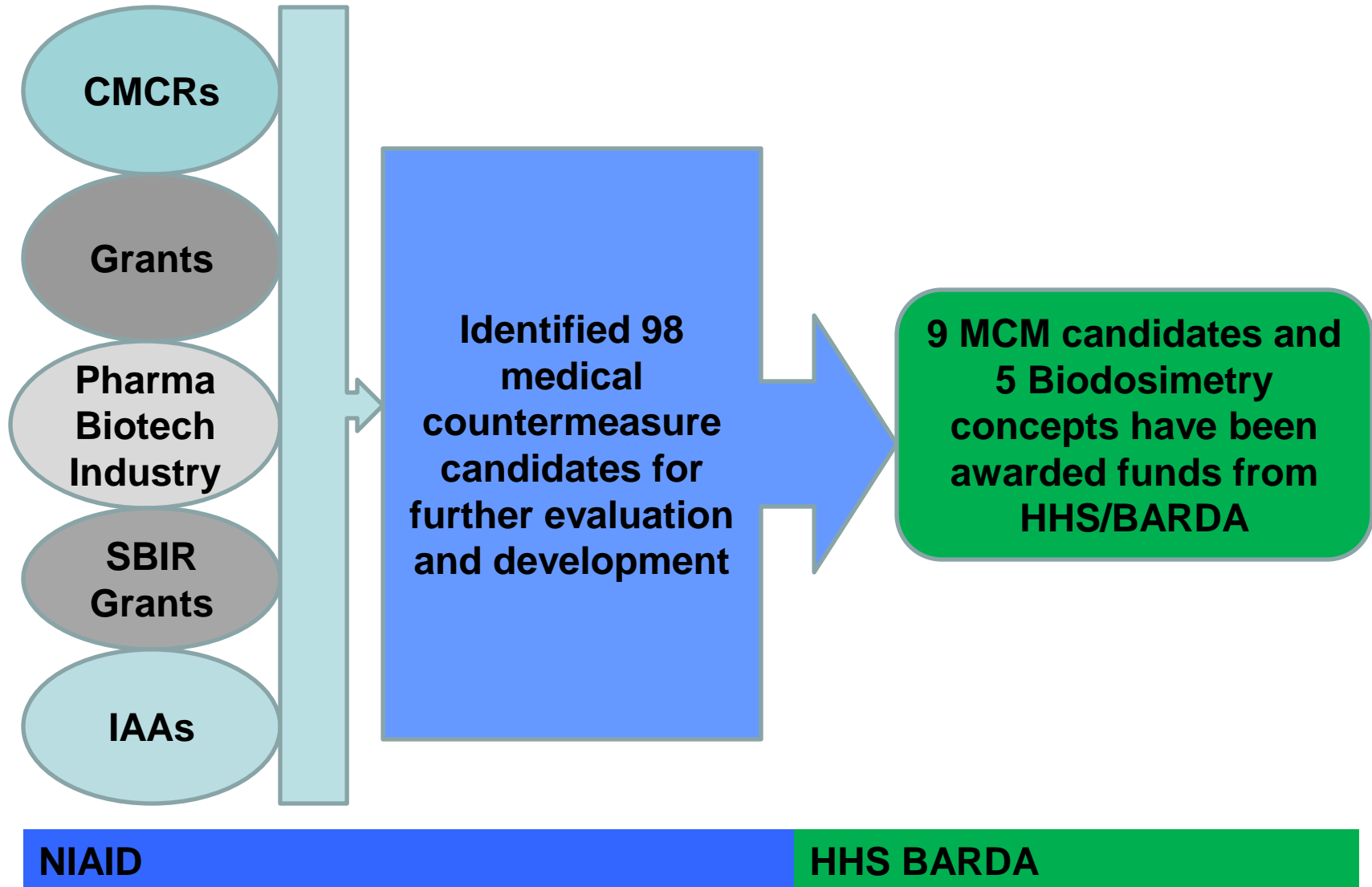
MCM Tissue Specific Injury Mitigation Grant Programs:

- **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

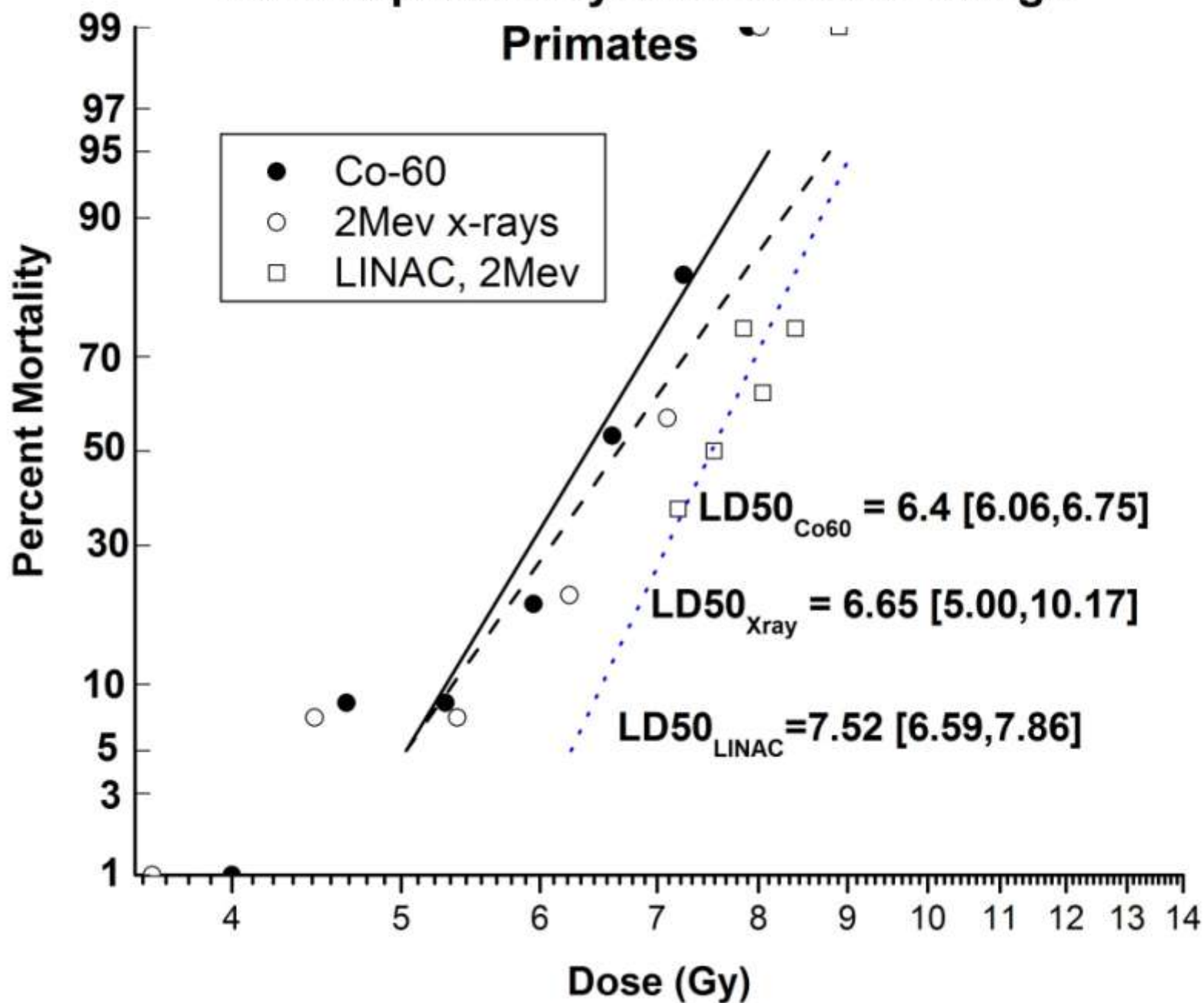
■ Mechanisms of Action

- Anti-oxidants**
- Anti-inflammatories**
- Anti-apoptotics**
- Growth factors and cytokines**
- Cell-based therapies**
- Others**

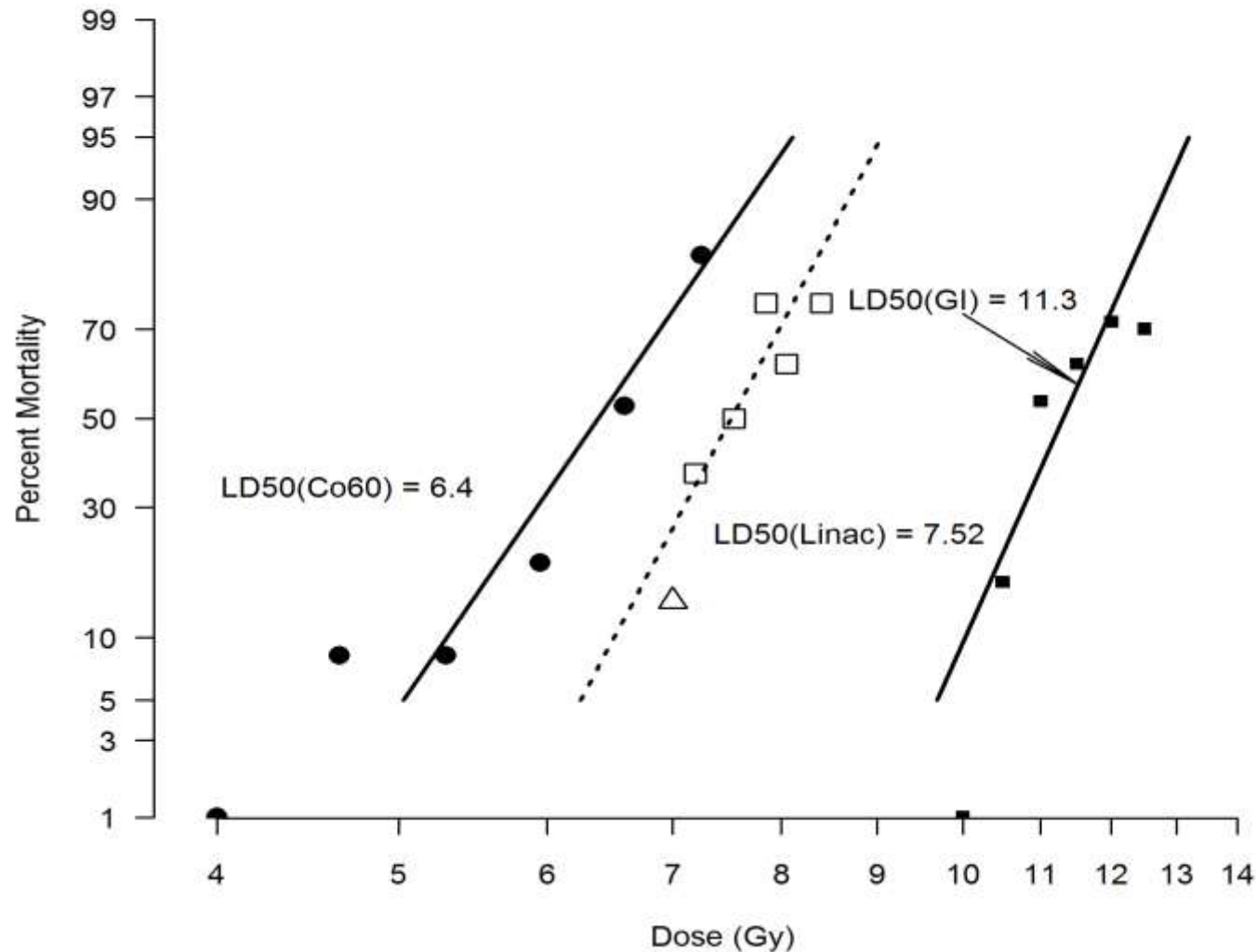
■ Radionuclides

- Blocking agents**
- Decorporation agents**
- Enhancement of mucociliary clearance**

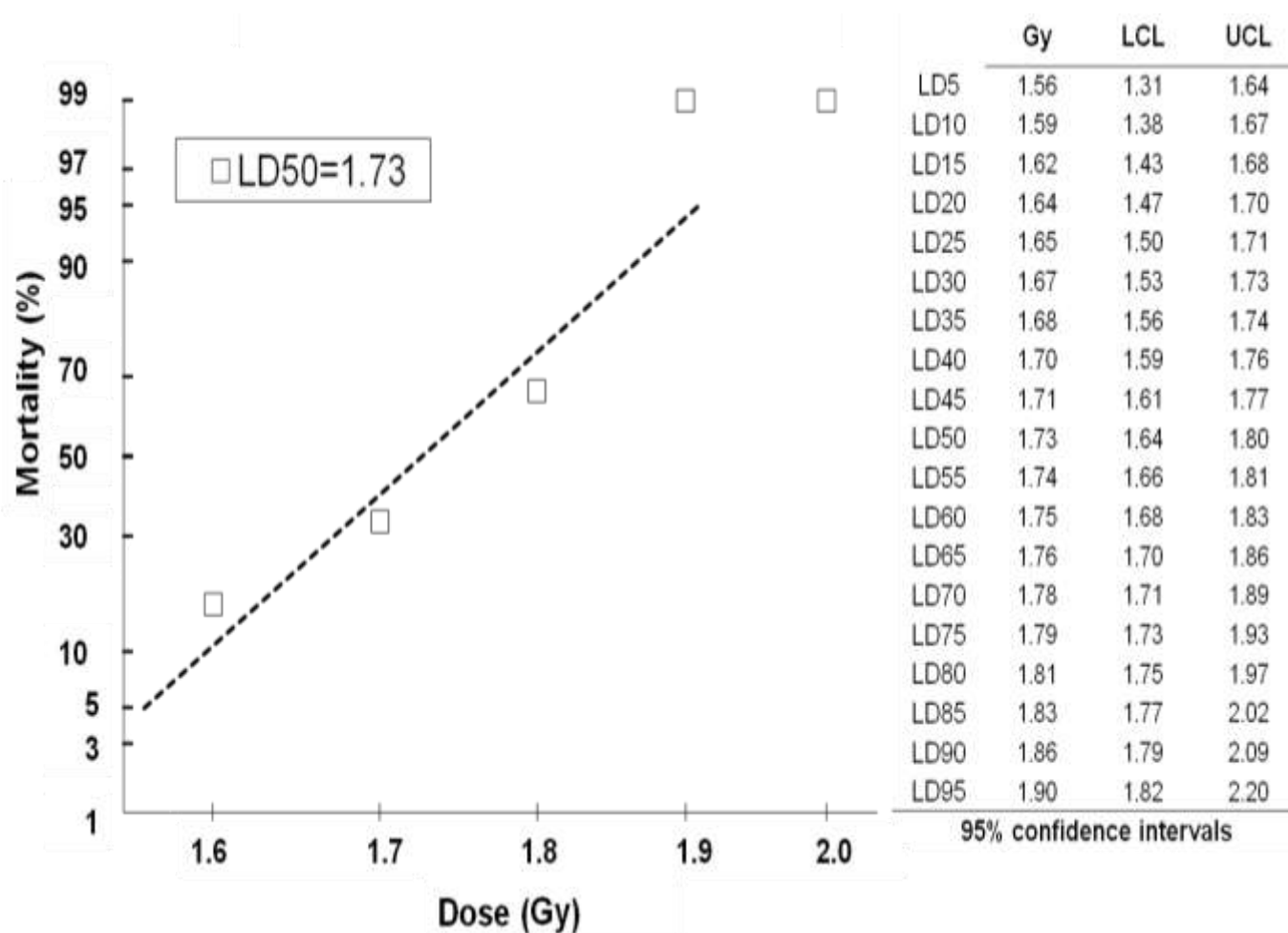
Hematopoietic Syndrome Dose Range Primates



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

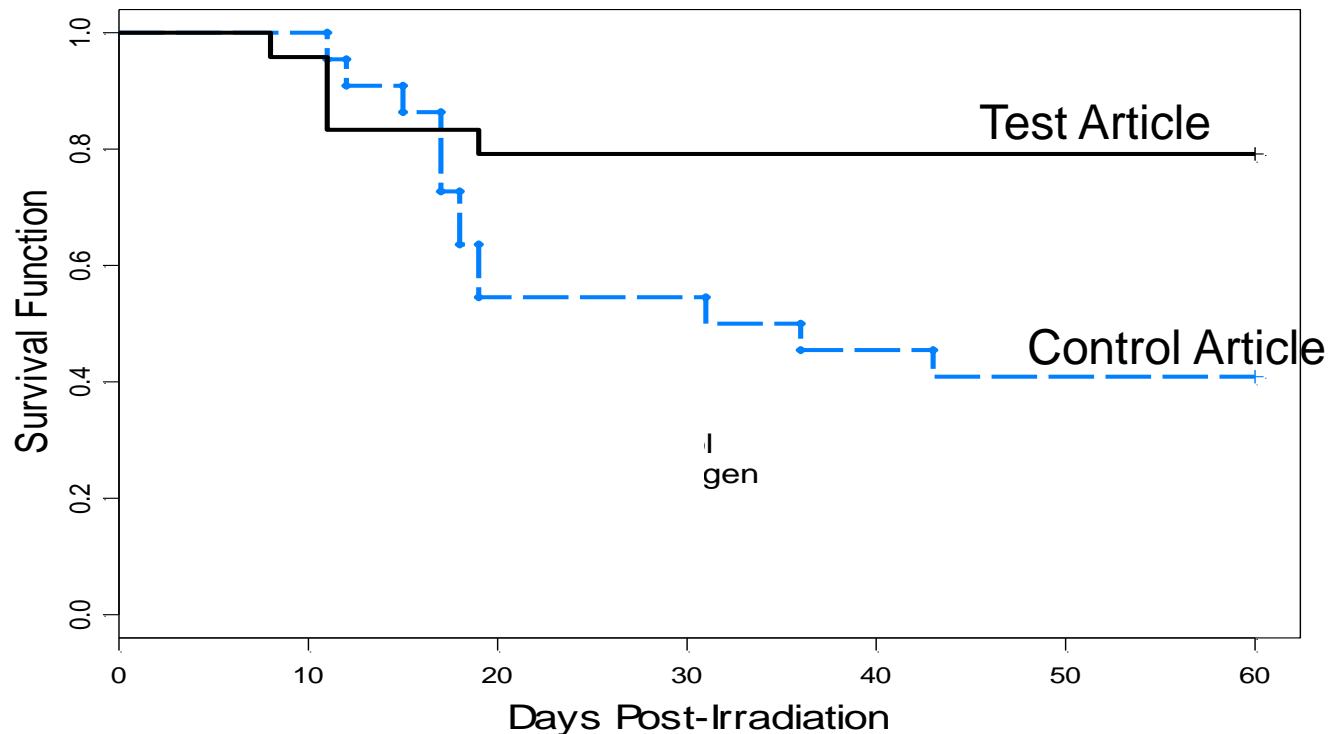


LD50/30 of Mini-pigs Exposed to 1.6 – 2 Gy Co-60 Radiation



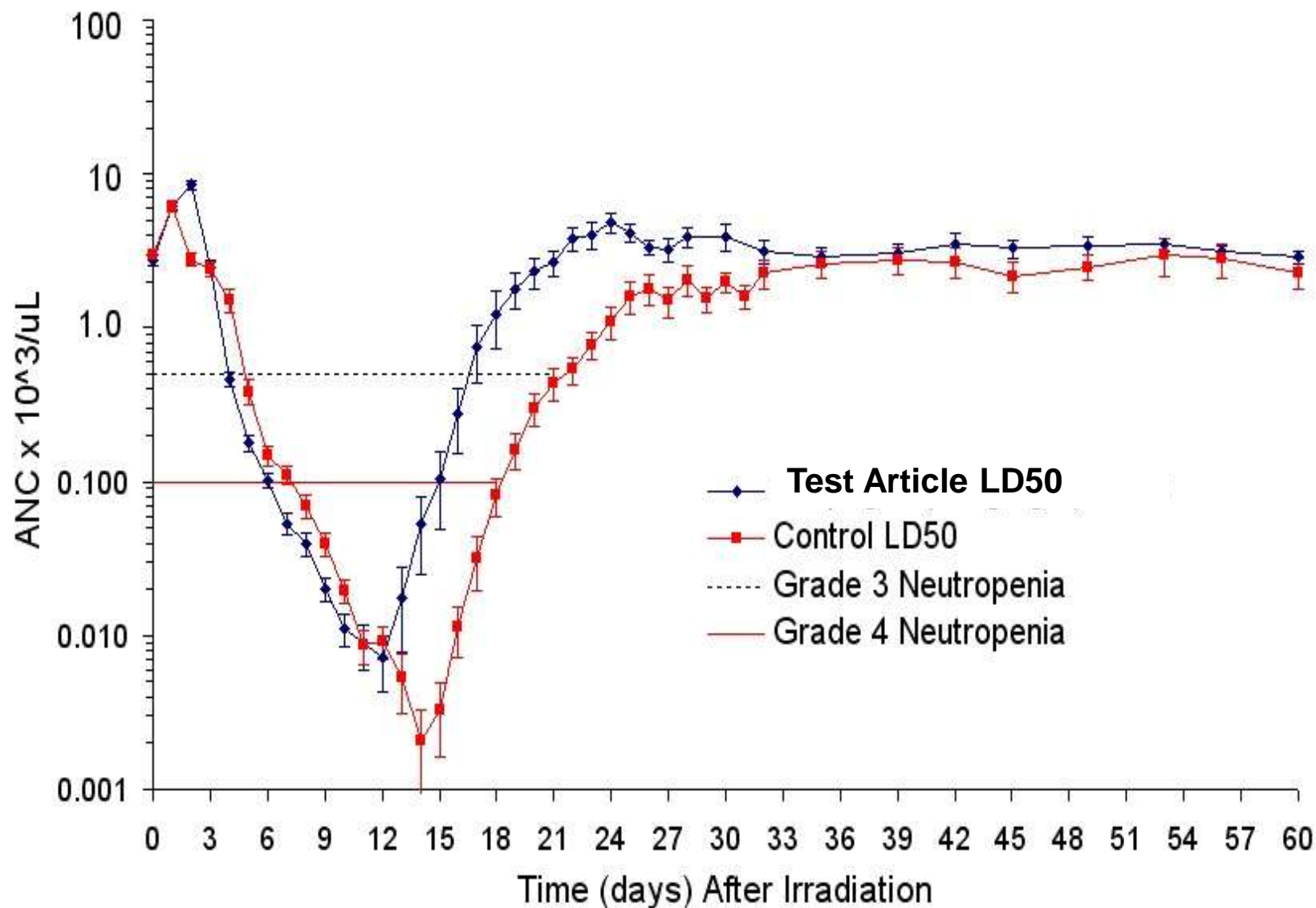
Hematopoietic Medical Countermeasure GLP Non-Pivotal Efficacy Study in NHPs

Kaplan-Meier Survival Curves



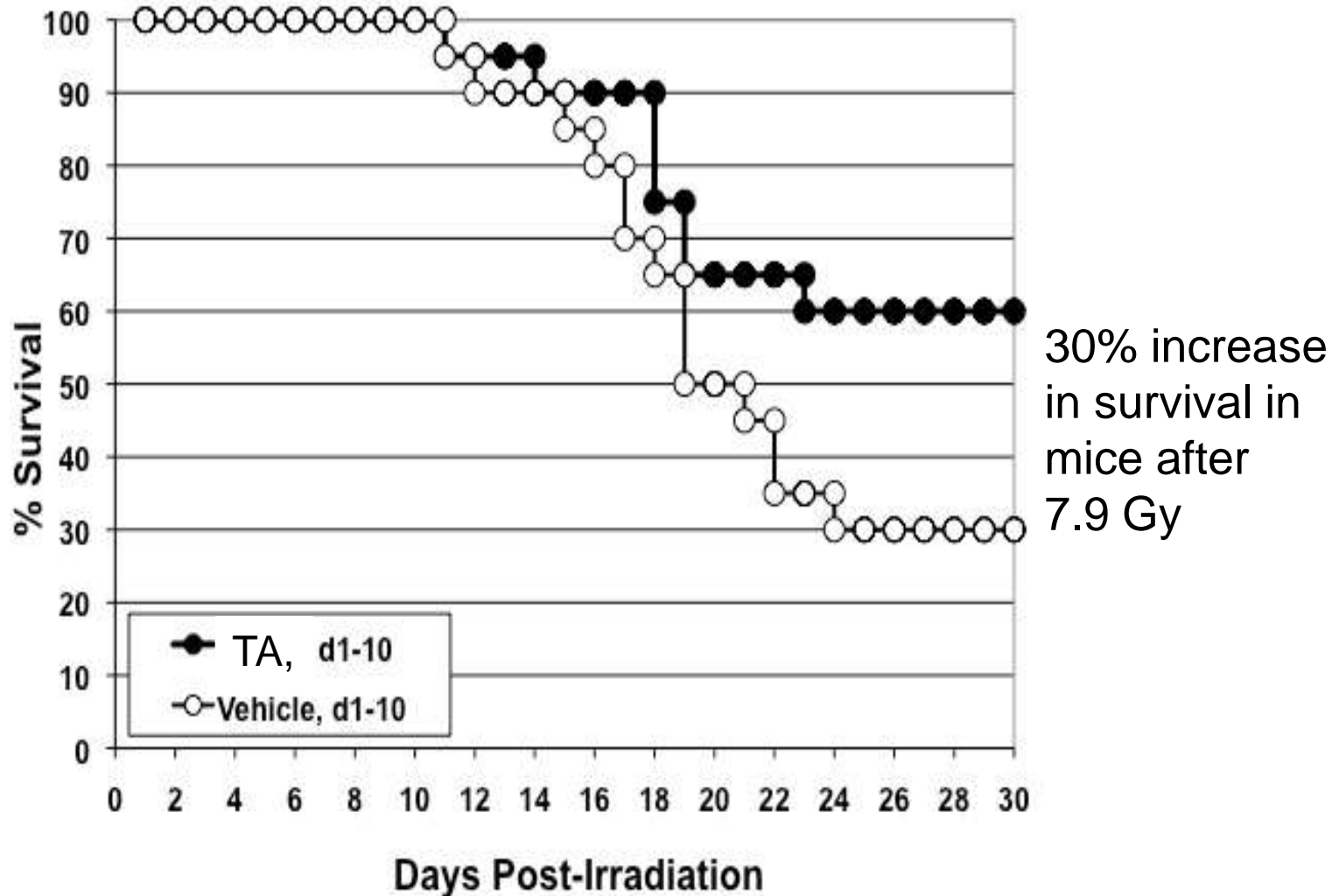
- Administered daily starting 24 hours after lethal irradiation ($LD_{50/30}$)
- Increased survival (80%) vs. control (41%) ($p=.004$)
- Accelerated neutrophil recovery

Neutrophil Recovery in NHPs



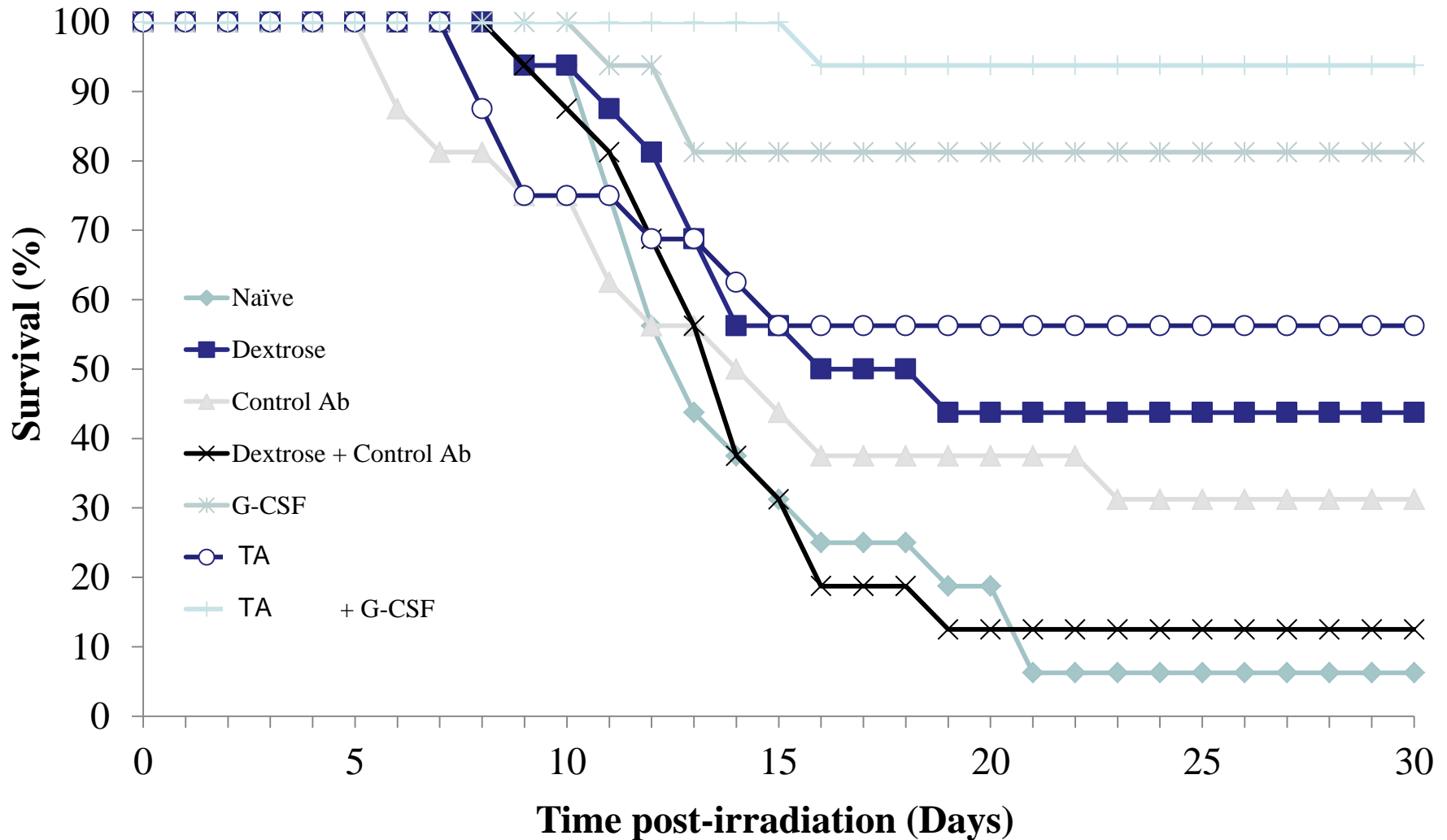
Hematopoietic Acute Radiation Syndrome

MCM Candidate (TPO)

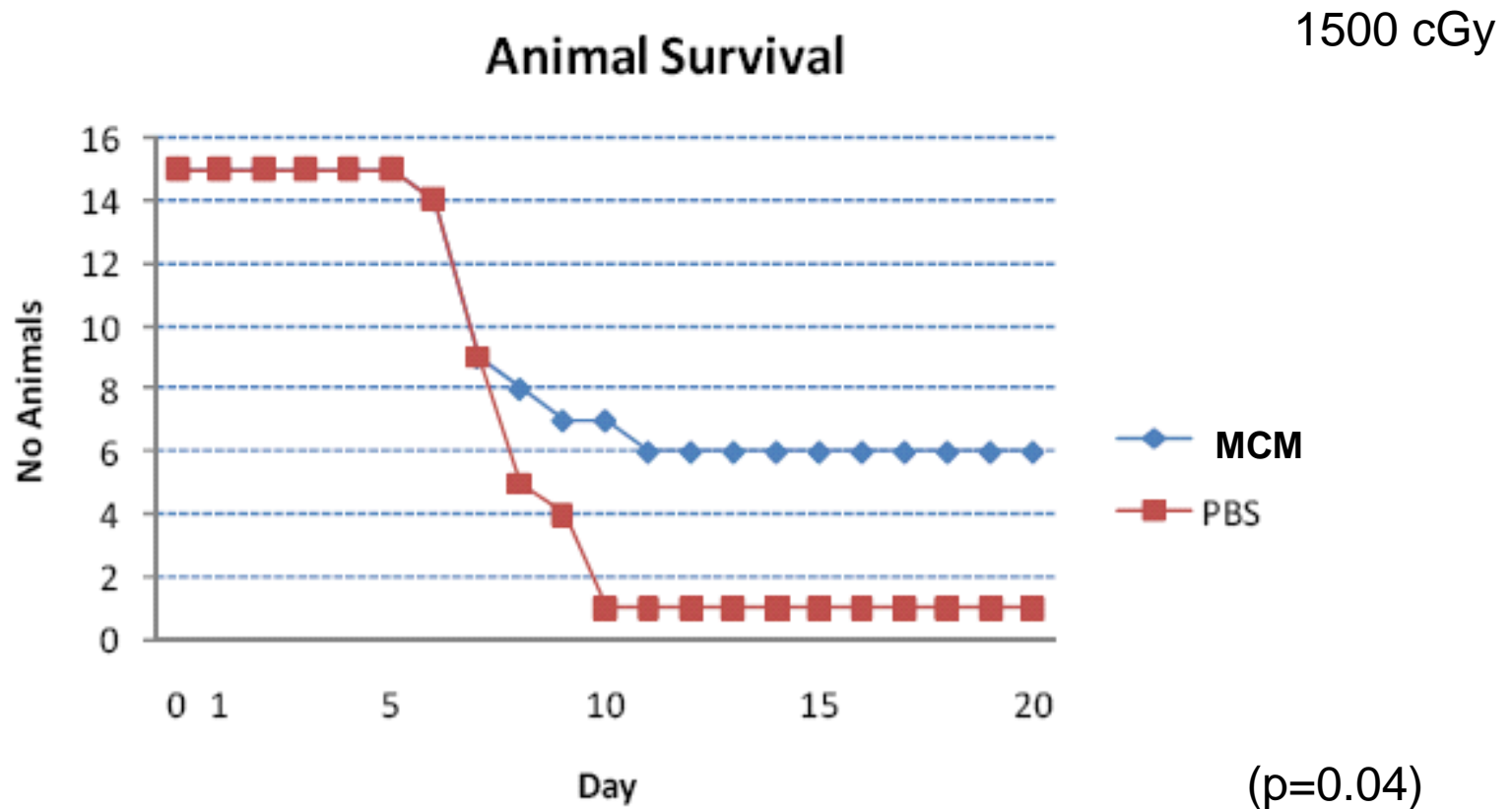


Combination with G-CSF and MCM

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



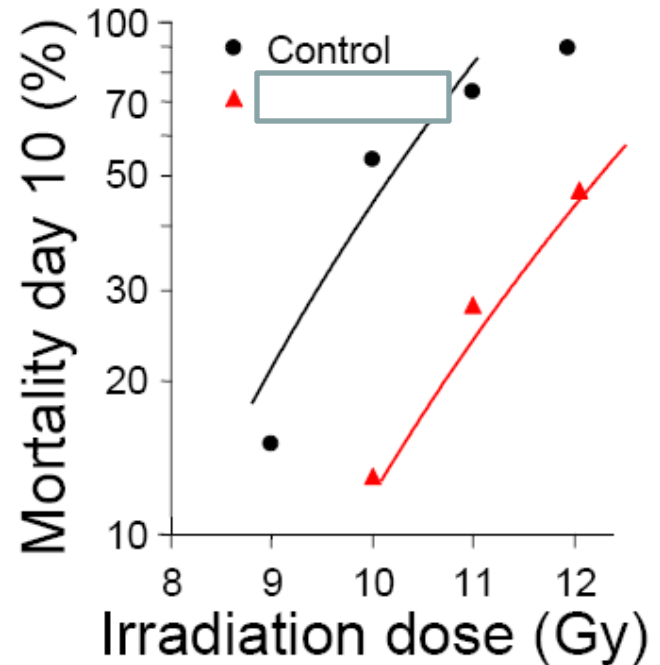
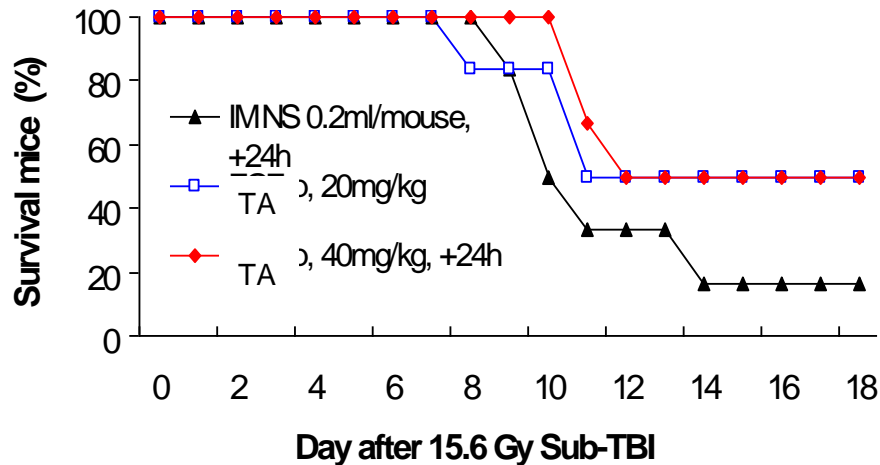
Evaluation of Candidate MCM in GI-ARS Rodent Screen after 15 Gy



RC1 - GI Medical Countermeasures

TA mitigates GI death at +24 hours after IR

Effects of TA on survival of NIH-Swiss mice
after 15.6 Gy Sub-TBI



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

For Official Use Only

Radionuclide Medical Countermeasures Development Programs

■ Background

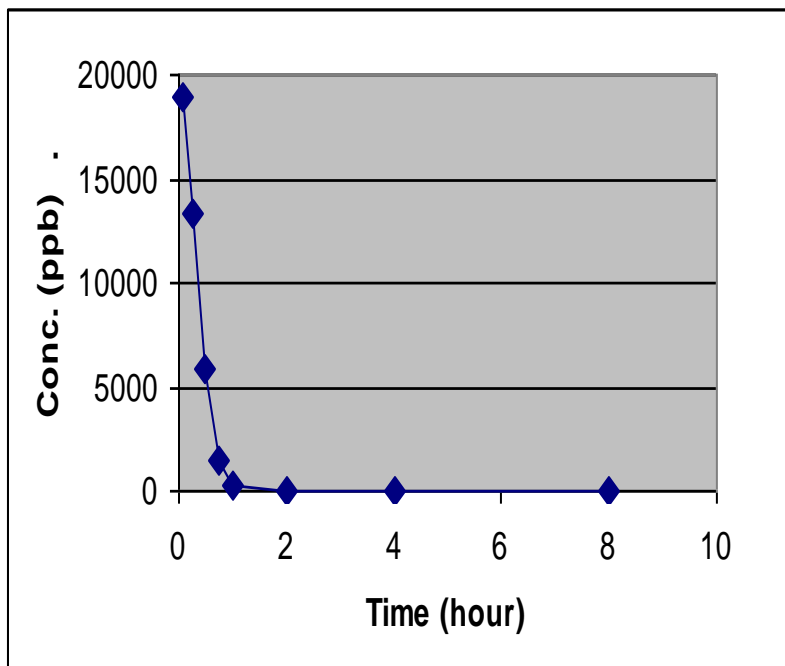
- Oral administration for mass casualty use
- Enhanced decorporation efficacy
- Increase range of radionuclides

■ Contract and Grant Programs

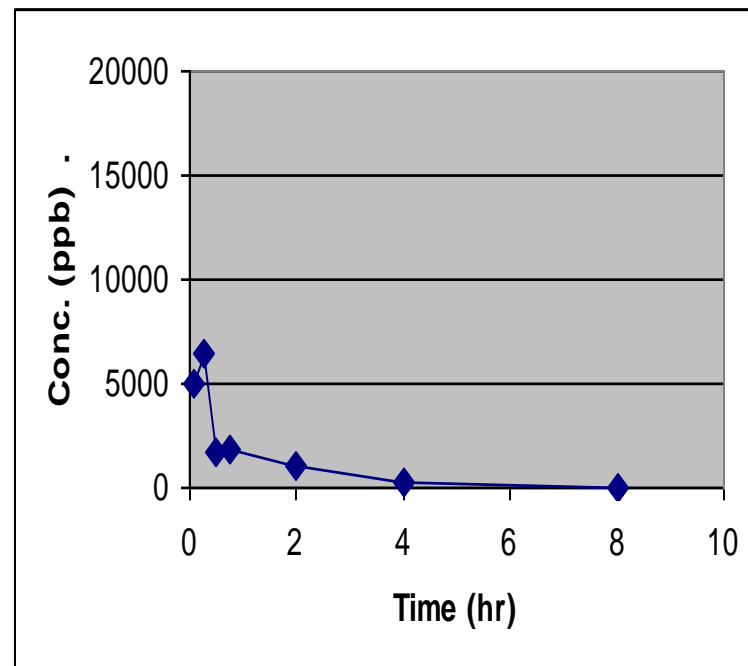
- Oral Form of Diethylenetriaminepentaacetate (DTPA)
- Oral Radionuclide Decorporation Agents

Pro-Drug -- Plasma Levels of DTPA

IV Administration of DTPA 5 mg



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



Biodosimetry Program

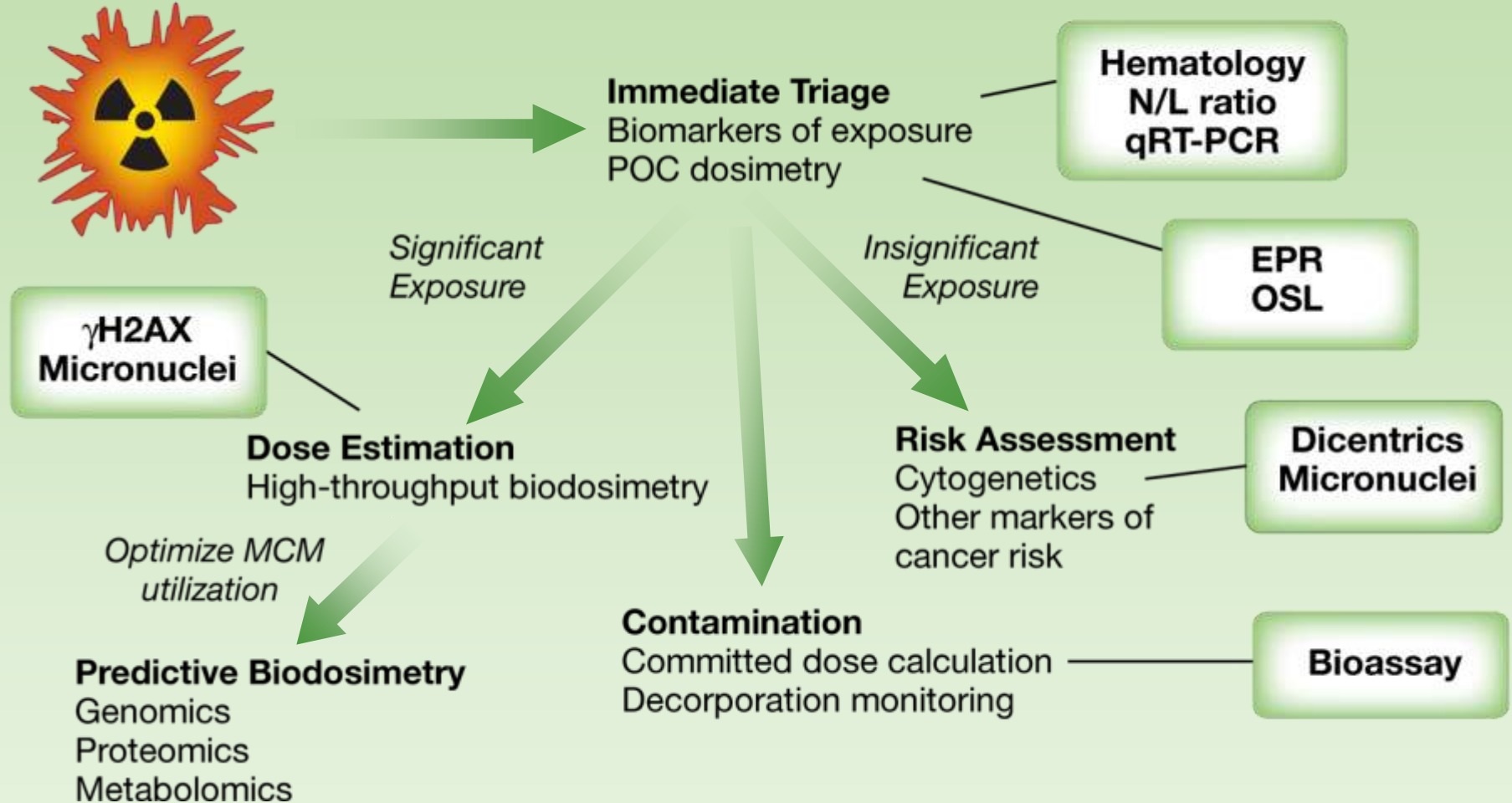
■ Technical Requirements of a Biodosimetry Architecture

- 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



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. Madmen, 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/>

