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

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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
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

- **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

- **Biodosimetry Methods and Devices**
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 Decomposition Agents Development

Biososimetry

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
Identified 98 medical countermeasure candidates for further evaluation and development.

9 MCM candidates and 5 Biodosimetry concepts have been awarded funds from HHS/BARDA.
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**

- Cytokines (filgrastim, pegfilgrastim, epoietin, ARA290)
- Combination cytokine therapy (Flt3L, IL-7, G-CSF)
- TPO receptor agonists (Romiplostim, PegTPOmp, Alx4100, TPIAO)
- Cell-based therapies (MPCs, cord blood, HSCs, endothelial cells)
- HGH
- P38 MAPK inhibitor (SB203580)
- KGF
- WW85
- Ethyl pyruvate
- HDAC inhibitors
Lethal Dose Response Curves for Hematopoietic and Gastrointestinal Acute Radiation Syndrome in NHPs

LD50(Co60) = 6.4

LD50(GI) = 11.3

LD50(Linac) = 7.52
LD50/30 of Mini-pigs Exposed to 1.6 – 2 Gy Co-60 Radiation

![Graph showing mortality vs dose with LD50=1.73 and 95% confidence intervals for different dose levels.]

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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

![Graph showing neutrophil recovery](image)

- **ANC x 10^3/uL**
  - **Test Article LD50**
  - **Control LD50**
  - **Grade 3 Neutropenia**
  - **Grade 4 Neutropenia**

**Time (days) After Irradiation**
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)

Survival (%) vs. Time post-irradiation (Days)

- Naïve
- Dextrose
- Control Ab
- Dextrose + Control Ab
- G-CSF
- TA
- TA + G-CSF
Evaluation of Candidate MCM in GI-ARS Rodent Screen after 15 Gy

1500 cGy

Animal Survival

(p=0.04)

NIAID: EpiStem Ltd.
TA mitigates GI death at +24 hours after IR

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

Rx100 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)
Biosdosimetry Architecture

- Immediate Triage
  - Biomarkers of exposure
  - POC dosimetry

- Significant Exposure
  - Dose Estimation
    - High-throughput biosdosimetry

- Insignificant Exposure
  - Risk Assessment
    - Cytogenetics
    - Other markers of cancer risk

- Contamination
  - Committed dose calculation
  - Decomposition monitoring

- Predictive Biosdosimetry
  - Genomics
  - Proteomics
  - Metabolomics

- OSL
  - EPR
- Bioassay
- Hematology
  - N/L ratio
  - qRT-PCR

\[ \gamma H2AX \]
Micronuclei
Bridging the Radiation/Nuclear Medical Countermeasure “Animal Rule Pathway”

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

Discovery, Research, and Development

Licensure and Procurement
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