Report Documentation Page

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<th>1. REPORT DATE</th>
<th>2. REPORT TYPE</th>
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<td>00-00-2011 to 00-00-2011</td>
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<td>NIH/NIAID Radiation/Nuclear Medical Countermeasures Development Program</td>
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<tr>
<td>National Institute of Allergy and Infectious Diseases, Division of Allergy, Immunology, and Transplantation, 6610 Rockledge Drive, Room 5321, Bethesda, MD, 20892-6612</td>
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<td>Presented during the Radiation Countermeasures Symposium, June 15, 2011 Armed Forces Radiobiology Research Institute at the Uniformed Services University in Bethesda, Maryland</td>
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Standard Form 298 (Rev. 8-98)
Prepared by ANSI Std Z39-18
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
Types of Radiation Exposure

- Radiological terrorist events
  - RDD (Dirty Bombs)
  - RED
  - Food or Water Contamination
- Nuclear detonation
- Accident
  - Power Plant Release
  - Sealed radiological sources
Components of NIH Strategic Plan and Research Agenda

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

- **Biososimetry Methods and Devices**
Radiation/Nuclear Medical Countermeasures

- **Mechanisms of Action**
  - Anti-oxidants
  - Anti-inflammatory agents
  - Anti-apoptotics
  - Growth factors and cytokines
  - Cell-based therapies
  - Others

- **Radiation Syndromes**
  - Acute radiation syndromes (HE, GI, CNS)
  - Delayed effects of radiation exposure (skin, lung, kidney, others)

- **Radionuclides**
  - Blocking agents
  - Decorporation agents
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**
Centers for Medical Countermeasures against Radiation – 2010-2014

- UCLA
- University of Pittsburgh
- University of Rochester Medical Center
- Dartmouth Medical School
- Columbia University Medical Center
- Albert Einstein Medical College
- Duke University
MCM Tissue Specific Injury Mitigation Grant Programs:

- Investigator-initiated awards (R01s); 11 grants
- Radiation Combined Injury (R21/R33s); 11 grants
- Thrombocytopenia; 7 grants
- Lung Radiation Injury; 9 grants
- Cutaneous Radiation Injury; 4 grants
- RC2 GO Grants; 5 GI and 1 Decorporation Agent
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
Radiation/Nuclear Medical Countermeasure Product Development Pathway

CMCRs/Univ/Pharma - Basic Research
- Discovery
- Initial efficacy studies
- Animal model development
- Determine lead compound
- Mechanism of action

NIAID Product Development Program - Nonclinical Development
- Protocol writing
- IND preparation
- Pre-IND meeting
- IND submission
- FDA review

HHS/BARDA - Clinical Development, Pivotal Trials
- NDA/BLA preparation
- NDA/BLA submission
- FDA review

- Screen efficacy rodent/NHP
- Optimize dose, route and schedule of administration
- Tox/Safety Pharm/PK/PD, ADME, cGMP manufacture

- Phase I safety/PK studies in humans
- Large scale cGMP manufacture
- GLP pivotal animal efficacy studies
- Phase II safety/efficacy in humans
- Phase III pivotal efficacy studies in humans

Regulatory Affairs

NIAID program capabilities are in blue.
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 Diethyleneetriaminepentaacetate (DTPA)
  - Oral Radionuclide Decorporation Agents
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

γH2AX
Micronuclei

Significant Exposure

Dose Estimation
High-throughput biodosimetry

Dicentrics
Micronuclei

Risk Assessment
Cytogenetics
Other markers of cancer risk

Optimize MCM utilization

Contamination
Committed dose calculation
Decorporation monitoring

Bioassay

Predictive Biodosimetry
Genomics
Proteomics
Metabolomics

Insignificant Exposure
Successful Radiation/Nuclear Medical Countermeasure Product Development

- Urgency and priority for national preparedness for rapid development and licensure of safe and effective medical countermeasures

- Success will require unprecedented collegial collaboration, communication, coordination, and interaction among:
  - Government agencies especially FDA, CDC, NIH, HHS, DOD
  - Pharmaceutical industry
  - Academia

- Product development plans need to be developed with label indication in mind
Bridging the Radiation/Nuclear Medical Countermeasure “Animal Rule Pathway”

Discovery, Research, and, Development

Government, Academia, Corporate Partnerships

Food and Drug Administration – CDER, CBER, and CDRH

National Institute of Allergy and Infectious Diseases

Licensure and Procurement

HHS/Biomedical Advanced Research and Development Authority
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
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- http://www3.niaid.nih.gov/research/topics/radnuc/