Medical Chemical and Biological Defense Research Program

Presented to the Advanced Planning Briefing to Industry

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Agenda

• Program Overview
• Product Development
• Medical Biological Defense Research Program
• Medical Chemical Defense Research Program
• Challenges and Opportunities
• Questions
Medical Chemical/Biological Defense Rationale for Investment

• “... the United States is likely to be challenged by adversaries who possess a wide range of capabilities, including asymmetric approaches to warfare, particularly weapons of mass destruction.” Quadrennial Defense Review (Sep 2001)

• Direct payoff of chemical/biological defense R&D: Reduction, even elimination, of casualties which would otherwise follow a CW/BW attack.

• Indirect payoffs: Effective products against CW/BW deter employment and proliferation of CW/BW capabilities.

• Efforts address Joint Service/Combatant Commanders requirements
Medical Chemical and Biological Defense Research Program
Mission & Vision

• Provide medical solutions for military requirements to protect and sustain the force in a Chemical and/or Biological Warfare environment

• To Preserve Total Warfighter Effectiveness on a CW/BW Battlefield
  – Prevent casualties
  – Provide effective treatment of casualties for rapid return to duty
  – Provide rapid, far-forward diagnosis of CW/BW disease
Organizational Structures

• U.S. Army Medical Research and Materiel Command manages and executes the tech base, or S&T portion of CBDP medical chemical and biological defense research program.

• Program Executive Office, Chemical and Biological Defense, Chemical and Biological Medical Systems (CBMS) manages and executes advanced development and procurement of chemical and biological defense materiel.

• Secretary of the Army is the Executive Agent.
S&T Management Structure

HQ U.S. Army Medical Research and Materiel Command (USAMRMC)

Oversight and guidance

MG Martinez-Lopez CG, USAMRMC
COL Glenn Deputy for R&D
Dr. Linden Research Area Director Medical Chem/Bio
COL Ross Director, Med Chem
LTC Skvorak Director, Med Bio

CHEM
- Nerve Agent Pretreatments
- Nerve Agent Therapeutics
- Vesicant Pretreatments
- Vesicant Therapeutics
- Diagnostics
- Casualty Care
- Emerging Chemical Agents
- Low Level
- Viral Vaccines
- Bacterial Vaccines
- Toxin Vaccines
- Diagnostics

BIO
- Viral Therapeutics
- Bacterial Therapeutics
- Toxin Therapeutics

PROGRAM DEVELOPMENT AND EXECUTION

Secretary of the Army serves as the Executive Agent for Medical Chemical and Biological Defense Programs
MCBDRP Locations

- Fort Detrick, MD
  - MCBDRP
  - U.S. Army Medical Research Institute of Infectious Diseases
- Forest Glen Annex, MD
  - Walter Reed Army Institute of Research
  - Naval Medical Research Center
- Washington D.C.
  - Armed Forces Institute of Pathology
- Aberdeen Proving Ground, MD
  - U.S. Army Medical Research Institute of Chemical Defense
- Natick, MA
  - U.S. Army Medical Research Institute of Environmental Medicine
Protecting Warfighters Through Integration and Teamwork

**Intelligence**
- Agent
- Delivery System
- Organization
- Time

**Education & Training**
- Military and Civilian Health Care Providers
- Electronic Communication
- Distance Learning

**Chem/Bio Defense Doctrine**

**Medical Countermeasures**
- Vaccines & Prophylaxes
- Diagnostics
- Therapeutics

**Physical Countermeasures**
- Detection
- Physical Protection
- Decontamination
Intelligence Requirements Process

**THREAT ASSESSMENTS**

- Prepared in discrete, tailored packages
- Evaluate impact on users
- Define mission needs

**REQUIREMENTS**

- Joint Requirements Office for Chemical, Biological, Radiological and Nuclear Defense (JRO-CBRN)
- Joint Requirements Oversight Council (JROC)

**PROGRAMS**

- Joint Service Materiel Group (JSMG)
- Defense Threat Reduction Agency (DTRA)/Joint Program Executive Office (JPEO)
- OSD coordinates/integrates funding requests

All programs driven by validated threats and defined mission needs
Sources of Guidance

Mission Area/Needs Analyses

Capabilities Documents*

JPL/CINC Requirements

Advanced Capabilities Enhancements

JRO-CBRN Joint FOCs

Services/CINC/ Joint Staff Evaluation

POM Funding

Programs

* ICD: Initial Capabilities Document (Milestone A)
* CDD: Capabilities Development Document (Milestone B)
* CPD: Capabilities Production Document (Milestone C)
Basic Principles

• Program requirements from the top
• Research should be planned
• Plans should be reviewed
  – Intramural review
  – Extramural review
• Outcomes should be evaluated
  – Intramural review
  – Extramural review
The “Tech Base” Products

- Basic Research Discoveries (Scientific Knowledge)
- Model Development for Agents of DoD Interest
- Vaccine/Pretreatment Candidates
- Therapeutic Candidates
- Diagnostic Tests and Reagents
- Information
- Education
- Expertise & Consultation
- Technology Watch

Our Readiness Posture For Meeting Future Threats And Avoiding Technological Surprise
Medical R&D Process

Tech Base

DISCOVERY

Scientific Steering Committee

Basic Research [6.1]

Applied Research / Adv Tech Dev [6.2/6.3]

Concept & Technology Development

Concept Exploration

Technology Development

Development

System Development & Demonstration

ACD&P / SDD [6.4/6.5]


Integrated Product Team

Chair - RAD IV

Chair – RAD IV/CBMS

Chair - CBMS

New Medical Countermeasures or Devices

Production & Deployment

ACD&P: Advanced Component Development & Prototypes
SDD: System Development and Demonstration

[6.5/Procurement]
# Technology Readiness Levels and Acquisition

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<tr>
<th>RAD 4/Research Laboratories</th>
<th>Technology Transition</th>
<th>CBMS/Prime Systems Contractor</th>
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## Technology Readiness Levels

### TRL-3
- Invent the vaccine
- Test in small animal model

### TRL-4
- Develop bench top manufacturing
- Evaluate different vaccine formulations
- Develop assays for vaccine potency and identity
- Expanded animal testing

### TRL-5
- Produce pilot lot of vaccine
- Develop surrogate marker of immunity
- Test in non-human primates

### TRL-6
- cGMP pilot lot of vaccine
- IND submission to FDA
- Phase I clinical trial

## Program Initiation Requires
- Safe in animals and humans
- Efficacy in animals
- Indicators of human efficacy
- cGMP production methods
Integration of DoD Acquisition and FDA Licensure

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<th>Research Laboratories</th>
<th>Research Labs/CBMS Cooperative Management</th>
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<td>BA1</td>
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**Milestone A**
- Component Advanced Development IPR

**Milestone B**
- System Development & Demonstration

**Milestone C**
- Production & Deployment

**Follow-on Production IPR**
- Sustainment & Disposal

**Program**
- Vaccine IPT

**Oversight**
- FDA Licensure

**SSC**
- PROGRAM

**Consolidated PDT**
- EXECUTION

**PSC**
- PROGRAM

- **Proof of Concept**
- Define Manufacturing Process
- Formulate Multivalent Vaccine (if required)
- Design Surrogate End-point of Clinical Efficacy
- Qualify Assays
- Test in Animal Models
- Characterize Candidates
- Manufacture Small-Scale Pilot Lots
- Pre-IND Activities

- **IND Application to FDA**
- Phase 1 Clinical Trials
- Validate Assays
- Manufacture cGMP Pilot Lots
- Perform Non-clinical Tests
- Manufacture Consistency Lots
- Phase 2a Clinical Trials
- Surrogate Efficacy Tests
- Phase 2b Clinical Trials
- Post-Marketing Surveillance
- Produce, Store and Maintain Vaccine Stockpile
- Prepare and Submit BLA
Medical CB Defense Research Program
Core S&T Program Task Structure

Medical Countermeasures (MC) against BW & CW Agents

Bio DTO Efforts
- CB.24 MC for Encephalitis Viruses
- CB.25 Multiagent Vaccines for Biological Threat Agents*
- CB.26 Common Diagnostic Systems*
- CB.31 MC for Brucellae
- CB.32 Alternative Delivery Methods for Recombinant Protein Vaccines
- CB.33 Recombinant Protective Antigen (rPA) Vaccine Candidate*
- CB.34 Recombinant Plague Vaccine Candidate
- CB.46 Recombinant Ricin Vaccine
- CB.47 Improved Immunodiagnostics Platform
- CB.54 Therapy for Smallpox & other Pathogenic Orthopoxviruses

Vaccines/Pretreatments

Therapeutics

Diagnostics

Chem DTO Efforts
- CB.28 Chemical Agent Prophylaxis II*
- CB.29 Active Topical Skin Protectant*
- CB.30 MC for Vesicant Agents II
- CB.48 Improved Oxime
- CB.51 Low Level CW Agent Exposure: Effects & Countermeasures**

* Defense Technology Objectives (DTOs) completed in FY02
** Joint medical & non-medical DTO
Medical Biological Defense Research
Medical Biological Defense
Potential Threats

• Bacteria:
  – Anthrax
  – Plague
  – Tularemia
  – Brucellosis
  – Glanders
  – Q-Fever
  – Other (food, H₂O)

• Viruses:
  – Smallpox
  – Encephalomyelitis
  – Ebola
  – Marburg

• Toxins:
  – Botulinum (Types A – F)
  – Staphylococcal Enterotoxins (SEB)
  – Ricin
  – Marine Neurotoxins
  – Mycotoxins
  – Clostridium perfringens
**Medical Biological Defense Supporting S&T Efforts**

**Underlined text:** Defense Technology Objectives (DTOs)

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**Vaccines**

Develop vaccines effective against bacterial, viral, and toxin agents.
- Bacterial: anthrax, plague, glanders/melioidosis, and Brucella
- Viral: filoviruses, orthopox viruses, alphaviruses
- Toxins: botulinum, ricin and staphylococcal enterotoxins
- Needle-less delivery methods and multiagent vaccines

**Diagnostics**

Develop a deployable, state-of-the-art diagnostic system: reagents, protocols, and devices. Identify multiple independent biomarkers from different agents simultaneously. Develop confirmatory assays.
- Common diagnostic system (CDS)
- Improved immunodiagnostic platform
- Common integrated diagnostic system

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**Therapeutics**

Identify/develop antibacterial, antiviral, immunotherapeutics, and other compounds effective against bacterial, viral, and toxin agents.
- Bacterial: anthrax, plague, glanders/melioidosis, and Brucella
- Viral: filoviruses and orthopox viruses
- Toxins: botulinum, ricin and staphylococcal enterotoxins

**Challenges**

- Threat Assessment
- Pathogenesis/Disease Mechanisms
- “Appropriate” Animal Models
- Immune Responses & Mechanisms
- Surrogate Markers
- Assay Sensitivity & “Appropriate” Reagents

**DARPA Transition**

MBDRP collaborates with DARPA BW Defense Programs.
- Unconventional pathogen CMs
- Tissue-based Biosensors
- FY01-05 Funding
Emerging Medical BD Products

• Recombinant Plague Vaccine
• Next Generation Anthrax Vaccine
• Multivalent Venezuelan Equine Encephalitis (VEE) Vaccine
• Recombinant Staphylococcal Enterotoxin Multivalent (SEA/SEB) Vaccine
• Recombinant Ricin Vaccine
• Antibiotics and Antiviral Drugs
• Comprehensive Integrated Diagnostic Systems for BD Threats and Infectious Diseases
  – PCR-based and immunodiagnostic systems
  – Supports program requirements for the Joint Biological Agent Identification and Diagnostic System (JBAIDS)
Future Trends

• Countermeasures for Genetically Engineered Microbes
  – Genomic sequencing of BW threat agents to identify and understand virulence factors, toxins, and drug resistance genes

• Immunomodulators and Therapies
  – Alternatives to agent-specific vaccines or therapies

• Multiagent Vaccines
  – Alternative to one vaccine for one BW threat agent

• Alternative vaccine delivery strategies
  – Immunization via mucosal and transdermal routes

• Early markers of infection/host response
DARPA Transition Programs

• Objective: Identify most promising approaches and focus on biological defense program objectives
• Source: DARPA Unconventional Pathogen Countermeasures and Tissue-Based Biosensors programs
• Process: 1) DARPA programs presented to MBDRP scientific panels, 2) MBDRP invites solicitations via the Broad Agency Announcement, 3) proposals receive in-house and external peer review, 4) highly rated proposals form basis for initiating contracts.
• Status: Nine programs selected to date
Current DARPA Transition Programs

• Research to develop broad-spectrum vaccines by molecular breeding (gene shuffling) strategies; focuses cross-protection against pathogenic equine encephalitis viruses. *(Maxygen, Inc.)*
• A novel class of antimicrobial drugs that bind RNA targets involved in the disease process. *(Ibis Therapeutics)*
• High-level plant-based expression system for vaccine antigens and humanized monoclonal antibodies for biological threat agents. *(Arizona State University)*
• Proprietary B-cell sensing technology for rapid and sensitive medical diagnostics for biological threat agents and endemic diseases. *(MIT Lincoln Labs)*
• *In vivo* countermeasures against biological toxin threats of the superantigen family (e.g., staphylococcal enterotoxin B) using a peptide or peptidomimetic antagonist. *(Hebrew University of Jerusalem)*
• Investigation of small molecule anti-genomic therapeutics (SMATs) as countermeasures against a broad spectrum of BW threats, including genetically engineered threats. *(GeneSoft)*
• Small-molecule antibiotics that target the cell-cycle regulated methyltransferase (CcrM) DNA methyltransferase enzyme. *(Anacor Pharmaceuticals, Inc.)*
• Investigation using *in silico* screening methods of structurally diverse small-molecule inhibitors of the zinc endopeptidase of BoNT A. *(contract award pending)*
• Development of nonspecific immunomodulatory agents using a synthetic lipid A analog (aminoalkyl glucosaminide phosphate). *(contract award pending)*
Medical Chemical Defense Research
Medical Chemical Defense
Potential Threats

• Vesicant Agents:
  – HD-Mustard
  – H-Mustard with Impurities
  – HN-Nitrogen Mustard
  – L-Lewisite
  – CX-Phosgene Oxime

• Nerve Agents:
  – GD-Soman
  – GB-Sarin
  – GF
  – VX
  – GA-Tabun
  – Novel Threat Agents

• Blood Agents:
  – AC-Hydrogen Cyanide
  – CN- Salts of: Sodium, Potassium, Calcium
  – CK-Cyanogen Chloride

• Respiratory Agent:
  – Phosgene
Medical Countermeasures Against Chemical Warfare Agents

**Technical Approach:**

- Identify mechanisms of action
- Develop and evaluate products (pre-treatments or drugs) to prevent or counter effects of various chemical warfare agents.
- Develop methods to measure effectiveness of countermeasures in animal models predictive of human response.
- Develop diagnostic systems and assays.

*Technology base provides medical product candidates*
Medical Chemical Defense Supporting S&T Efforts

Underlined text: Defense Technology Objectives (DTOs)

Pretreatments/Prophylaxxes
A prophylactic to detoxify nerve agents. A protective cream to prevent penetration and detoxify CWAs on contact.
- Chemical agent bioscavenger
- Active topical skin protectant
- Vesicant pretreatments
- Cyanide countermeasures (CMs)

Therapeutics
Determine a treatment strategy to minimize pathology and maximize early return to duty to sustain OPTEMPO. Identify leading strategies to treat nerve agent and vesicant casualties.
- Advanced vesicant CMs
- Improved oxime
- Advanced anticonvulsant system
- Neuroprotection against damage caused by nerve agent poisoning
- Non-traditional agent (NTA) CMs
- Inhalation toxicology

Challenges
- Threat Assessment
- Mechanisms of Action
- “Appropriate” Animal Models
- Understanding Pharmacokinetics
- Surrogate Markers
- Assay Sensitivity & “Appropriate” Reagents

Diagnostics
Laboratory diagnostic assays with potential transition to forward battlespace areas. Diagnose, prognose, and manage the CWA casualty.
- Diagnostic assays
- Cyanide diagnostics
- Nerve agent exposure

Low Level CWA Research
- Characterize concentration-time (Ct) relationship for low level / longer time CWA vapor exposures.
- Identify alternative, but medically significant, toxicological endpoints (e.g., other than acetylcholinesterase inhibition) for nerve agents.
- Conduct integration studies linking experimental data sets with predictive human health effect assessments.
- Low level CWA exposure effects & CMs
Fielded Medical Chemical Defense Products

- Nerve Agent Antidote Kit (MARK I)
- Convulsant Antidote for Nerve Agent (CANA)
- Medical Aerosolized Nerve Agent Antidote (MANAA)
- Pyridostigmine Bromide
- M291 Skin Decontamination Kit
- Test Mate Cholinesterase Kit
- Antidote Treatment – Nerve Agent Autoinjector (ATNAA)
- Skin Exposure Reduction Paste Against Chemical Warfare Agents (SERPACWA)
Medical Chemical Defense
Investment in the Future

• Catalytic bioscavengers
• Advanced anticonvulsant
• Field deployable diagnostics
• Ocular treatment for sulfur mustard exposure
• Improved oximes
• Medical treatment of sulfur mustard wounds
Challenges and Opportunities

• Critical infrastructure
  – Animal biocontainment
  – Aerosol exposures

• Critical human resources
  – Expertise
  – Numbers

• New FDA “Animal” Rule
  – Allows consideration of animal efficacy studies in support of licensure requests
  – Additional requirements
    • Understand mechanisms of action of the disease-causing agent
    • Understand basis of action of the vaccine or drug
    • Demonstrate efficacy in relevant animal models
    • Identify surrogate markers of efficacy
United States Army Medical Research Acquisition Activity
Broad Agency Announcement Website

• Pre-proposal and proposal submission information:
  – http://www.usamraa.army.mil
  – Open Broad Agency Announcements (BAA) under Business Opportunities
  – Open USAMRMC BAA 02-1 General Information.

• Research Areas of Interest:
  – Medical Biological Defense Research Program
  – Medical Chemical Defense Research Program
Summary

• Medical chemical and biological defense research presents unique challenges
  – Chemical threat agents
  – Biological threat agents
  – Medical regulatory compliance and DoD acquisitions
• We need cutting edge technologies to develop medical countermeasures for the warfighter
  – Biotechnology
  – Informatics
  – Genomics and Proteomics
• Partnerships with the science community & industry are essential
  – CRADAs
  – Contracts
Questions?