Medical Biological Defense Research Program

LTC John P. Skvorak, DVM, Ph.D.
Director
Chemical and Biological Defense Program
Medical S&T Office
(301) 619-7439/DSN 343-7439
john.skvorak@det.amedd.army.mil

8 September 2003
Agenda

- Program Overview
- Product Development
- Medical Biological Defense Research Program
- Department of Health and Human Services Cooperation
- Challenges and Opportunities
- Summary
Protecting Warfighters Through Integration and Teamwork

Chem/Bio Defense Doctrine

Intelligence
- Agent
- Delivery System
- Organization
- Time

Medical Countermeasures
- Vaccines and Prophylaxes
- Diagnostics
- Therapeutics

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

Physical Countermeasures
- Detection
- Physical Protection
- Decontamination
DoD Program – Secretary of the Army serves as Executive Agent

USAMRMC supports DTRA in management and execution of medical CB defense science and technology (S&T) efforts
  - DTRA/CB – Manage and integrate CB defense S&T efforts
  - JRO-CBRN – Manage and integrate CB defense requirements/capabilities
  - JPEO-CBD – Manage and integrate CB defense acquisition programs
Medical CB Defense Research Program
Mission and Vision

◆ Provide medical solutions for military requirements to protect and sustain the force in a Chemical & Biological Warfare (CBW) environment

◆ To Preserve Total Warfighter Effectiveness on a CBW Battlefield
  • Prevent casualties
  • Provide effective treatment of casualties for rapid return to duty
  • Provide rapid, far-forward diagnosis of CBW exposure
Medical CB Defense Research Program (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
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**
- 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.
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
Medical Research and Development Process

DISCOVERY

Integrated Product Team

Scientific Steering Committee

Basic Research [6.1]

Applied Research / Adv Tech Dev [6.2/6.3]

Concept Decision

Pre-Systems Acquisition

Technology Development

Adv Tech Dev / ACD&P

ACD&P / SDD [6.4/6.5]

Concept Refinement

System Development & Demonstration

Chair - RAD IV CBMS

Chair - CBMS

Production & Deployment

[6.5/Procurement]

New Medical Countermeasures or Devices

ACD&P: Advanced Component Development & Prototypes

SDD: System Development and Demonstration

Chair – RAD IV CBMS

Chair - RAD IV

Adv Tech Dev / ACD&P

ACD&P / SDD

[6.4/6.5]
Medical Biological Defense Research Program
Potential Threats

- **Bacteria**
  - Anthrax
  - Plague
  - Tularemia
  - Brucellosis
  - Glanders/Melioidosis
  - Q Fever
  - Cholera
  - Typhus
  - Shigellosis

- **Virus**
  - Smallpox
  - Encephalomyelitis viruses (VEE, EEE, WEE)
  - Ebola
  - Marburg

- **Toxin**
  - Botulinum (Types A – G)
  - Staphylococcal Enterotoxins (SEA/B)
  - Ricin toxin
  - Marine Neurotoxins
  - Mycotoxins
  - Clostridium perfringens toxins
Medical Biological Defense Supporting S&T Efforts

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

**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
- Alternative delivery methods and multiagent vaccines

**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

**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
- Nucleic acid-based system
- Improved immunodiagnostic platform
- Common integrated diagnostic system

**DARPA Transition**
MBDRP collaborates with DARPA BW Defense Programs
- Unconventional pathogen CMs
- Tissue-based Biosensors
- FY01-05 Funding
### Licensed Medical Biological Defense Products

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>Licensed Medical Products:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-exposure Prophylaxes</td>
<td>• BioThrax™ Anthrax Vaccine</td>
</tr>
<tr>
<td>Therapeutics</td>
<td>• Dryvax vaccine (1:1 dilution)</td>
</tr>
<tr>
<td></td>
<td>for smallpox pre- and post-</td>
</tr>
<tr>
<td></td>
<td>exposure prophylaxis</td>
</tr>
<tr>
<td></td>
<td>• Ciprofloxacin for anthrax</td>
</tr>
<tr>
<td></td>
<td>post-exposure prophylaxis and</td>
</tr>
<tr>
<td></td>
<td>treatment</td>
</tr>
<tr>
<td></td>
<td>• Penicillin V Potassium and</td>
</tr>
<tr>
<td></td>
<td>penicillin for anthrax post-</td>
</tr>
<tr>
<td></td>
<td>exposure prophylaxis and</td>
</tr>
<tr>
<td></td>
<td>treatment, respectively</td>
</tr>
<tr>
<td></td>
<td>• Doxycycline for anthrax,</td>
</tr>
<tr>
<td></td>
<td>plague, Q Fever, and tularemia</td>
</tr>
<tr>
<td></td>
<td>post-exposure prophylaxis</td>
</tr>
<tr>
<td></td>
<td>• Doxycycline for anthrax</td>
</tr>
<tr>
<td></td>
<td>treatment</td>
</tr>
<tr>
<td></td>
<td>• Gentamicin, doxycycline,</td>
</tr>
<tr>
<td></td>
<td>streptomycin, tetracycline for</td>
</tr>
<tr>
<td></td>
<td>plague treatment</td>
</tr>
<tr>
<td></td>
<td>• Streptomycin, doxycycline, and</td>
</tr>
<tr>
<td></td>
<td>tetracycline for tularemia</td>
</tr>
<tr>
<td></td>
<td>• Doxycycline and tetracycline</td>
</tr>
<tr>
<td></td>
<td>for Q Fever treatment</td>
</tr>
<tr>
<td>Technology Approach: Confirmatory Identification of Pathogens</td>
<td>Transitioned To: Advanced Development:</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>• Gene Probe- Polymerase Chain Reaction</td>
<td>• Joint Biological Agent Identification and Diagnostic System (JBAIDS) – FY2002</td>
</tr>
<tr>
<td>- Amplication of select genetic sequences</td>
<td></td>
</tr>
<tr>
<td>• Development of reagent sets for agent identification and diagnostics</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vaccine Candidates</th>
<th>Advanced Development:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Development and qualification of assays for vaccine candidates</td>
<td>• Vaccinia, cell culture derived vaccine candidate – FY94</td>
</tr>
<tr>
<td>• Identification of surrogate markers of efficacy</td>
<td>• Tularemia LVS vaccine candidate – FY00</td>
</tr>
<tr>
<td>• Aerosol challenge studies in animal models</td>
<td>• Recombinant Venezuelan Equine Encephalitis virus vaccine (V3526) – FY00</td>
</tr>
<tr>
<td></td>
<td>• Recombinant Botulinum toxin serotypes A and B – FY00</td>
</tr>
</tbody>
</table>
# Technology Dev Pre-Systems Acquisition:

- Recombinant Plague vaccine candidate (F1-V) – FY02
- Recombinant protective antigen (rPA Next Generation Anthrax Vaccine candidate)
  - NIAID selected RIID rPA candidate for Phase I clinical trials
  - IND submitted in 2QFY03 in support of Phase I and II clinical trials
  - Phase I clinical trials initiated in 4QFY03
- Staphylococcal enterotoxins (SEA and SEB)
  - Ready to transition pending advanced developer (JPEO-CBD) funding decision
  - Effort limited to stability analysis on pilot lots for use in future clinical trials

<table>
<thead>
<tr>
<th>Technology Approach:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine Candidates</td>
</tr>
<tr>
<td>- Development and qualification of assays for vaccine candidates</td>
</tr>
<tr>
<td>- Identification of surrogate markers of efficacy</td>
</tr>
<tr>
<td>- Aerosol challenge studies in animal models</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Transitioned To:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technology Dev Pre-Systems Acquisition:</td>
</tr>
<tr>
<td>- Recombinant Plague vaccine candidate (F1-V) – FY02</td>
</tr>
<tr>
<td>- Recombinant protective antigen (rPA Next Generation Anthrax Vaccine candidate)</td>
</tr>
</tbody>
</table>
  - NIAID selected RIID rPA candidate for Phase I clinical trials |
  - IND submitted in 2QFY03 in support of Phase I and II clinical trials |
  - Phase I clinical trials initiated in 4QFY03 |
| - Staphylococcal enterotoxins (SEA and SEB) |
  - Ready to transition pending advanced developer (JPEO-CBD) funding decision |
  - Effort limited to stability analysis on pilot lots for use in future clinical trials |
**Bacterial Vaccine Candidates**

**Recombinant Protective Antigen (rPA) Anthrax Vaccine:** U.S. and UK tech base research generated two recombinant vaccine candidates

- National Institute of Allergy and Infectious Diseases (NIAID) selected the USAMRIID rPA candidate for Phase 1 clinical trials
- USAMRIID rPA candidate and UK rPA candidate also part of long-term NIAID strategy for 25M dose stockpile

**Plague:** Tech base research generated two recombinant vaccine candidates

- Both rely on F1 and V antigens
- U.S. candidate is a recombinantly produced fusion protein
- UK candidate is a combination of the two individually produced proteins
Live attenuated VEE vaccines derived by site-directed mutagenesis of a full length infectious cDNA clone

Identification of attenuating mutations:
- sequence of attenuated variants
- mutagenesis of conserved sequences

Multivalent VEE vaccine requirement can be met through the use of a single component vaccine (V3526), eliminating interference issues while greatly simplifying clinical trials and formulation issues
Toxin Vaccine Candidates

**Botulinum Neurotoxin (BoTN):** Tech base research generated a recombinant vaccine candidate

- Current vaccine candidate comprised of recombinant protein fragments of botulinum serotypes A and B produced from genetically engineered yeasts
- Research continues to explore innovative technologies to develop multivalent recombinant candidate vaccine to protect against the remaining BoTN serotypes C, E & F

**Staphylococcal Enterotoxin (SE) A and B:** Tech base research generated recombinant SE mutant protein vaccine candidates

- Demonstrated efficacy of combination vaccine (SEB, SEA) in non-human primates
- Produced cGMP pilot lot of SEB vaccine candidate
- Prepared a Master Cell Bank for production of the SEA vaccine candidate

**Ricin:** Classical approaches to producing a ricin toxoid vaccine proved unsuitable

- Recombinant expression vectors will be used to produce mutated A-chain immunogens capable of protecting against ricin toxicity
Multiagent Vaccines for Biological Threats

- A vaccine or delivery approach that can concurrently immunize an individual against a range of biological warfare threats
- Exploit bioengineering and recombinant vaccine technologies to achieve vaccines directed against multiple agents
  - RNA Replicon
  - DNA Vaccine

To move away from this…

25 Shots
Plus Boosters

To this…

Or this…

Botulinum toxin

Marburg Virus

Anthrax

Ebola-Z

Ebola-S

Marburg-Ci67

Marburg-Musoke

Marburg-Ravn

“Panfilovirus vaccine”
Alternative Vaccine Delivery Methods

- Respiratory, transdermal, oral immunization that is safe, efficacious and expedient for stimulating mucosal and systemic immunity
- Simplify administration of the multiple vaccines
- Evaluation of multiple novel adjuvants in combination with alternate deliveries

BD Technologies Proprietary Alternate Vaccine Delivery Devices Currently Under Evaluation

Micromedica™ micro-needles

SoloVent™

OnVax™ “swipe and go”
Therapeutics

Bacterial
- Licensed antibiotics/novel antimicrobials
- Immunotherapy/immunomodulators

Viral
- Antivirals for smallpox (oral) and filoviruses
- Immunotherapies for filoviruses

Toxin
- Botulinum neurotoxins
- Staphylococcal enterotoxin
- Ricin (basic research effort)

- FDA-Approved Compounds
- DARPA
- Academics

- NCI-DTP library
- Commercial Sources
- Combinatorial Lib.

- Sarnoff
- Functional Genetics
- Hawaii Biotech
- Academics

- FDA
- IND
- Primates
- Mouse Model
- Cell-Based Assay
- In Vitro Evaluation
- Modeling
- Lead optimization
- Screening
- Lead Identification
- In Vitro Evaluation
- Assay Development
- Target Identification
- Target Validation
Medical Diagnostic Technologies

- Polymerase chain reaction (PCR)-based technologies being developed and fielded

- An immunologically based diagnostic capability research effort ongoing as an adjunct to nucleic acid detection
  - Primarily for detection and identification of toxin threats
  - Also provides confirmatory assay for other medical diagnostic tests

Technology Options:

- Electrochemiluminescence (ECL) Reaction - First Generation Device
  - ORIGEN®

- Magnetic Field Detection

- Luminex
Host Responses to Threat Agents

- Similarities in host gene expression responses are observed among biothreat agents particularly regarding inflammatory mediators.
- These inflammatory mediators may not differentiate among pathogenic agents, but may still be useful markers to gauge illness progression.
Genetically Engineered Threats

◆ Concern
  ➢ Benign microorganisms genetically altered to produce
    • Toxins
    • Venoms
    • Bioregulators
  ➢ Infectious microorganisms genetically altered to
    • Be resistant to antibiotics
    • Have enhanced aerosol and environmental stability
    • Defeat standard diagnostic methods

◆ Approach: Bioinformatics
  ➢ Compile function-based structural elements that constitute known toxin and virulence factors of BW threats into integrated, searchable databases
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, and (4) highly rated proposals form basis for initiating contracts
- **Status:** Ten programs selected to date
DARPA Transition Programs, Examples

- Research to develop broad-spectrum vaccines by molecular breeding (gene shuffling) strategies; focuses cross-protection against pathogenic equine encephalitis viruses (Maxygen, Inc.)
- 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)
- Investigation using in silico screening methods of structurally diverse small-molecule inhibitors of the zinc endopeptidase of BoNT A (Mayo Clinic)
FY03 Congressional Interest

- **Objective**: Ensure sponsorship of good medical science, as requested by Congress, that can benefit DoD and civilian sector
- **Source**: Funds not in President’s Budget; added to DoD’s Chemical & Biological Defense Program (CBDP) Budget by Congress
- **Process**: Proposals receive in-house and external peer review; contracts managed by CBDP Medical S&T Office at USAMRMC
- **Status**: Eight medical S&T efforts funded by Congress in CBDP
  - Engineered Pathogen Identification and Countermeasures Program (Sarnoff Corporation)
  - Monoclonal Antibody-based Technology “Heteropolymer” (HP) System (EluSys Therapeutics, Inc.)
  - Bioadhesion Research (Ligocyte Pharmaceuticals, Inc.)
  - Mustard Gas Antidote (Mustard Consortium)
  - Needleless Delivery Methods for Recombinant Protein Vaccines (Becton Dickinson)
  - Vaccine Stabilization (University of Kansas)
  - Bioprocessing Facility (University of Nebraska)
  - Organic Vaccine Production (TBD)
Chem-Bio Defense Initiatives Fund

♦ Objective
- The Senate Appropriations Committee (SAC) established a $25M (FY03) “Chem-Bio Defense Initiatives Fund” (CBDIF) within the DoD’s Chemical and Biological Defense Program. The Congress provided a list of program proposals for consideration by the Secretary of Defense.
- Senior Review Panel established by the DATSD(CBD) reviewed the proposals. Award decisions were made in Feb 03.

♦ Selected medical biodefense research proposals include
- Virtual Drug Development Inc (VDDI): Oral anthrax antibiotics proposal
- George Mason University: National Center for Biodefense proposal
- EluSys Therapeutics, Inc: Heteropolymer technologies for anthrax proposal
- Diversa Corp: Rapid antibody-based countermeasures proposal
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
Cooperation with the Department of Health and Human Services

- NIAID/CDC/FDA anthrax therapeutics
- NIAID/USAMRIID/JVAP rPA clinical trials
- NIAID/USAMRMC/USAMRIID Biodefense Campus
  - Program coordination
  - Program management
  - Infrastructure
- NIAID/NINDS/USAMRICD counterterrorism initiative
  - Medical chemical defense programs
- USAMRIID/CDC
  - Smallpox research program
  - Anthrax antibodies
Pre-proposal and proposal submission information

- [http://www.usamraa.army.mil](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
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
Medical Chemical & Biological Defense Research Program

- DoD program, management by Defense Threat Reduction Agency, Army is Executive Agent
- Based on threat-driven requirements
- Product candidates from pretreatment/prophylaxis, vaccine, therapeutic, and diagnostic research areas
- Extramural collaborations represent a significant portion of the program
? Questions ?