NDIA Joint CBRN Conference & Exhibition
March 2012

“Investing in transformational ideas, innovative people, and actionable technology development for Chemical Biological Defense solutions”

Dr. Jason Paragas
Senior Scientist, DTRA RD-CB
The Threat is Real

- **Established Bioterrorism Programs**
  - Al-Qaeda: Kandahar, Afghanistan
  - Aum Shinrikyo: Tokyo, Japan

- **Call for BW expertise**
  - Al-Qaeda public call for scientists to develop and test biological weapons

- Emerging infectious diseases create an unpredictable source of pathogens

- Dual Use Research of Concern

- Proliferation of unsafe bio-containment labs

- WMD Commission: Biological attack more likely than nuclear

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Related Images:
- [Tarnak Farms, Al Qaeda training camp, Kandahar, Afghanistan](http://www.globalsecurity.org/intell/library/imint/images/011031-D-6570C-003.jpg)
- [Aum Shinrikyo Hq.](https://www.cdc.gov/ncidod/EID/vol10no1/03-0238.htm)
- [Anthrax Spraying, Tokyo](http://www.globalsecurity.org/intell/library/imint/images/011031-D-6570C-003.jpg)
Evolving Policies Drive Preparedness

**HSPD-10, 2004**
Biodefense for the 21\textsuperscript{st} Century

“The essential pillars of our national biodefense program are: Threat Awareness, Prevention and Protection, Surveillance and Detection, and Response and Recovery”

**HSPD-21, 2007**
Public Health and Medical Preparedness

“The United States must develop a nationwide, robust, and integrated biosurveillance capability”

**NSCBT / PPD-2, 2009**
National Strategy for Countering Biological Threats

“Building Global Capacity for Disease Surveillance, Detection, Diagnosis, and Reporting”
Addressing the Challenge of Preparedness

The nation does not yet have adequate capability to meet fundamental expectations during a large-scale biological event. Bi-Partisan WMD Terrorism Center: Bio-Response Report Card October 2011

"If achieving national goals for developing MCMs is likened to climbing a mountain, then most of the mountain remains to be climbed"

WHERE ARE THE COUNTERMEASURES?
PROTECTING AMERICA’S HEALTH FROM CBRN THREATS March 2010 A REPORT OF THE NATIONAL BIODEFENSE SCIENCE BOARD

Ten years after the anthrax letters—and after billions of dollars of investment in labs and research—debate continues over how much safer the country is
Science September 2011

Pentagon rethinks bio-terror effort
Critics say US$1.5-billion initiative has not delivered results
Nature News 477, 380-381 2011

How Ready Are We For Bioterrorism?
NY Times 10/30/2011
This Requires Global Engagement

Return on Investment:
- Leverage/Harvest Technologies
- Access to Diseases of Interest
- Biosurveillance
- Building Partner Capacity

NATO—HFM, JCDG
Sweden—Oxime Cooperation
Czech Republic (IEA, PA)—MCM (Tularemia)
Poland—TaCBRD, CPWG
UK (IEA, TTCP)—DX, MCM, Detection, M&S, HM
Canada (TTCP)—DX, MCM, Detection, M&S, HM
Israel (IEA, PA)—M&S and MCM, CPWG
France—Biosurveillance

NAMRU-6—Advanced Pathogen Detection and Discovery and Dx
RDECOM—Americas—Technical cooperative opportunities within South America
Chile—Biosurveillance and M&S
Brazil—Technical Cooperation Developing

India (IEA, PA)—CB Defense S&T Workshops, Dx, MCM (Alpha Viruses), M&S, Bilateral RD Cooperation Forum
Singapore (IEA, PA)—MCM (Burkholderia), M&S, Biosurveillance
Republic of Korea—Able Response Excercise, Comparative Genomics, M&S, Detection
Japan—CDWG, Decon, M&S (Threat Assessment), MCM
Thailand—Test point of care Dx, Biosurveillance, MCM
Australia (TTCP)—DX, MCM, Detection, M&S, HM
New Zealand (TTCP)—DX, MCM, Detection, M&S, HM
AFRIMS—Pathogen Discovery, Genomics
NAMRU-2—Biosurveillance. Dx

MCM—Medical Counter Measure
DT—Diagnostics
M&S—Modeling and Simulation
IEA—Information Exchange Annex
PA—Project Agreement
HM—Hazard Management
Rapid Response to Outbreaks: *E.coli* 0104:H4 Characterization Efforts

- To exercise real world challenge to rapidly explore deep genomic information for a emerging infectious threat agent using a combination of three 2nd-generation sequencing systems coupled with conventional finishing techniques.

- Correlate physical, clinical, and phenotypic observations to the improved genome using the suite of phenotypic assays available to a DoD/CDC lab consortium.

- Link Laboratory Response Network (LRN) to Defense Lab Network (DLN)

Also part of an ongoing organic DoD process for enhancing therapeutic and diagnostic countermeasures

## Strategic Thrusts and Enablers

### Disease Surveillance, Threat Detection and Point of Need Diagnostics
- Broad-Spectrum Detection
- Fieldable Dx Sequencing
- Molecular Recognition
- Host Response
- Exposure Prediction
- Functional Consequences

### Threat Activity Sensing and Reporting
- Point Detection
- Agent Characterization
- Mathematical Recognition
- Transport & Dispersion
- Risk-Based Hazard Plots
- Agent Fate

### Adaptive Medical Countermeasures and Technologies
- Vaccines
- Immune Modulators
- Bio-Prophylaxes
- Bio-Therapeutics
- Regulatory Sciences
- Mfg Technologies

### Rapid Response and Restoration Science and Technology
- Individual Protection
- Nanostructured Materials
- Smart Materials
- Simulation and Analysis
- Decision Support
- Decontamination

### Novel Threat Research
- Multifunctional Materials
- Systems Biology

### Applied Math Tools
- Flexible Design & Manufacturing
Strategic Thrust: Disease Surveillance, Rapid Threat Detection, and Point of Need Diagnostics

**AGENT/HOST TARGET IDENTIFICATION**
- Antibiotic Resistance Markers
- Pre-symptomatic Biomarkers
- Host Biomarkers
- Rapid Pathogen ID

**ENABLING CAPABILITIES**
- Sample Prep & Preserve
- Platform Technologies

**Bioinformatics**
- High Content Data Backbone
  - Pathogen Sequences
  - Host-Agent Dynamics Signatures
  - Characterized Reagents

**Future Systems Development**
- Enabled by informatics and device innovations
- Configurable for emerging threats
Delivering Diagnostic and Biosurveillance Solutions Across Three Key Areas

- **Biosurveillance (BSV) / Disease Surveillance**
  - Real-time BSV Ecosystem
- **Device Platforms**
  - Point-of-Need Medical Device Platforms
- **Assays & Reagents**
  - Biomarker Assays for Early Detection
  - Enabling Capabilities
    - Threat Identification and Characterization
    - Biomarker Discovery
    - Informatics Data Management
New Modalities for Surveillance, Investigation and Response

Public Cloud
citizen sensors,
presumptive
indicators,
Social networks

Open Source
Data

DoD Cloud
Sensors,
Confirmatory
diagnostics

Surveillance

Investigation

Response

"One Health" Surveillance
+ Early Detection + Rapid Dx
+ Collaborative Response
= LIVES SAVED

Level 0 Diagnostics

Level 1 Diagnostics
Link Highly Distributed Affordable Point of Care Diagnostic Devices to Cloud Network

- Levels 0-1 provide rapid, in-field data capture to support biosurveillance and/or medical decision-making
- Common use assay panels, including biodefense-specific agents, can accept different panels congruent with end user needs
- FDA-cleared or on pathway for clearance
  - Used in open architecture format for non-FDA-cleared detection
  - Clinical use with FDA clearance
- Sample-to-Answer systems, CLIA-waived

**Level 0***

**HOME USE**
- Akin to paper-based platform
- Lower plexity

*Also includes uses with non-human samples (e.g. insect vectors, livestock, food, environment), which will be performed by technical operators*

**Level 1**

**TRAINED MEDICAL PROVIDER**
- Increased functionality
- Higher plexity
Provide Early Warning and Diagnosis to Ensure Successful Countermeasures

**Mission:**
Advance the state of the art in prediction and early detection of epidemiological indications and warning, and forecasting of disease spread

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**Information Management Ecosystem**
- Third party operated
- Open source

**Surveillance, Investigation, and Response Activities**

**Diagnostic Systems**
- Role 0
- Role 1
- Role 2

**Expanded Surveillance Domain Enables Decision Superiority**

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**DoD Data Cloud**

**Social Media Cloud**

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**Medical Countermeasure Development**

**Biomarker Discovery**

**Target ID and Threat Characterization**

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*Key prototype elements for Device, Biosurveillance and Information Management will be demonstrated in the next 24 months

** Data clouds are pervasive information sources that do not need to be developed or maintained by DTRA*
Strategic Thrust: Adaptive Medical Countermeasures

Wide Spectrum Rx Threat and Host Strategies:
- Anti-virals
- Anti-bacterials
- Host Immunomodulators
- Chem/Rad Therapeutics

Pretreatments

Dx-Directed Treatments & Countermeasures

Therapeutics

- Antibiotic Resistance Markers
- Pre-symptomatic Biomarkers
- Host Biomarkers
- Pathogen ID

Flexible Adaptive Manufacturing

Regulatory Sciences

High Content Data Backbone
- Pathogen Sequences
- Host-Agent Dynamics Signatures
- Characterized Reagents

Disease Targets
Translational Medicine S&T Responsibility and Risk Reduction

Establish early criteria and translational teams for robust transition

Team 1: S+T ad
Team 2: S+T AD
Team 3: AD + s+t

Minimum Criteria

PK/PD in Relevant Animal Models
Pre-clinical Safety & Efficacy (NHP)
Therapeutic Index for Military Utility
Route of Administration
Standard of Care Comparisons
Biomarker Utility
Phase 0 exploratory IND

Robust Decision to Human Phase I studies
“FIRST IN HUMAN” TRIALS

- Recombinant vaccine antibody molecule (RVEc) binding to Ricin toxin
  - Pre-Clinical RVEc experiments
    - Tested parenteral and aerosol challenge
    - 6+ month protection following last vaccination
    - Passive transfer studies against lethal subcutaneous challenges (i.e., 2.5, 5 or 10 LD50s) indicate antibody-mediated immunity
  - Clinical Phase 1 escalating, multiple-dose study (June - Sept 2011)
    - 9 first vaccinations w/ only minor adverse events; those vaccinated producing antibodies directed against the Ricin toxin
  - PI: USAMRIID investigators

- Transformational Medical Technologies Division funded the early stages
Bacterial Therapeutics

• Strategies
  1. Discovery of unprecedented compounds (not necessarily a new target)
     • antimicrobials targeting bacterial biosynthetic pathways, virulence factors, resistance mechanisms, & host factors
     • antibiotic potentiators and immunomodulators
  2. Evaluation/re-purposing of FDA-approved antibiotics against select agents of interest

• Technical Highlights
  - 90% protection from death in mice after aerosol Y. pestis exposure with moxifloxacin
  - Greater than 90% survival in mice treated with GSK0944 after F. tularensis infection
  - ACHN-975 provides 100% protection from aerosolized Y. pestis
New Medical Countermeasures Initiative: S&T Into Advanced Development Capability

Developmental Path

- DOD/USG Programs
- Non-USG Inputs
- Novel Platforms*
- Advanced Development Capability
- Regulatory Science Technologies**

DTRA/BAA
Rapid Design of Medical Countermeasures

• Novel Computational Design
  - Demo to inhibit influenza hemagglutinin infective potency
  - Promoting energetically-favorable clustered interactions between disembodied amino acid residues and target surface area patches to anchor de novo designed interfaces
  - Incl. proxies to Negative Design: design for binding and precluding of binding to off-target molecules
  - May 13 issue of Science
  - PI: Dr. David Baker, University of Washington

• DTRA Transition of DARPA Protein Design Program

"Computational design of proteins targeting the conserved stem region of influenza hemagglutinin"
Fleishman, Baker, et al
Science. 332(6031), 816-21.
Platforms & Research Tools Thrust Area Strategy

- Invest in enabling technologies required to develop candidate vaccines against known and emerging threats

Multi-use expression platforms

adjuvants

stabilization methodologies

Human System responses

Delivery technologies

Packaging

Signal

5' - nsP1 nsP2 nsP3 nsP4 Filo Gene -3' 5' Capsid -3' 5' GPs -3'

26S promoter

Helpers

Human System responses
Goals:

- Reduced thermal burden – target thermal burden to Fire Resistant Army Combat Uniform (FRACU)
- Integrate CB ensemble with warfighter ensemble to reduce cognitive burden
- Demonstrate network integration
**Rapid Response and Recovery S&T**

**WIDE AREA DECONTAMINATION**

- *B. anthracis* is virulent, persistent, and resistant to decontamination
  - Spores a threat for decades
  - Current decontaminants corrosive or hazardous
  - Large volumes of decontaminant needed

- **Seeking Innovative approaches to mitigate the effects of wide area dissemination of spores**
  - Fast-acting and robust
  - Low-cost
  - Logistically acceptable
  - Long shelf & pot life
  - Environmentally-friendly

**Breakthroughs will be leveraged for new innovative solutions**

- Restorational Decon < 2 weeks
- 4-6 log reduction of spores

- Improved Logistics
- 6+ hour pot life (if applicable)
- 3+ year shelf life

- Tarmac, buildings, soil, veg
- Min environmental impact

*CwlJ1 germination enzyme germination of B. Cereus spores faster than L-Alanine*
How We Are Addressing The Challenge

• **Establish S&T Imperatives** that emphasize urgency and accountability surrounding knowledge creation and translation into robust pipeline of CBRN capabilities and products

• **Create New Opportunities For Sourcing and Managing Innovation**
  
  – Sourcing new Investments through Poractive Scouting and Competition
  – Managing investments to Milestones and Ceasing unproductive investments
  – Addressing the pipeline of products and capabilities needed for enhanced preparedness
  – Focusing investments into critical mass programs – Focused Innovative Technology Programs (FITs)
  – Measuring performance of knowledge products and holding ourselves accountable
“Those who have knowledge, don't predict. Those who predict, don't have knowledge.”

Lao Tzu