



## U.S. ARMY MEDICAL RESEARCH AND MATERIEL COMMAND

USAMRMC

# Medical Countermeasures to Chemical and Biological Threats

## Mission

The U.S. Army Medical Research and Materiel Command's (USAMRMC's) mission is to provide medical knowledge and materiel life-cycle management to protect, treat, and optimize Warfighter health and performance across the full spectrum of operations. USAMRMC provides research and development in a variety of areas, including chemical and biological defense. Medical chemical and biological research at USAMRMC supports the mission of the Chemical and Biological Defense Program (CBDP) to provide chemical and biological defense capabilities in support of national military strategies.

## Background and Environment

The Department of Defense (DoD) established the CBDP in 1994 to provide chemical and biological defense capabilities in support of national military strategies. In accordance with 50 USC 1522, research, development, and acquisition (RDA) of chemical and biological defense programs within the DoD are overseen by a single office within the Office of the Secretary of Defense. The Assistant to the Secretary of Defense for Nuclear and Chemical and Biological Defense Programs (ATSD[NCB]) serves as this single office. The Deputy Assistant for Chemical and Biological Defense and Chemical Demilitarization Programs serves as the principal deputy to the ATSD(NCB) for accomplishing overall oversight and integration of the DoD CBDP.

CBDP science and technology (S&T) programs are managed by the Defense Threat Reduction Agency's (DTRA's) Joint Science and Technology Office for Chemical and Biological Defense (JSTO-CBD). The JSTO-CBD is designated as the Chemical and Biological Technologies Directorate of the DTRA and is responsible for the management, integration, and execution of medical chemical and biological defense S&T programs within the DoD. The Chemical Biological Defense Partnership Support Directorate (PSD), which is a staff office under the Commanding General, USAMRMC, supports JSTO-CBD through the development and maintenance of an interactive web site for the management of all intramural chemical and biological defense S&T proposals. The Joint Chemical Biological Defense Research Program web site facilitates proposal management for all laboratories within the DoD, as well as other U.S. Government agencies, including the Department of Energy, Department of Health and Human Services, NASA, and others.

To accomplish the objectives and purposes of the defense-wide medical chemical and biological defense S&T program, USAMRMC supports JSTO-CBD's planning and program management of that portion of the CBDP assigned to the Army Medical Department, including research performed at the following key USAMRMC laboratories: U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), U.S. Army Medical Research Institute of Chemical Defense (USAMRICD), and Walter Reed Army Institute of Research (WRAIR). In support of

JSTO-CBD, the PSD, through its web-based program build process, facilitates planning for chemical and biological defense research at other service laboratories as well as other government laboratories and federally funded research and development centers. The PSD assists USAMRIID, USAMRICD, and WRAIR in reporting on the execution of medical chemical and biological S&T research funded by JSTO-CBD. The PSD also assists JSTO-CBD in executing assigned congressional special interest chemical and biological S&T research.

On 30 September 2008, the CBDP Strategic Plan was published. This plan outlined the need to maintain a robust S&T base and promote and exploit scientific discoveries. The CBDP will continue to segment the goals of S&T into the following key thrusts:

- Transition technologies
- Ensure a robust S&T base
- Answer scientific questions
- Enterprise excellence

## Key Themes and Messages

USAMRMC laboratories provide critical medical research capabilities to support national strategies against chemical and biological threats. The Command's capabilities include unique infrastructure, dedicated personnel, and scientific and technical expertise that keep the United States on the cutting edge of the development of scientific information and technology development.

The nature of the chemical and biological threat is complex and diverse. The threat comes from various players, from nation-states to small terrorist organizations. The threat comes in various forms, including, but not limited to, bacteria, toxins, viruses, blisters, blood, and nerve agents. The threat of exposure comes from airborne exposure (i.e., inhalational), contact (i.e., dermal), and other means (e.g., ingestion.) Consequently, research and development include a variety of countermeasures, including vaccines and pre- and postexposure prophylaxes, therapeutics, and medical diagnostics (i.e., assays, reagents, and protocols).

Partnerships and collaborations are critical to the success of USAMRMC laboratories. USAMRMC partners with industry, academia, other government agencies, and international partners. These collaborations include Cooperative Research and Development Agreements, Material Transfer Agreements, Patent License Agreements, Clinical Trial Agreements, Test and Evaluation Agreements, Partnership Intermediaries, Data Exchange Agreements, and Memoranda of Agreement.

USAMRMC laboratories also provide education and training to military and civilian medical and public health professionals to provide proficiency in recognizing that a chemical or biological attack has occurred, activating the appropriate agencies and personnel to investigate the event, treating casualties, and preventing the spread of disease.

## Questions and Answers

***Q1. What USAMRMC laboratories are responsible for performing chemical and biological defense research?***

A1. Key USAMRMC laboratories conducting research and development of medical countermeasures against chemical and biological threats include:

- USAMRIID – The mission of USAMRIID is to conduct basic and applied research on biological threats resulting in medical solutions to protect the Warfighter. USAMRIID plays a key role as the only laboratory in the DoD equipped to safely study highly hazardous infectious agents requiring maximum containment at biosafety level 4. As the center of excellence for DoD medical biological defense research, USAMRIID’s challenge is to maintain its world-class S&T base while being responsive to its primary customer—the Warfighter. Additional information about USAMRIID is available at <http://www.usamriid.army.mil/index.htm>.
- USAMRICD – The mission of USAMRICD is to discover and develop medical countermeasures to chemical warfare agents for the U.S. military and U.S. citizens; train and educate personnel in the medical management of chemical casualties; and provide subject matter expertise in developing defense and national policy and in proper crisis management. The institute is the nation’s leading S&T laboratory in the area of medical chemical countermeasures research and development. With sophisticated laboratories located at Aberdeen Proving Ground, Maryland, USAMRICD manages a diversified portfolio of medical chemical warfare agent research projects for the DoD and other federal agencies. Additional information about USAMRICD is available at: <http://chemdef.apgea.army.mil/Default.aspx>.
- WRAIR – The mission of WRAIR is to conduct biomedical research that is responsive to DoD and U.S. Army requirements and delivers lifesaving products, including knowledge, technology, and medical materiel that sustain the combat effectiveness of the Warfighter. WRAIR’s mission and capabilities address biomedical research and development more broadly than chemical and biological defense and include related areas such as infectious diseases, dental health, and laser eye injury. Key research capabilities at WRAIR include:
  - Antigen discovery and vaccine development for militarily relevant pathogens
  - Drug discovery to address military needs
  - Testing of candidate vaccines, drugs, and devices in endemic areas to counter infectious diseases
  - Development of devices for diagnosis and treatment
  - Producing solutions that monitor, predict, and enhance human performance under field conditions

***Q2. What are your research priorities in developing countermeasures to chemical and biological threats?***

A2. Research priorities for medical chemical and biological defense are established by the JSTO-CBD in collaboration with the Joint Requirements Office for Chemical, Biological, Radiological, and Nuclear (CBRN) Defense and the Joint Program Executive Office for Chemical and Biological Defense.

For the fiscal year 2010–2011 (FY10–FY11) period, JSTO-CBD released a solicitation for research proposals for chemical and biological defense. Research ranges from basic research (6.1 funding) to more mature applied research (6.2 funding) and advanced technology development (6.3 funding). It encompasses a broad spectrum of topics that address chemical and biological defense S&T requirements. Medical chemical and biological research topic areas included the following:

- **Medical Basic Research:** Provides the supporting sciences to expand basic knowledge in threat agent biology and chemistry to enable the development of lead candidate vaccines, treatments, and pharmaceuticals against chemical and biological threat agents. Biologically based basic research focuses on understanding biological warfare agents of interest and their pathways, virulence, immunization factors, and identification. Chemically based basic research focuses on understanding chemical warfare agents of interest and their mechanisms of action, toxicity, cellular mechanisms of injury, and identification.
- **Biological Pretreatments:** Dedicated to research and development of vaccines and technologies given to the service member prior to potential exposure to biological agents. The goal is to reduce or prevent entirely adverse effects of exposure.
- **Biological Therapeutics:** Dedicated to providing medical solutions for military requirements to sustain and protect the force in biological environments. Biological Therapeutics deals primarily with medical countermeasures to bacterial, viral, and toxin agent exposure.
- **Biological Diagnostics:** Dedicated to developing improved screening procedures and analytical methods to verify exposure and determine effects of exposure to biological warfare agents.
- **Chemical Medical Countermeasures:** Dedicated to developing medical countermeasures (i.e., pretreatments, therapeutics, and diagnostics) to protect the Warfighter against chemical warfare agents, both traditional and nontraditional.

***Q3. How can ideas be submitted for a research proposal?***

A3. For extramural organizations, including universities, industry, or other private institutions, the primary means for submitting research preproposals is through the DTRA Broad Agency Announcement. Chemical and biological defense S&T programs are managed by JSTO-CBD at DTRA.

DTRA solicits proposals for its requirements through the Federal Business Opportunities (FedBizOpps) and the DoD Small Business Innovation Research (SBIR) Program solicitations. For information regarding DTRA business opportunities, please visit [http://www.dtra.mil/be/business\\_opp/procurement/acq\\_procopp.cfm](http://www.dtra.mil/be/business_opp/procurement/acq_procopp.cfm).

In addition to submitting proposals directly to DTRA, extramural partners may instead choose to partner with an intramural laboratory. There are a variety of mechanisms available for USAMRMC to work together with industry, including the following mechanisms:

- Cooperative Research and Development Agreements
- Material Transfer Agreements
- Patent License Agreements
- Clinical Trial Agreements
- Test and Evaluation Agreements
- Technical Assistance Agreements
- Partnership Intermediaries

The DTRA JSTO-CBD also invites U.S. Government laboratories to submit research proposals on chemical and biological defense, and proposals for these intramural efforts are managed on the Joint Chemical and Biological Defense Science and Technology Program web site at <http://www.jcbdrp.org>.

***Q4. What are some other organizations that I might partner with in the development of a new technology?***

A4. The DoD CBDP is the lead organization providing RDA of capabilities to protect the Warfighter. Other federal agencies are providing related capabilities, especially in the protection of civilians and emergency personnel. Other organizations conducting related research include:

- The Department of Health and Human Services, including the National Institute of Allergy and Infectious Diseases (NIAID), the Biomedical Advanced Research and Development Authority, and the Centers for Disease Control and Prevention (CDC).
- The Department of Homeland Security, especially the National Biodefense Analysis and Countermeasures Center.

The roles and responsibilities of the various federal agencies are outlined in *Biodefense for the 21st Century* (HSPD-10) and *Medical Countermeasures Against Weapons of Mass Destruction* (HSPD-18).

***Q5. Where would I find out more information about chemical and biological research, development, or acquisition?***

A5. The CBDP RDA Plan details mid- and long-term CBDP goals, objectives, and transition of materiel within each phase of the acquisition process consistent with the Under Secretary of Defense for Acquisition, Technology, and Logistics' comprehensive RDA strategy in accordance with the *National Military Strategy to Combat Weapons of Mass Destruction*. To request a copy of the January 2009 DoD CBDP RDA Plan, contact the CBRN Defense Program Analysis and Integration Office RDA Manager at 410-436-5743 or the RDA Coordinator at 410-436-2080.

***Q6. What are some examples of successes of medical chemical and biological defense research and development?***

A6. Medical S&T successes in FY07 included the establishment of assay standards and the focus on knowledge-based publications, which resulted in more than 150 peer-reviewed publications and 33 patents.

Other medical chemical and biological S&T program research accomplishments are outlined in the May 2008 *DoD CBDP Annual Report to Congress* and include the following:

Medical Biological Defense – Pretreatments:

- The DoD recombinant ricin vaccine was demonstrated to be safe and effective in nonhuman primates (NHPs); the investigational new drug application is expected in 2008.
- Four candidate vaccine platforms demonstrated protection against both Ebola and Marburg viruses in NHPs; downselection is expected in 2008.

Medical Biological Defense – Diagnostics:

- The U.S. Food and Drug Administration (FDA) cleared the Q-flow kit for DNA extraction from blood, and it is currently being fielded in the Joint Biological Agent Identification and Diagnostic System Block I deployment package. This kit addresses the main user-identified issues of the previous kit by eliminating the need for a large tabletop centrifuge and decreasing the sample volume required by approximately 1,000-fold.
- Established standards for reporting data on assay design, optimization, and performance. These also are being adopted for use by the environmental and infectious disease communities and have been presented to our international partners.



#### Medical Biological Defense – Therapeutics:

- Sponsored the establishment of a clinical field site for orthopoxvirus in the Democratic Republic of Congo.
  - Enrolls more than 100 patients with monkeypox annually; these patients are provided the current standard of care for this disease.
  - Collects human pathogenesis data, which are compared with similar data generated in current animal models.
  - Advanced clinical developers, NIAID, and SIGA Technologies will manage the site in the future.
- ST-246 (SIGA Technologies)—an oral antiviral therapeutic drug.
  - Demonstrated 100% protection against monkeypox and human smallpox virus in NHP trials and is the first drug to do so.
  - Developed an intravenous monkeypox animal model that is being used as the pivotal animal model in the FDA licensure process.
  - At the CDC's request, it was used recently to successfully treat a child having significant atopic dermatitis and a disseminated case of the disease acquired from contact with a parent's smallpox vaccination.

#### Medical Chemical Defense – Pretreatments:

- Recombinant BioScavenger pretreatment of guinea pigs followed by exposure to soman or VX resulted in 100% survival with no signs of toxicity or behavioral impairment.
- Developed and validated physiologically based pharmacokinetic/pharmacodynamic models for intravenous, subcutaneous, and inhalational administration of soman in three animal models.
- Further refined and analyzed the x-ray structure of candidate bioscavenger yCE.
- Cloned, sequenced, expressed, purified, and kinetically characterized more than eight mutants of yCE to increase organophosphorous acid anhydrase.
- Achieved up to a 20-fold increase in the specificity constant for carboxyl acid ester (pNPA) hydrolysis and at least a 200-fold increase in paraoxon reactivity through site-directed mutagenesis of candidate bioscavengers.
- Continued characterization of human serum paraoxonase 1 as a third-generation bioscavenger.

#### Medical Chemical Defense – Diagnostics:

- Completed development of a robotic, whole-blood diagnostic system for nerve agent exposure.
- Continued comparative research into field-sampling techniques and technologies for postexposure diagnosis.

#### Medical Chemical Defense – Therapeutics:

- Developed a mathematical molecular model to clarify the reactivation of inhibited AChE, as well as the effect of substituent groups on the reactivation event.
- Initiated research into technologies to enhance blood–brain barrier penetration for nerve agent countermeasures.
- Used site-directed mutagenesis to better identify the role of the key amino acids in the reactivation event.

- Used proteomic analysis to identify changes to proteome and genome of neuronal tissue following exposure to nerve agent.
- Evaluated effects of nerve agents on mitochondrial function and tested efficacy of cyclosporine A and its analogs at mitigating damage.
- Continued investigation of gross, cellular, and subcellular alterations of central nervous system tissue following exposure; identified temporal and spatial progression of damage in small animal models.
- Evaluated galantamine and huperzine A as potential replacements for pyridostigmine bromide.
- Testing putative compounds to ameliorate seizures and reduce lethality using established animal models; tested compounds included FDA-licensed drugs and proprietary compounds obtained through a Cooperative Research and Development Agreement.
- Identified and tested several potential compounds in small-animal seizure models for medical countermeasures for nontraditional agents.
- Investigated basic mode and mechanism of injury for nontraditional agents.

***Q7. What chemical and biological defense training opportunities exist for members of the U.S. military?***

A7. USAMRICD and USAMRIID have developed a number of training programs in chemical and biological defense, as follows.

- Field Identification of Biological Warfare Agents Course – This course was designed to allow students to set up, maintain, and operate a deployable laboratory under field conditions.
- Field Management of Chemical and Biological Casualties Course – This course focuses on emergency treatment, triage, decontamination, and evacuation of casualties.
- Hospital Management of Chemical, Biological, Radiological/Nuclear, and Explosive Incident Course – This course focuses on diagnosis, treatment, and incident management in response to mass casualty events of all types, including incidents involving weapons of mass destruction.
- Medical Management of Chemical and Biological Casualties Course – This course focuses on the pathophysiology, diagnosis, and treatment of chemical and biological casualties.
- Computer-Based Training – Computer modules offer service members a variety of interactive, multimedia learning courses both online and in compact disc format.