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Jack Rabbit II Trials

Predicting the Next Epidemic

On-Demand Biosynthesis Manufacturing is Here

Lead DoD science and technology to anticipate, defend and safeguard against chemical and biological threats for the warfighter and the nation.

DEFENSE THREAT REDUCTION AGENCY &
USSTRATCOM Center for Combating WMD
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J9 Research and Development Directorate
Joint Science and Technology Office

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On the front cover:
Harshini Mukundan, Los Alamos National Laboratory's Physical Chemistry and Applied Spectroscopy group, leads a team for innovative research on integrative biosurveillance. Photo by Los Alamos National Laboratory.

On the back cover:
Sailors with Chemical Biological Incident Response Force (CBIRF) examine a contaminated chamber using a Multi-Rae monitor at Guardian Centers, Perry, GA. This exercise tests the levels of each individual CBIRF capability with lane training and culminating with a 36-hour simulated response to a nuclear detonation. CBIRF is an active duty Marine Corps unit that, when directed, forward-deploys and/or responds with minimal warning to a chemical, biological, radiological, nuclear or high-yield explosive threat. (Official U.S. Marine Corps photo by Lance Cpl. Maverick S. Mejia)

Modeling for Hairy Situations with JACK RABBIT II TRIALS

Warfighters face a variety of threats including chemical substances, such as chlorine, that have the potential to be turned into weapons. First discovered in 1774 and later used as a chemical weapon during World War I and the ongoing Syrian conflict, chlorine is one of the most commonly manufactured chemicals in the United States. Chlorine plays an integral role in our daily lives – from a disinfectant in the water we drink to the production of paper and plastic. As such, hundreds of millions of tons of chlorine are transported every year by road, water and rail systems.

Either the accidental or intentional release of chlorine, or any toxic industrial chemical, could have a devastating impact on warfighter and civilian lives. Such a release poses a risk to Department of Defense forces at home and abroad, making it vital to understand the behavior of chemical plumes in the event of a large-scale chemical release.

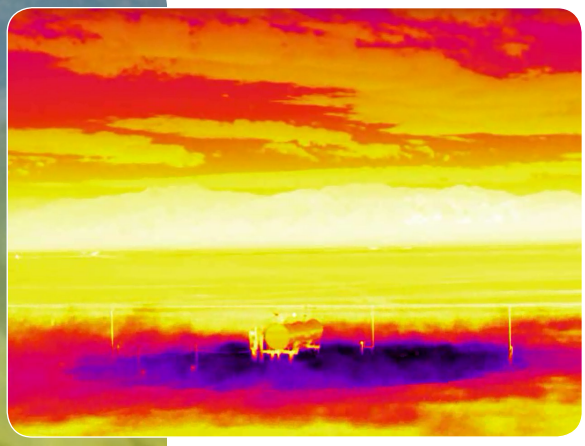
A dual-agency program with the Defense Threat Reduction Agency's Joint Science and Technology Office and the Department of Homeland Security (DHS) Chemical Security Analysis Center is conducting a series of large-scale, controlled, outdoor chlorine release trials known as Jack Rabbit II. These field trials are critical to providing accurate models of plume trajectory for the purposes of safeguarding our troops.

Although the DHS department has previously conducted chemical hazard modeling, it has never been validated for toxic industrial chemical releases from large-scale transport containers such as rail cars and tanker trucks. The joint DTRA and DHS team's goal is to better understand the impacts of such a release in the immediate vicinity and downwind up to seven miles.

The four-year program, which began in 2013, began field trials between 2015 and 2016, releasing five to 20 tons of chlorine in a variety of release mechanisms. Several measurements were taken within the testbed, downwind, within a mock urban setting and around vehicles.

Currently, data collected is being analyzed to understand chemical infiltration of buildings and vehicles, plume behavior within an urban environment, chlorine reactivity and deposition, and cloud reactions with multiple surfaces such as vehicles, soil and vegetation.

This analysis will improve warfighter safety in the event of a chemical release through increased accuracy of chemical hazard modeling, more efficient and effective emergency response and improved mitigation measures to reduce the impact to affected populations and infrastructure.



Infrared image of a chlorine release during the field trials.

Chlorine is expelled from a tank during the 2016 Jack Rabbit II field trials. Official U.S. Department of Homeland Security Images.

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PREDICTING THE NEXT EPIDEMIC: LIKE FINDING A NEEDLE IN A HAYSTACK

Today's digitally connected world is filled with clues about the next epidemic. People across the globe post and share real-time information that includes indicators of potential disease, but piecing together key bits of data amidst the terabytes of tweets, news reports and blog posts is similar to finding a needle in a haystack. In an ongoing effort by the Defense Threat Reduction Agency's Joint Science and Technology Office, scientists are addressing this challenge by developing the Biosurviellance Ecosystem (BSVE), an open-sourced software tool that will improve warfighter decision-making capabilities.

A cutting edge technology, BSVE is an open-architecture, cloud-based service that analyzes public information from social media, news reports, diagnostics tools and health organizations to predict health concerns for warfighter and civilian safety.

A novel element of the BSVE program is that it allows third party developers to create applications to increase the utility of the program. These apps provide analytic solutions such as anomaly detection, geospatial analysis, forecasting, prediction and data fusion. JSTO and the EcoHealth Alliance, a global environmental health nonprofit organization dedicated to protecting wildlife and public health from the emergence of disease, collaborated to develop several new, unique applications to enhance the BSVE platform.

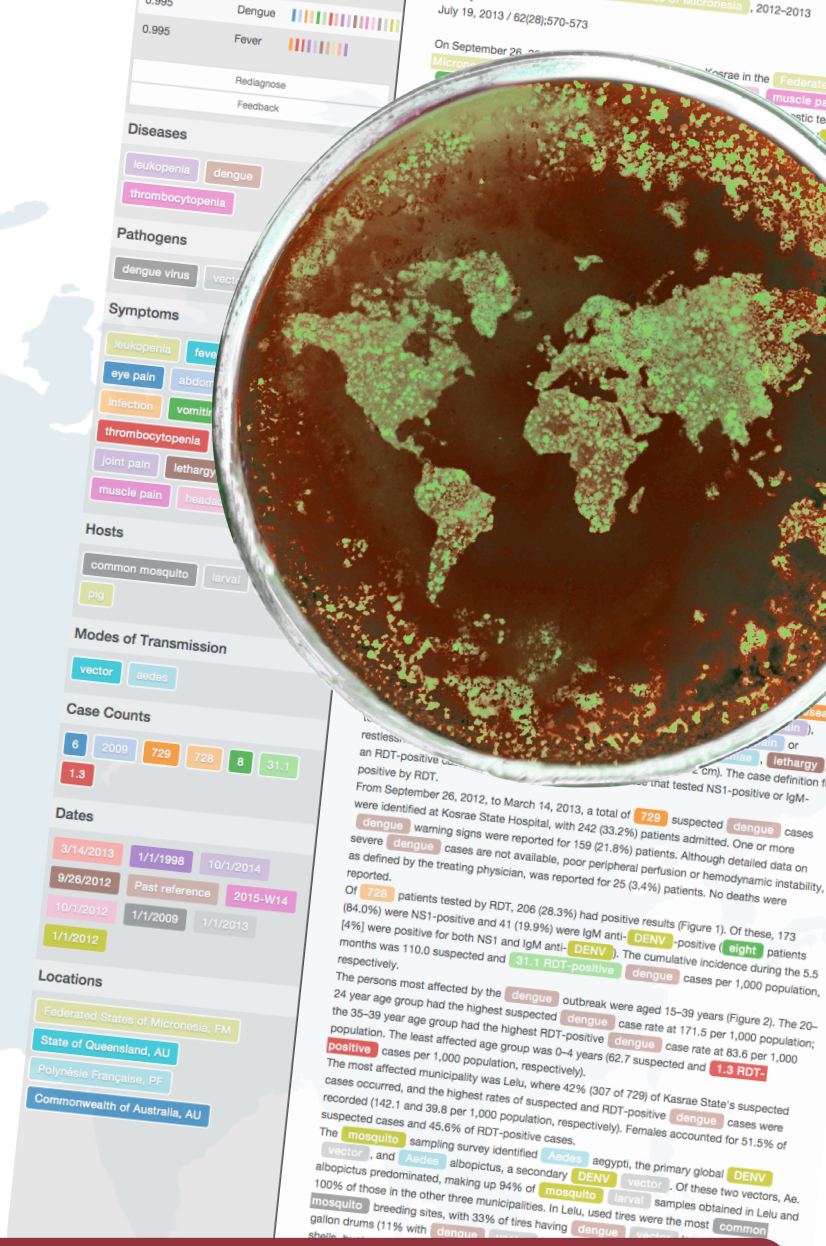
One application created is the Global Rapid Identification Tool Set. The application, also known as GRITS, analyzes textual data sources, such as online news outlets, ProMED reports and blogs by identifying, extracting and succinctly mapping critical public health information. GRITS translates non-English sources before searching for case-counts, symptoms, pathogens, transmission types, hosts, dates and locations to suggest possible outbreaks of infectious diseases. Providing a timeline and map of potentially related diseases based on probability, GRITS allows analysts to visualize potential threats before they occur.

Another application, the Novel Infectious Agent Monitor, or NIAM, is dedicated to understanding whether or not a news article is reporting on an emerging disease occurrence. NIAM scans for mentions of diseases in online news feeds and indicates a disease's prevalence by measuring the time since the prior mention. The application then compares the current frequency of mentions to historical averages. Using NIAM, analysts can view disease trends over weekly, monthly or annual periods and correlate a disease's trend strength.

The Flight Risk Tracker, or FLIRT is another new tool in the BSVE suite. FLIRT enables users to examine transportation and travel networks to identify where infected travelers and contaminated goods are likely to travel. Increased globalization means that an infectious disease can quickly become an epidemic. Consider the 2009 H1N1 outbreak. In just 90 days, the disease spread throughout 70 countries and was declared a pandemic. FLIRT's interactive interface allows users to query a database of more than 1.6 million commercial airline flights departing and arriving from all major international airports. By better anticipating epidemics through travel patterns, analysts and local communities can prepare for an outbreak and take preventative measures, reducing the overall cost and burden of mitigating disease spread.

Finally, the Emerging Infectious Disease Repository, or EIDR, allows analysts a historical context to view potential diseases. EIDR includes a curated, expansive and transparent repository of information on past emerging infectious disease events.

GRITS, NIAM, FLIRT and EIDR all currently assist surveillance analysts in anticipating the next outbreak. Additional applications will be developed to increase the accuracy and usability of the BSVE toolset. Tackling the problem of disease surveillance is daunting and no single analyses or application can do it all, but increasing prediction accuracy is critical to warfighter health and troop safety.



Current BSVE Applications

Global Rapid Identification Tool Set

- ✓ Analyzes textual data such as news outlets, ProMED reports and blogs
- ✓ Searches for cases, symptoms, pathogens, transmission type and location of infected persons

Novel Infectious Agent Monitor

- ✓ Analyzes news feeds
- ✓ Compares frequency of disease mentions to historical averages
- ✓ Measures trends over periods of time
- ✓ Correlates a disease's trend strength

Flight Risk Tracker

- ✓ Analyzes more than 1.6 million transportation and travel networks
- ✓ Identifies where contaminated goods and infected travelers are likely to travel to predict the next outbreak

Emerging Infectious Disease Repository

- ✓ Provides analysts a historical context for pathogens
- ✓ Serves as a repository for past infectious diseases

Just Add Water:

On-Demand Biosynthesis Manufacturing Is Here

Synthetic biology offers many benefits to the military in the form of advanced therapeutics, crucial vaccines and highly sensitive diagnostic tools developed to protect our warfighters from disease. However, a major challenge is the need for living cellular hosts, specialized equipment and technical expertise for their production and transport. Once produced, refrigeration is necessary both during distribution and storage, which further limits their application, especially in low-resource areas.

In order to overcome these limitations, researchers led by Dr. James Collins, from the Massachusetts Institute of Technology (MIT), developed a novel cell-free approach for the on-demand manufacturing of therapeutics and biomolecules with the addition of water. Funded by the Defense Threat Reduction Agency's Joint Science and Technology Office and managed by DTRA's Dr. Ilya Elashvili, the project builds upon earlier DTRA-funded efforts.

Previously, researchers focused on freeze-drying cell-free (FD-CF) protein expression machinery onto paper, creating a diagnostic platform that retains the protein synthesis capability of live cells, while remaining abiotic, sterile and portable. Combined with "toehold switch" RNA sensors, the researchers demonstrated proof-of-concept, low-cost diagnostics for thirteen pathogens, including the Zika virus.

The new system expands this technology beyond diagnostics to portable bio-manufacturing and is also rooted in FD-CF protein expression machinery utilizing dry reaction pellets. Combined with the DNA encoding, the instructions for biosynthesis, these pellets can be transported and stored for up to a year at ambient temperature. When water is added at the point-of-care, biosynthesis begins and yields the therapeutic within one to two hours.

The lack of accessibility to modern therapeutics has prompted the recent proposal of various systems which are often costly and require highly trained personnel and large, specialized equipment. However, the low-cost FD-CF bio-manufacturing system solves the accessibility issues while remaining easy to use. The system also offers the general benefits and flexibility inherent to in-vitro biosynthesis.

The MIT-team demonstrated this flexibility by producing a wide range of biomolecules, including antimicrobial peptides (AMPs), antibodies, enzymes for small-molecule therapeutics synthesis and vaccines. The team began with the production, purification and functional validation of AMPs, which have broad activity against bacteria, viruses, fungi and cancer cells. To produce the AMPs, the researchers utilized the standard FD-CF format by adding water to reaction pellets containing the DNA templates for ten different AMPs and then incubating at body temperature for two hours.

Antibodies against 15 specific targets were also generated, which can be used directly for protein-based diagnostics and therapeutics or conjugated to other proteins produced using the system in order to expand their functions depending on an end-user's preference.

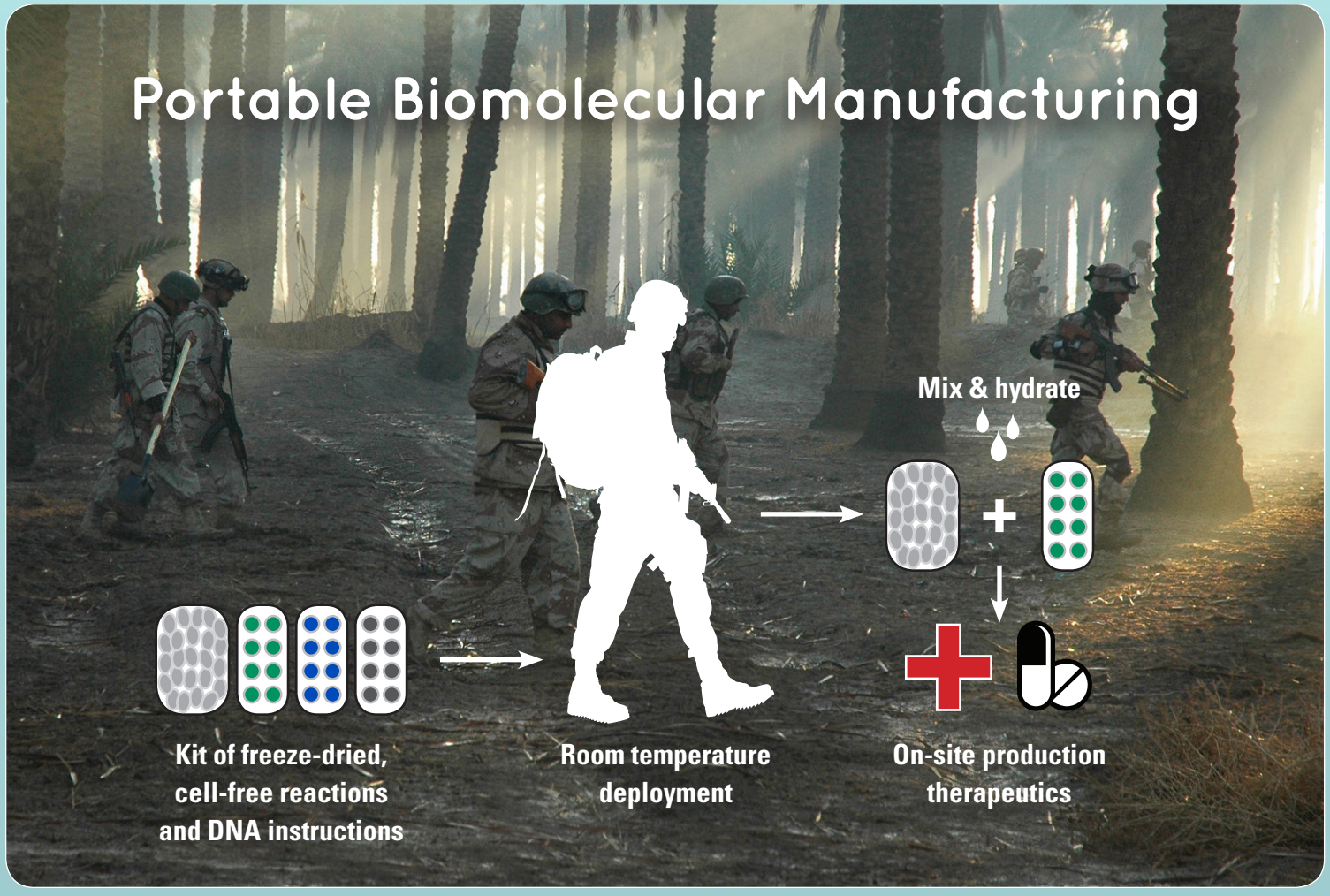
Using FD-CF, the reconstitution of a complex, five-enzyme pathway for the biosynthesis of a high-value, small-molecule compound, violacein, was also presented. Violacein has antimicrobial, antitumor, and antiparasitic properties. This procedure demonstrated the expansion of

the FD-CF platform beyond peptide and protein production to the biosynthesis of small molecules as the end product.

The team also verified the expression of vaccines for botulinum, anthrax and diphtheria. Due to its sensitivity to both heat and freezing, the researchers chose to subject the diphtheria antigen to further testing. Using FD-CF reagents, two versions of the vaccine, DT5 and DT6, were successfully produced and interacted with commercial anti-diphtheria antibodies. Next, the researchers scaled up the production of the DT5 antigen (33 human doses) and tested it in mice, which resulted in the induction of immunity within five weeks of injection.

A platform for the portable biosynthesis of biomolecules on-demand provides new capabilities for the Department of Defense and may have significant global health benefits. The production of essential therapeutics and vaccines would greatly reduce the logistical and economic burden when deploying warfighters to underdeveloped environments and improve overall troop safety and health.

For more information, read the *Cell* article, "Portable, On-Demand Biomolecular Manufacturing."



By combining freeze-dried, cell-free (FD-CF) reaction pellets with DNA instructions for protein synthesis, therapeutics and other molecular tools can be manufactured on-site, on-demand with the simple addition of water, circumventing the need for cold-chain distribution and storage. The utility and versatility of this portable biomanufacturing platform was demonstrated for the production of a diverse range of products, including antimicrobial peptides, vaccines, antibodies and small molecules. Graphics courtesy of Dr. James J. Collins, Massachusetts Institute of Technology.

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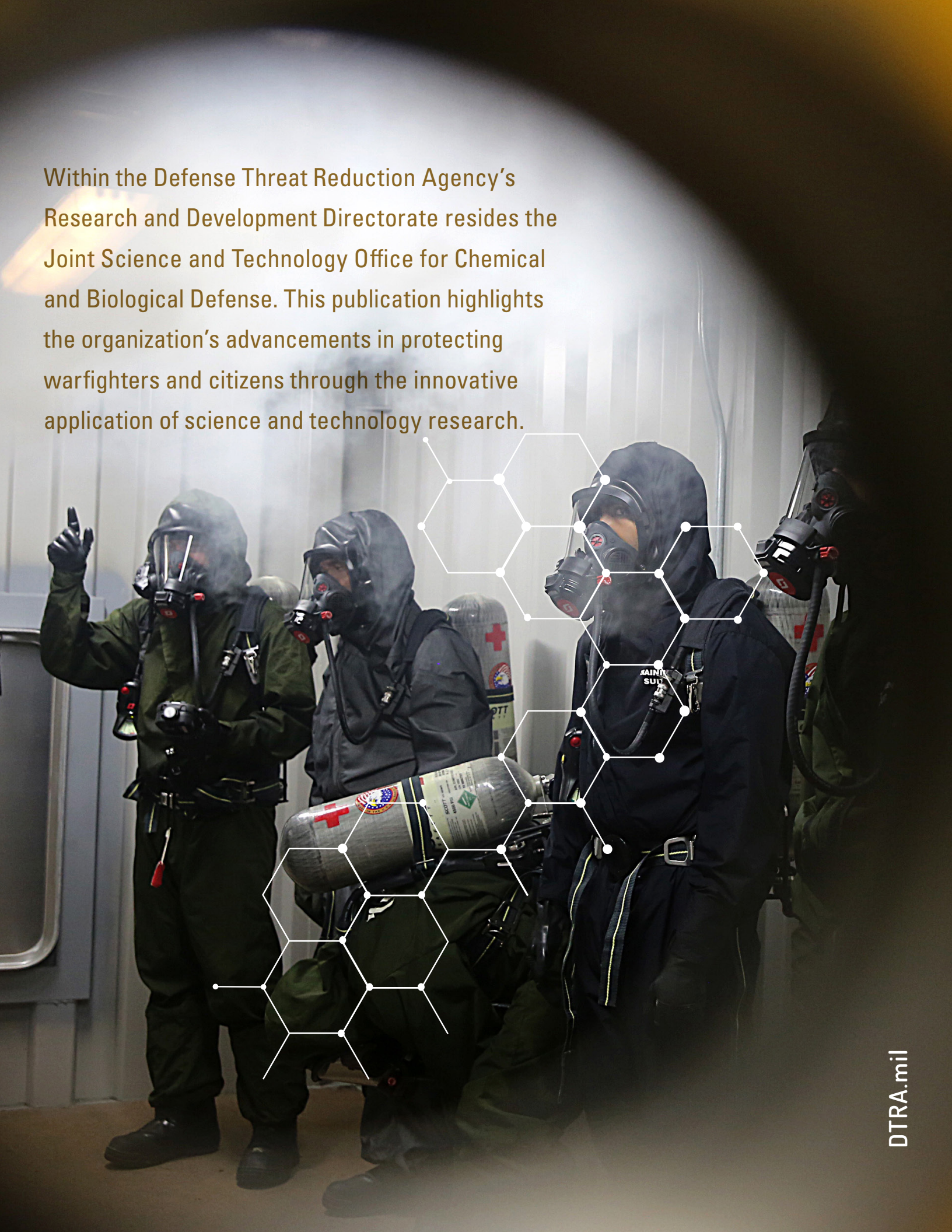
Within the Defense Threat Reduction Agency's Research and Development Directorate resides the Joint Science and Technology Office for Chemical and Biological Defense. This publication highlights the organization's advancements in protecting warfighters and citizens through the innovative application of science and technology research.



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