JSTO in the News

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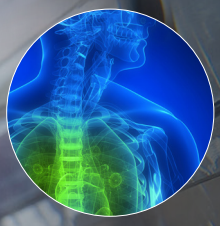
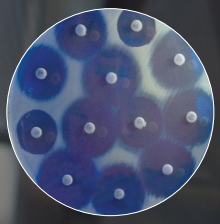
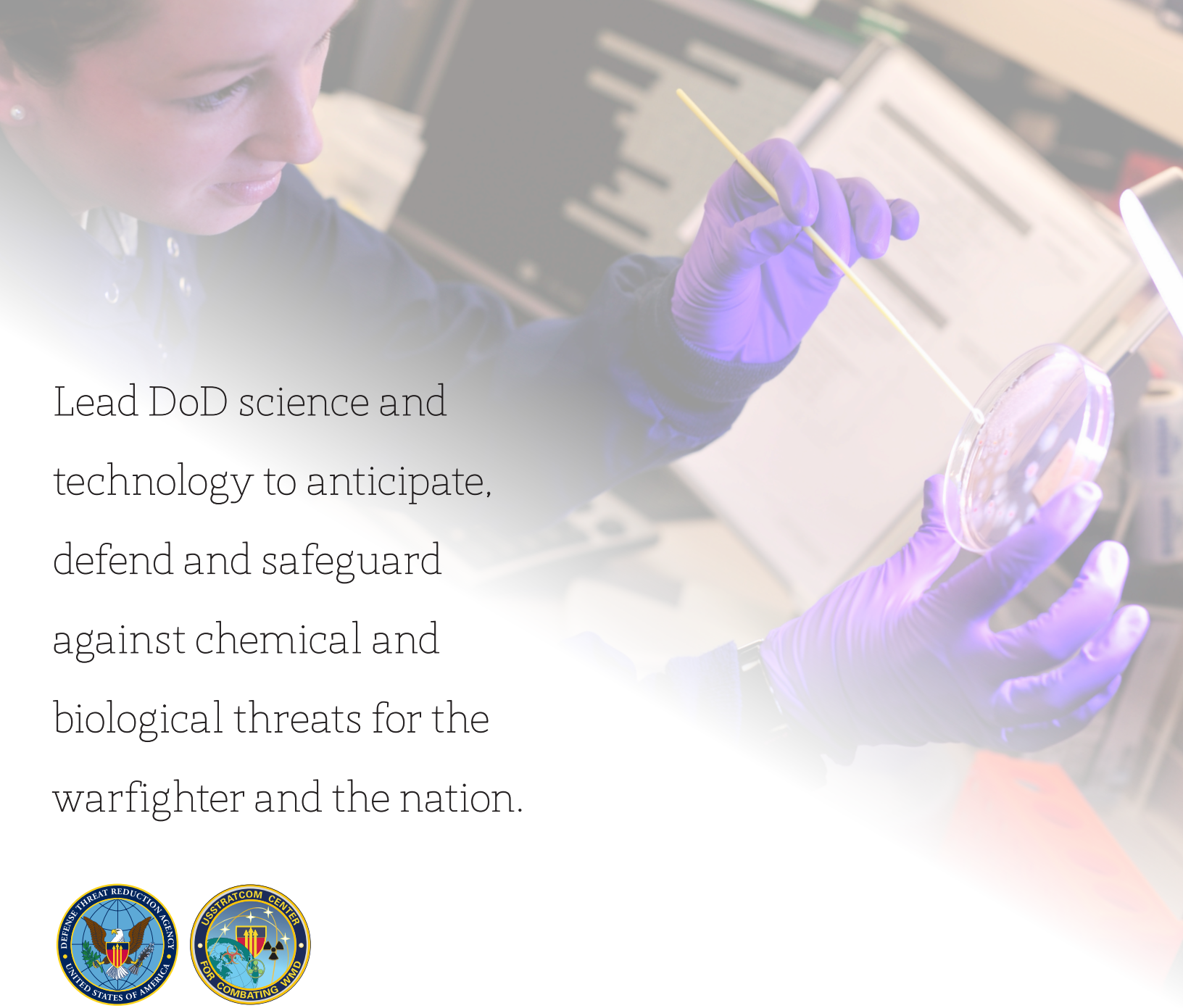


Antibiotic-Resistant Infections

Oscar Goes to "Organ-on-a-Chip"



Omadacycline to Treat Bacterial Infections



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

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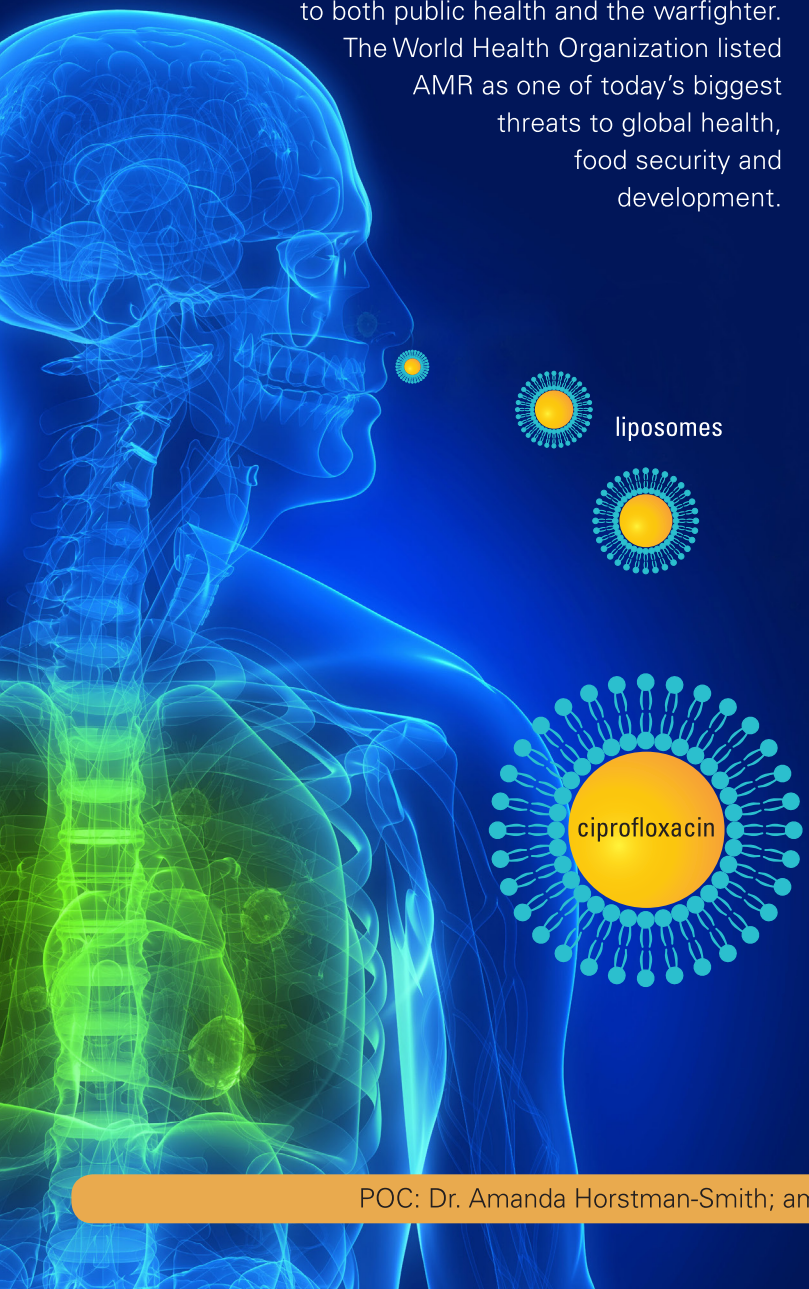
Front cover:
Hyun-Wook Kang, Ph.D., oversees the 3-D printer that will be used to print miniature organs for the 'Body on a Chip' system. Photo courtesy of Wake Forest Institute for Regenerative Medicine.

Back cover:
Sgt. 1st Class Erika Richardson, a flight medic assigned to C Company DUSTOFF, 3rd Battalion (General Support), sets up a blood transfusion device during training at Bagram Airfield in Parwan Province, Afghanistan. (Photo by Staff Sgt. Todd Pouliot, 10th Combat Aviation Brigade)

CHANGING THE TIDE OF Antibiotic-Resistant INFECTIONS

The rising tide of antimicrobial resistance (AMR), or the ability of a microbe to resist the effects of medication previously used to treat them, is a growing threat to both public health and the warfighter. The World Health Organization listed AMR as one of today's biggest threats to global health, food security and development.



While the natural prevalence of AMR in traditional biowarfare agents remains relatively low, the potential for genetic manipulation, acquired or deliberate, makes the possibility of a resistant threat a reality too dangerous to ignore.

To address this issue, the Defense Threat Reduction Agency's Joint Science and Technology Office is working to develop more effective broad-spectrum antibacterials to overcome resistance by developing innovative formulations of approved antibiotics and increasing their efficacy through improved administration methods. This approach expands the Department of Defense's medical countermeasure portfolio through a decreased development timeline and cost, supporting the tenets of the Better Buying Power 3.0 initiative.

In addition, JSTO and the Defence Science and Technology Laboratory, a component of the U.K. Ministry of Defence, in conjunction with Aradigm Corporation, are exploring the use of Pulmaquin to treat biological threats. Pulmaquin is an antibiotic formulation composed of a mixture of encapsulated liposome and unencapsulated ciprofloxacin, a widely prescribed fluoroquinolone antibiotic.

Pulmaquin is currently undergoing two Phase 3 clinical studies to determine its safety and effectiveness as an inhaled formulation for the treatment of patients with non-cystic fibrosis bronchiectasis, cystic fibrosis or non-tuberculous mycobacteria. However, Pulmaquin and an alternate formulation, Lipoquin, both demonstrated proof-of-concept efficacy in rodent models of inhalational tularemia, plague and Q-fever.

The inhaled liposomal ciprofloxacin approach delivers the antibiotic rapidly and in high concentration to the respiratory tract, the area of primary infection in an aerosol attack. The liposomal formulation retains the antibiotic over a prolonged period of time and facilitates intracellular uptake, essential to treat these life-threatening intracellular infections. In addition to offering dose sparing and a less invasive route of administration over IV-delivered ciprofloxacin, the increased concentration and residence time in the lung may overcome bacterial threats engineered to be resistant to fluoroquinolones.

This effort represents a valuable partnership between our government, allied countries and industry to develop treatments for common biological threats. This increased capability will bolster military resources to combat effects of a biological attack, expanding the capability of an FDA-approved antibiotic to treat biothreats and potentially antibiotic-resistant biothreat infections. The program also develops less invasive treatments with a shorter duration of treatment for bacterial infections for our nation's warfighters.

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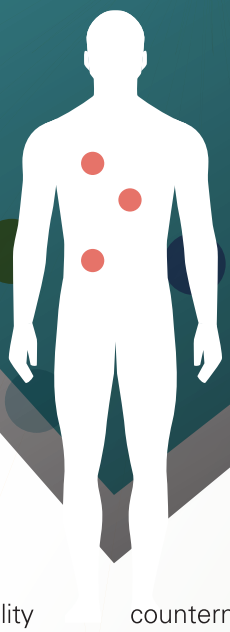
And the Oscar Goes to "ORGAN-ON-A-CHIP"



In a world of nanotechnologies and microchips, the ability for large-scale processes to take place on the microscale are becoming increasingly prevalent, even in the environment of combating chemical and biological threats to our warfighters. A research effort by the Defense Threat Reduction Agency's Joint Science and Technology Office, Los Alamos National Laboratory (LANL) and Wake Forest University (WFU) has resulted in an award-winning miniature technology in the eX-vivo Capability for Evaluation and Licensure (XCEL) program, the Pulmonary Lung Model (PuLMo). Commonly referred to as an "organ-on-a-chip," the model will offer faster and less expensive processes for drug delivery to our warfighters facing chemical and biological threats.

In order to bridge the gap between *in vitro* human assays, animal testing and clinical trials, this new technology allows researchers to assess real-time drug interactions on key human organs during the development of medical countermeasures. The PuLMo uses a unique combination of miniaturized organoid constructs derived from human cells to engineer an advanced 3D system that mimics four vital human organs (heart, lung, liver and kidney) either alone or in integrated circuits. To assess damages, these 3D human organoids are exposed to drugs, drug metabolites, chemical and biological agents or other toxicants.

For example, if a drug or its metabolite demonstrates an adverse effect on organ tissue that was not identified during animal testing, scientists can reassess the compound structure and other metabolic attributes to mitigate the risk factor. In addition, the ability to test multiple compounds rapidly offers the potential to mitigate safety risk without extensive animal testing. The FDA and other regulatory authorities view this as an important step in reducing animal use and improving our understanding of compound liabilities.

Recently, DTRA's JSTO, WFU, the Space and Naval Warfare Systems Command, the U.S. Army Medical Research Institute for Infectious Diseases, the National Institutes of Health and the FDA participated in the first demonstration of this technology. Scientists at LANL validated the remarkable progress on each of the miniature organoid constructs, which incorporates both airway-type cells and alveolar cells, each with different morphology and functionality.

To mimic the structure of the human lung, the PuLMo team developed two different lung models. The first model focuses on tissue engineering and co-culture of multiple cell types and consists of two major units—bronchiole and alveoli. These units are connected via a microfluidic chip, known as a Fluid Circuit Board, to help manage the flow of air and media.

The second model focuses on mimicking the air-flow dynamics in the human lung and tissue engineering. It does not have a Fluid Circuit Board, but the model mimics the branching of the late generations of the respiratory bronchiole and the alveolar sacs from a human lung.

Both models co-culture at least three different cell types from three different regions of the lung, the Bronchiolar Epithelial, Alveolar Epithelial and Microvascular cells. They incorporate several physiological characteristics such as air-liquid interface, ciliated cells, mucus production, cyclic stretching of membranes, surfactant production and shear flow on microvascular cells and breathing.

R&D 100 Magazine designated the PuLMo technology a Top 100 Technology Development for 2016. This prestigious award, often known as the "Oscars of Invention," is a clear indication of the success of the XCEL program and its place on the leading edge of medical technologies.

DTRA, LANL and WFU scientists continue to be at the forefront of medical innovation by integrating, refining and expanding their capabilities in exposing key human organs with real-time evaluation of drugs and their metabolites. Additionally, unique to DoD, the organ-on-a-chip platform provides a capacity for threat agent characterization which is not possible in humans. This new capability enables researchers to deliver targeted medical countermeasures for the warfighter.

Dr. Hann, Director of the Joint Science and Technology Office at the Defense Threat Reduction Agency, examines the liver module of the XCEL project at Los Alamos National Laboratory.

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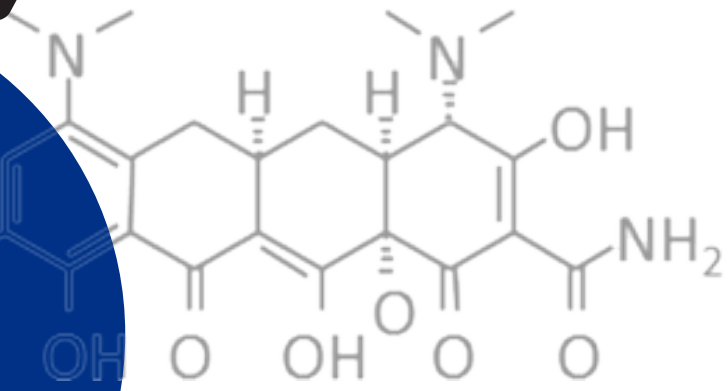
OLD ANTIBIOTICS



New Tricks

More than 100 antibiotic compounds have been discovered since Alexander Fleming invented penicillin in 1928, but none within the past 30 years. Now a joint venture between the Defense Threat Reduction Agency's Joint Science and Technology Office, U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), Joint Program Executive Office (JPEO) and Paratek Pharmaceuticals, a U.S.-based biopharmaceutical company, is exploring a new class of tetracycline that could combat biological threats to our warfighters.

TO COMBAT BIO AGENTS

While a new antibiotic is necessary to combat drug resistant biowarfare pathogens, there are inherent challenges in antibiotic discovery, such as difficulty in establishing a broad-spectrum application while avoiding potential toxicity. In addition, in order to be suitable for warfighter use, new antibiotics must exhibit superiority or equivalence compared to the current military standard of care.

Biowarfare pathogens also require special handling and biosafety precautions, such as Biosafety Level (BSL)-3 containment and compliance with Food and Drug Administration requirements for development under the Animal Rule, as clinical trials in humans are unethical or unfeasible. USAMRIID provides expertise in both handling biowarfare pathogens and testing compounds against biowarfare pathogens through animal models.

The group's Core Antibiotic Screening Project, with funding from JSTO, screens antibacterial compounds against BSL-3 select agents and identifies which compounds have activity. Within this core capability, small molecules are screened against a panel of 150 bacterium strains (30 strains per select agent of interest including *B. pseudomallei* (melioidosis), *B. mallei* (glanders), *Bacillus anthracis* (anthrax), *Yersinia pestis* (plague), and *Francisella tularensis* (tularemia)) to establish effectiveness against select agents.

The antibacterial compounds demonstrating good *in vitro* efficacy are advanced to *in vivo* evaluation in biological warfare agent challenge models. Ultimately, the compounds will become part of the FDA's Animal Rule studies through the Label Expansion program. This program assesses whether or not a specific drug can treat additional types of patients and diseases beyond the drug's original intended use.

In 2015, the Label Expansion program yielded FDA approval of a supplemental New Drug Application for moxifloxacin for the oral and IV treatment and post-exposure prophylaxis of infection caused by *Y. pestis*. This success spurred JSTO and JPEO to provide additional funding, expanding USAMRIID's Label Expansion program to integrate a pipeline of potential late-development candidates for repurposing against biowarfare agents. This approach allows the Department of Defense to reduce the development cycle for new medical countermeasures while increasing warfighter safety, supporting efficiency and cost-saving initiatives.

Omadacycline, a Paratek-developed antibiotic, is currently under evaluation by USAMRIID's Label Expansion program. The well-tolerated, once-daily oral and IV antibiotic is the first in a new class of tetracyclines, known as aminomethylcyclines, with broad-spectrum activity against gram-positive, gram-negative and atypical bacteria.

The joint DTRA, JPEO, USAMRIID and Paratek effort represents a valuable partnership within the Chemical and Biological Defense Program. The work highlights continuing efforts to engage industry and reduce biological threats to our warfighters.

In June 2016, the new antibiotic demonstrated positive results for efficacy and safety in a Phase 3 clinical study for skin structure infection and acute bacterial skin. The Phase 3 registration study for community-acquired bacterial pneumonia comparing IV-to-oral omadacycline to IV-to-oral moxifloxacin was initiated in November 2015.

Enrollment figures are on track to report top line data as early as the third quarter of 2017. The FDA granted omadacycline 'Qualified Infectious Disease Product' designation and 'Fast Track' status. The Animal Rule studies, performed in collaboration with USAMRIID, are designed to confirm humanized dosing regimens of omadacycline and establish the efficacy of omadacycline against biodefense pathogens, including *Yersinia pestis* and *Bacillus anthracis*.

The joint DTRA, JPEO, USAMRIID and Paratek effort represents a valuable partnership within the Chemical and Biological Defense Program. The work highlights continuing efforts to engage industry and reduce biological threats to our warfighters. The resulting capability will bolster the military's medical defense toolbox, increasing the number of options available to combat infections in the event of a biological attack.

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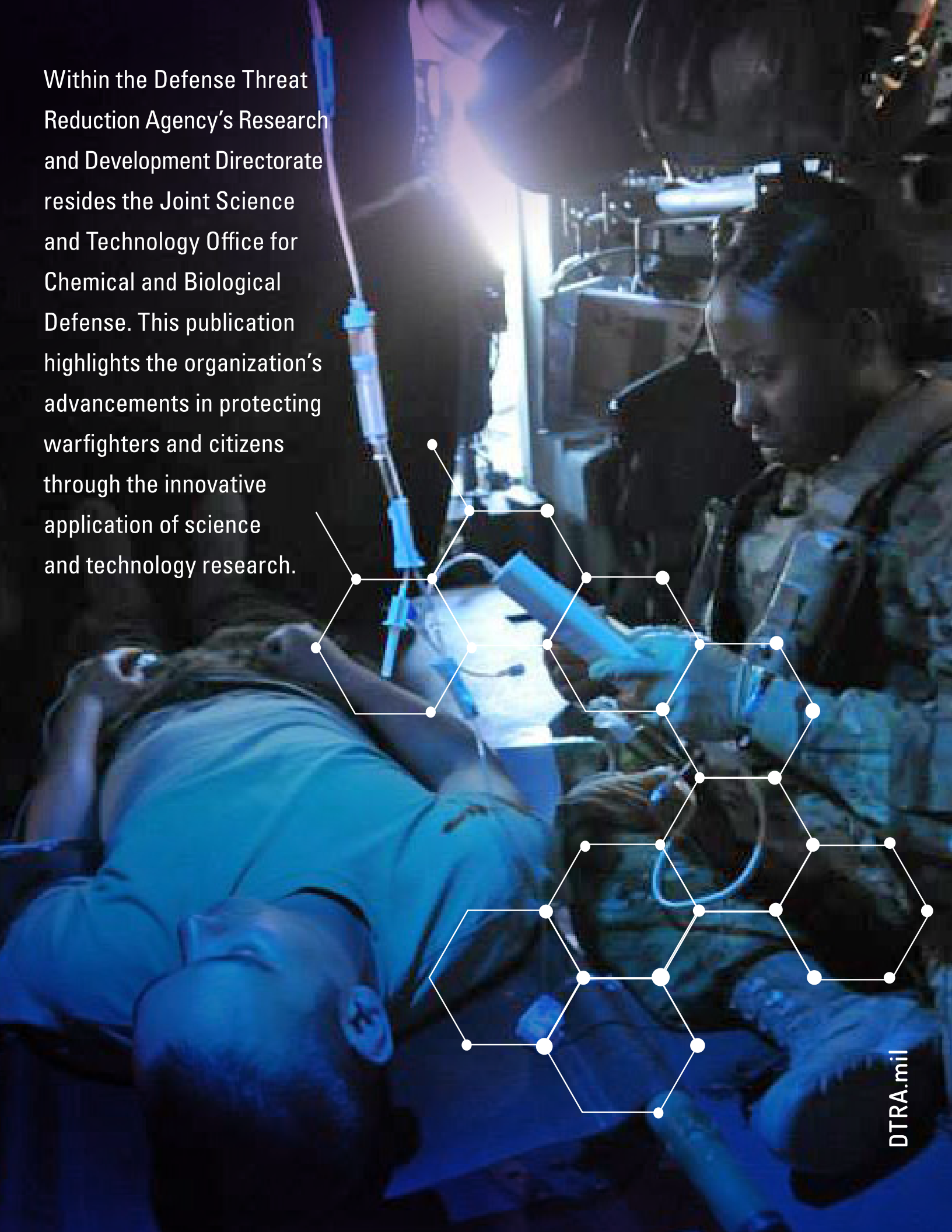

Within the Defense Threat Reduction Agency's Research and Development Directorate resides the Joint Science and Technology Office for Chemical and Biological Defense. This publication highlights the organization's advancements in protecting warfighters and citizens through the innovative application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

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