JSTO in the News

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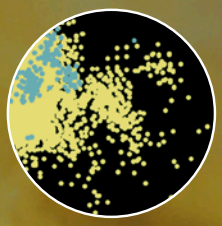
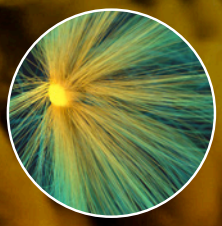


Talking the Same Talk

Down the Line



Assessing Biohazards Lurking in the Air

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

Research and Development Directorate
Chemical and Biological Technologies Department
Joint Science and Technology Office for Chemical and Biological Defense

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Front cover: U.S. Marine Corps Lance Cpl. poses for a portrait in an M50 joint service general protective mask. (U.S. Marine Corps photo by Zachary Zephir)

Inside cover: Army Spc. analyzes basic metabolic panels. About 500 soldiers from Fort Carson, Colo., and Joint Base Lewis-McChord, Wash., are setting up an Army field hospital at the center in support of the Defense Department's COVID-19 response. (U.S. Army photo by Brent C. Powell)

Back cover: U.S. Air Force Senior Airman prepares to give a shot during the base's Ebola-like disease containment exercise. The base simulated responding to an Ebola outbreak after a deployment. (U.S. Air National Guard photo by Amber Powell)

TALKING THE SAME TALK

Years of chemical research has produced huge repositories of "big data." DTRA-JSTO's support of chemical informatics will help link that information for faster and more effective chemical medical countermeasure development.

The advent of "big data" from medical field research helps bring chemical medical countermeasure (cMCM) solutions to the warfighter faster and at a reduced cost as cMCM development is more efficiently focused on treatments highly likely to be effective.

The Defense Threat Reduction Agency's (DTRA) Chemical and Biological Technologies Department in its role as the Joint Science and Technology Office (JSTO) uses *chemical informatics*, or "chemoinformatics," to mine a Department of Defense (DoD) repository of this composite data. Chemoinformatics focuses on storing, indexing, searching, retrieving, and applying information about chemical compounds. Researchers receiving DTRA-JSTO investments perform together to streamline the formatting, standardization, capture, transfer mechanisms, analysis, storage, and querying processes associated with big data generated by various performers' cMCM discovery campaigns.

Advances in biotechnology that enable more drug discovery data than ever before to be generated at a fixed cost also compound challenges associated with big data,* but the following technologies in drug development aid performers to more rapidly create effective candidate cMCMs:

- **High-throughput screening (HTS)**—an automated method to rapidly test hundreds to thousands of predictions about the behavior of different compounds
- **Artificial intelligence (AI)**—intelligence as demonstrated by machines, unlike the natural intelligence displayed by humans and animals
- **Machine learning (ML)**—an application of AI that provides systems the ability to automatically learn and improve from experience without being explicitly programmed

While ultra-HTS of a chemical library against one target can produce millions of data points, multiple HTS efforts by a single performer can result in big data sets so large that they cannot be processed by conventional methods such as using reports or spreadsheets.

This coordination and collaboration between performers will overcome known issues associated with applying AI/ML to big data, and fully utilizing big data will:

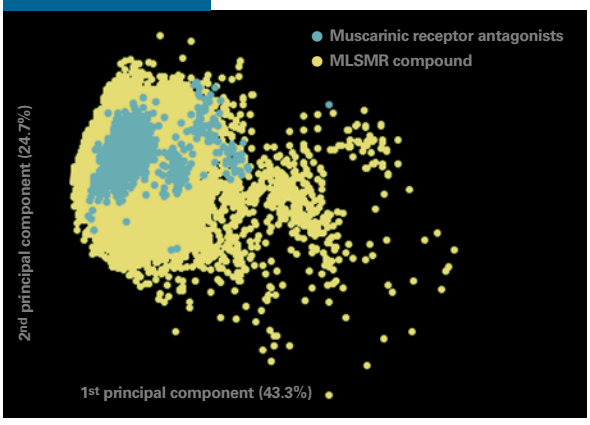
- Enable earlier safety and efficacy assessments of candidate cMCMs
- Enhance candidate cMCM hit-to-lead down-select decisions—the pairing down of identified candidate cMCMs to a smaller number of leading candidates based on safety and efficacy data
- Reduce redundancy of the unintentional duplication of testing or screening of the same candidate cMCMs by different performers
- Increase the efficiency of cMCM development

This system will deliver novel candidate cMCMs to the warfighter faster and potentially save lives. For example, DTRA-JSTO research performed at Alchem Laboratories Corporation is using ultra-HTS to screen 370,000 compounds in the National Institutes of Health Molecular Libraries Small Molecule Repository library for several receptors that can be targeted by cMCMs to protect against nerve agent poisoning.

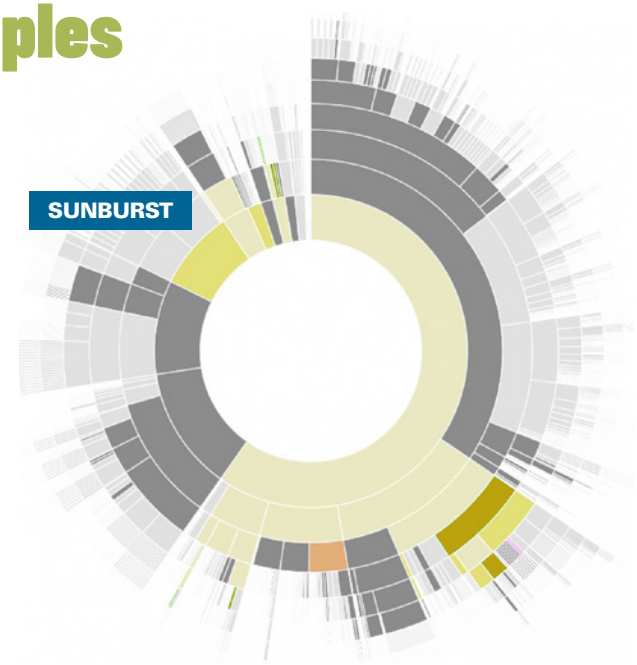
Data Visualization Samples

This central repository will visualize datatypes from chemicals in the screening libraries. Data visualization is the graphical representation of information and data. These are two types of data visualizations.

SCATTER PLOT

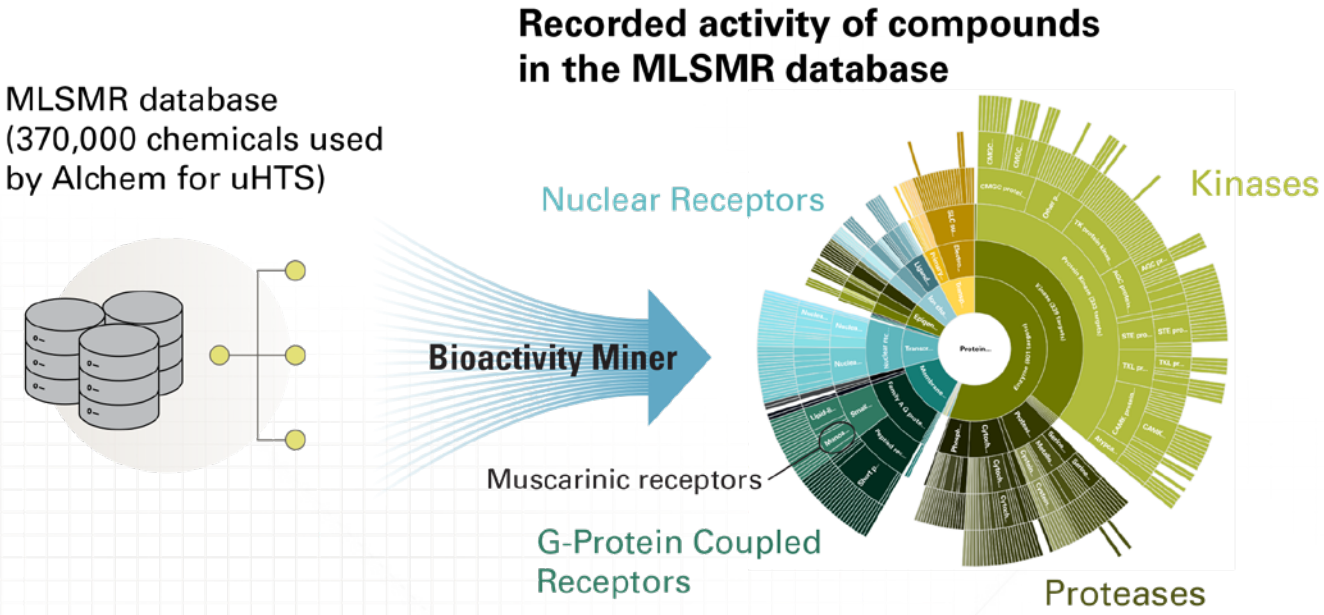


SUNBURST



* Brown, N., Cambruzzi, J., Cox, P. J., Davies, M., Dunbar, J., Plumbley, D., Sellwood, M. A., Sim, A., Williams-Jones, B. I., Zwierzyna, M., & Sheppard, D. W. (2018). Big Data in Drug Discovery. Progress in medicinal chemistry, 57(1), 277–356. https://doi.org/10.1016/bs.pmch.2017.12.003

Bioactivity Miner



Anticipating the increased informatics and computational requirements needed to curate, prioritize, store, analyze, and manage this data, DTRA-JSTO also funds researchers at the Biotechnology High Performance Computing Software Applications Institute (BHSAI) of the U.S. Army Medical Research and Development Command Telemedicine and Advanced Technology Research Center to provide AI/ML and computational chemistry expertise in support of Alchem and other similar efforts in the cMCM portfolios.

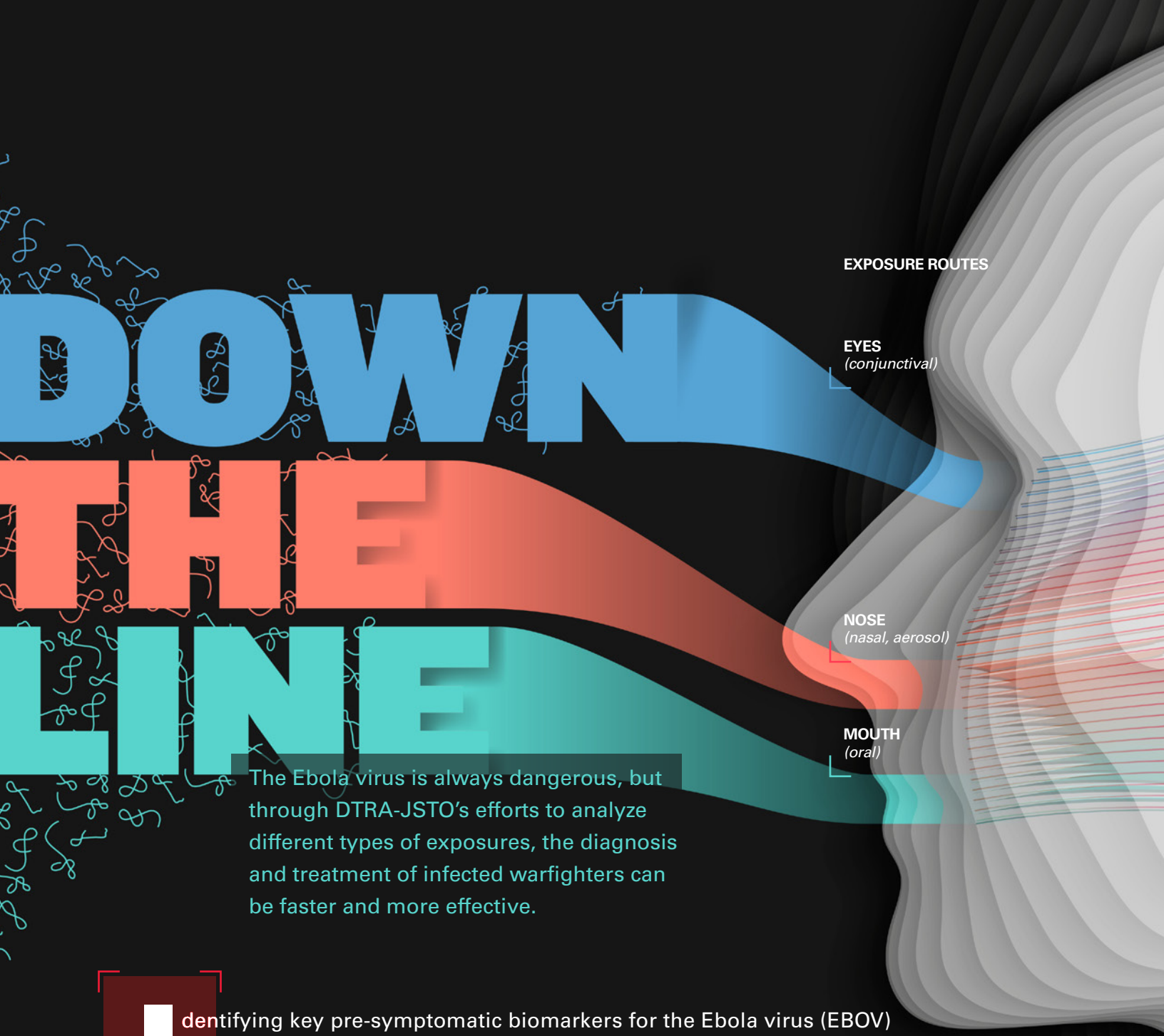
BHSAI's current effort involves creating an HTS database and deploying AI-based algorithms to mine that database and support hit prioritization integrated into BHSAI's access-controlled Chemoinformatics System. This central repository will capture, store, and visualize datatypes from chemicals in the screening libraries and results from the HTS biological assays generated from DTRA-JSTO funded performers across the cMCM Enabling Science portfolio.

The HTS database interfaces with existing and new in-house BHSAI computational tools to predict features of candidate cMCMs that are important for drug development, such as standard absorption, distribution, metabolism, excretion, and toxicity parameters.

The HTS data will also be used as training sets to develop deep-learning algorithms to identify which chemicals in a screening library fit the profile of a good drug: maximum efficacy with minimal safety concerns. The data produced by HTS efforts will help to train new ML algorithms.

The BHSAI DoD repository for the central collection, standardization, storage, and AI/ML-based analysis of HTS candidate cMCM data will enable DTRA-JSTO to make the most out of combining AI/ML and big data to more rapidly create effective cMCM for the warfighter at a reduced cost. ●

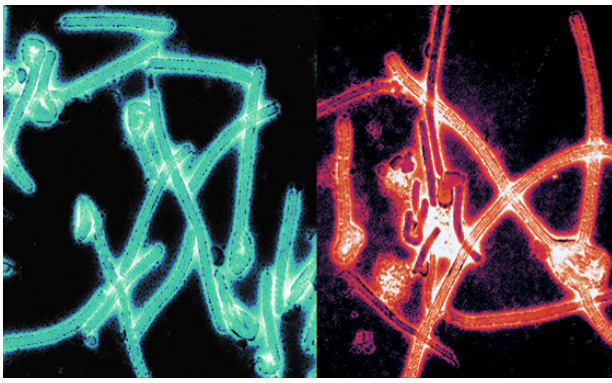
DOWN THE LINE



The Ebola virus is always dangerous, but through DTRA-JSTO's efforts to analyze different types of exposures, the diagnosis and treatment of infected warfighters can be faster and more effective.

Identifying key pre-symptomatic biomarkers for the Ebola virus (EBOV) disease can lead to faster, more reliable detection and diagnostic testing, which will improve treatment and increase survivability for the warfighter. EBOV, also known as Ebola hemorrhagic fever, is a severe, often fatal illness affecting humans and non-human primates. The World Health Organization notes that case fatality rates varied from 25% to 90% in past outbreaks.

The Defense Threat Reduction Agency's (DTRA) Chemical and Biological Technologies Department in its role as the Joint Science and Technology Office (JSTO) studied EBOV infection from different routes of exposure, assessing lethal dose amounts and biological markers ("biomarkers") of infection. Biomarkers are detectable or quantifiable indicators of some phenomenon such as disease, infection, or environmental exposure.



Zaire ebolavirus, more commonly known as Ebola virus. (DTRA CB photo)

Understanding the differences in the course of infection can assist efforts to identify and counter Ebola infection resulting from natural outbreaks or in situations where warfighters could be exposed to EBOV—either naturally, accidentally, or intentionally.

Researchers at the University of Texas Medical Branch at Galveston (UTMB) led a team that demonstrated EBOV infection from *Zaire ebolavirus* Makona strain of the 2014 outbreak. Breathing in the virus (an aerosol route) was far deadlier than infection resulting from eye (conjunctival) or mouth (oral) exposure routes. UTMB studies showed that a lethal inhaled dose could be several orders of magnitude smaller than for the other two routes and more dangerous.

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The researchers also discovered pre-symptomatic biomarkers that identify EBOV infection before outward symptoms are present. These biomarkers offer information about the host's response to infection and the pathogen activity and so they can be used along with signs and symptoms to make better healthcare decisions for the patient. Biomarker data can also influence the development of diagnostic and therapeutic countermeasures, a critical step toward rapidly diagnosing EBOV infection to improve outcomes through early intervention and supportive care.

In this study, researchers sought biomarkers produced during and because of EBOV infection by comparing transcriptomes—the set of ribonucleic acid products that are manufactured by an organism's genetic material—from infected and non-infected hosts (a method called transcriptomics). Comparing healthy to infected transcriptomes can identify genes that are differentially expressed during stages of the infection, which is a key element of developing detection and diagnostic tools along with studying the natural history of the disease.

One significant biomarker finding in this study was identifying specific transcriptomic signatures that could be directly linked to the EBOV exposure route and dose that related to the survival or death of the host. Infection by the aerosol route resulted in an immediate, identifiable, and reproducible increase in transcriptomic signatures—in this case, transcriptome differences between infected hosts and control populations—where researchers detected the transcriptomic signatures before the presence of virus in blood was detectable. Identifying these biomarkers could increase survivability where fatality could nearly be a given. ●

POC: Donald Cronce, Ph.D., donald.t.cronce.civ@mail.mil

ASSESSING BIOHAZARDS LURKING IN THE AIR:

They can be tasteless, odorless, invisible, and have a lethally potent reach.

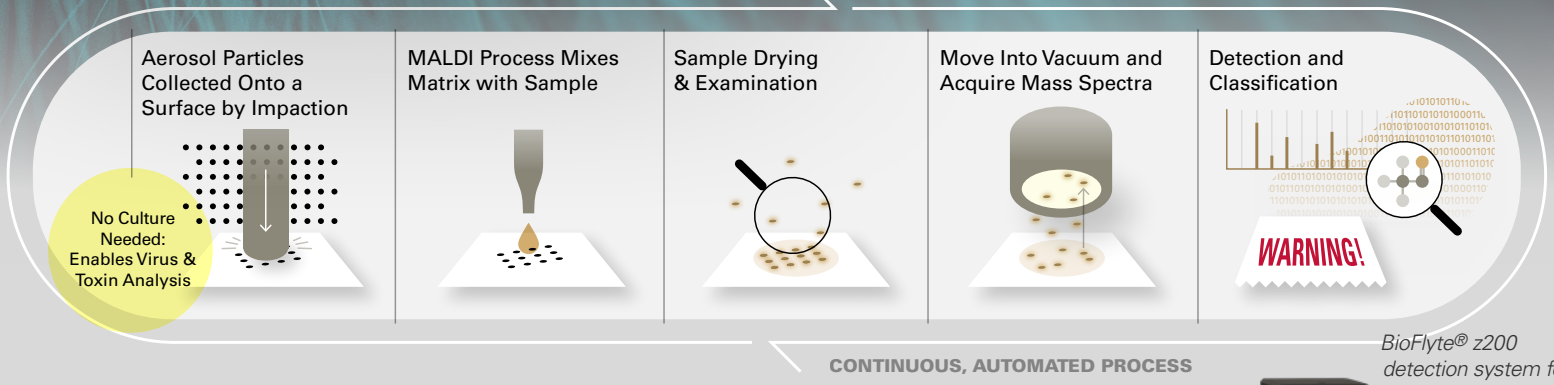
New technology the size of a carry-on bag can augment the way warfighters monitor and detect indoor biological hazards. An automated, intricate, and analytical technique that detects and identifies bioaerosol threats without being monitored provides enhanced capability and decreases burden for warfighters.

The Defense Threat Reduction Agency's (DTRA) Chemical and Biological Technologies Department in its role as the Joint Science and Technology Office (JSTO) worked in partnership with the Army Research Office to fund Zeteo Tech Inc. through a Small Business Innovation Research Phase III award to create an instrument capable of detecting bioaerosol threats that can continuously monitor an indoor environment for anomalous bioaerosol activity and be run remotely.

Bioaerosols are microscopic airborne particles of biological origin that can be dead or alive and pathogenic (capable of causing disease) or non-pathogenic. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which causes COVID-19, is just one example of a microbe that can be transmitted by aerosols and become a serious threat to warfighters and the public.

Aerosolized pathogens can secretly lurk in the air without activating any of the human senses—they are tasteless, odorless, inaudible, and invisible to the human eye. Their surreptitious nature gives them the advantage of invading, transmitting, and infecting people days before any onset of symptoms. This has pushed the Department of Defense to think creatively on how to innovate and develop technology capable of providing early warning and detection of bioaerosol hazards.

BioFlyte® Fully Automated Robotic Process Mimics Lab/Clinic



BioFlyte® z200 detection system for critical infrastructure protection. (BioFlyte photo)

This technology is called the BioFlyte z200, and it provides a cost-effective, rapid biological detection system that collects air samples to identify potential biological aerosol hazards in near real time, while costing just pennies per test to run a sample.

This detection technology packages and automates intricate laboratory processes using novel Matrix-Assisted Laser Desorption Ionization – Time of Flight Mass Spectrometry and can complete sample to result in under five minutes. It processes and interrogates the sample for unique features by:

- Mixing the sample with a matrix solution
- Depositing and drying the sample onto a test ticket
- Using laser pulses to vaporize the sample where ions travel through the time-of-flight tube
- Measuring the sample based on mass-to-charge ratio and mass resolution
- Conducting data analysis and displaying results

These measurements can then be cross-referenced with a spectral library database and further analyzed to determine if a potential threat is present.

The instrument is capable of continuously running and monitoring an indoor environment as it can be set to automatically collect samples and test the air in the room to assess if there is anomalous activity or if a potential threat can be detected. In addition to continuous monitoring, the instrument can be remotely triggered by an operator at any time a sample is needed.

Through DTRA-JSTO investments, additional characterization studies were conducted to further develop a robust spectral library and to best allow the BioFlyte instrument, with the capability of detecting and identifying a variety of biological threats, to add to the library's collection.

One example is the initial study and characterization of SARS-CoV-2 on the BioFlyte. This not only helps support the potential population of the spectral library but, more importantly, helps to compare the performance of the BioFlyte against other mass spectrometers that can be physically larger and more expensive, and also compare the signatures from the BioFlyte instrument with the expected signatures for SARS-CoV-2 already published.

These results are being evaluated and will be used to help determine the mass resolution of the instrument and identify any potential areas for improvement. Once anomalous activities are reported, mass resolution may play a critical role in reducing false alarms by correctly parsing out threats from benign bioaerosols based on the spectral library. ●

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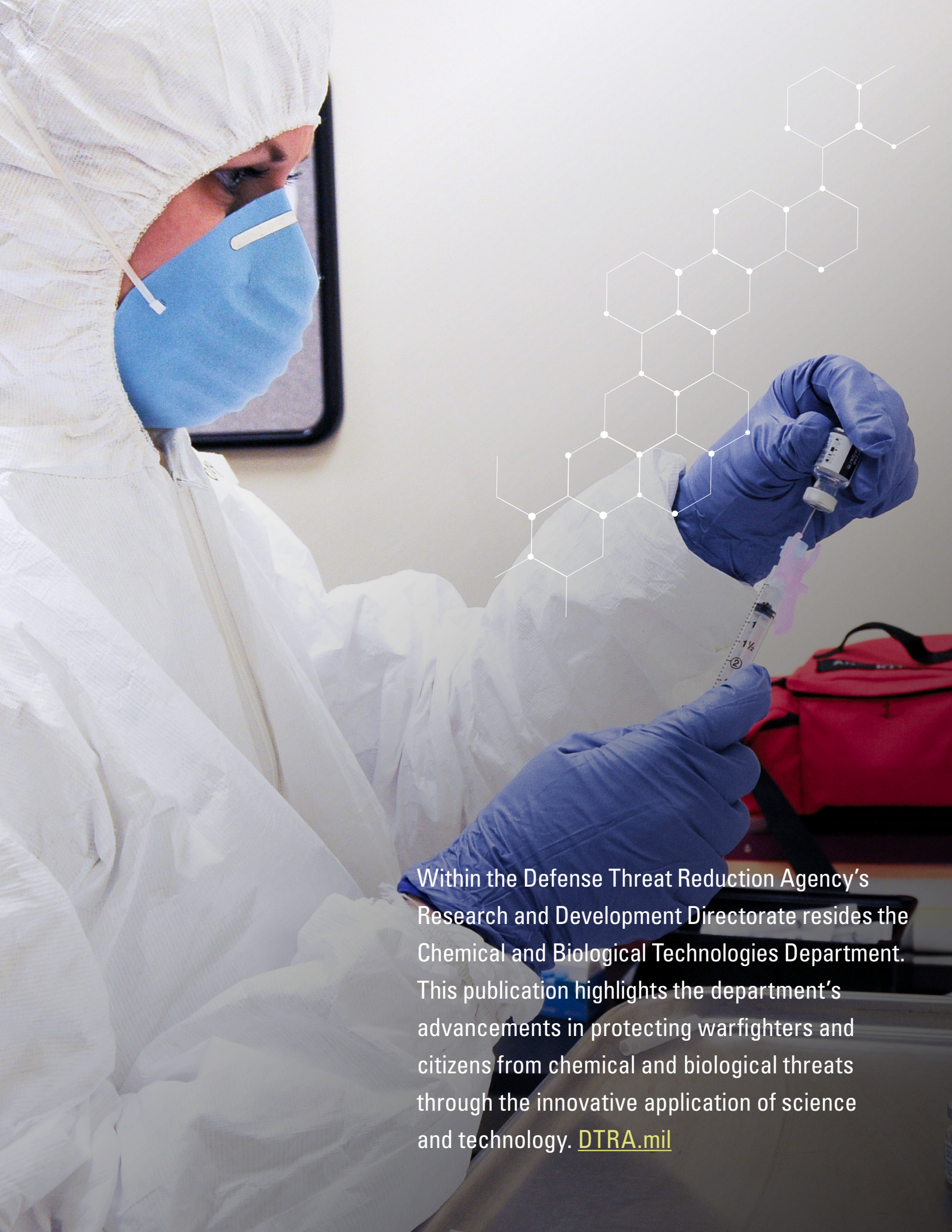

Within the Defense Threat Reduction Agency's Research and Development Directorate resides the Chemical and Biological Technologies Department. This publication highlights the department's advancements in protecting warfighters and citizens from chemical and biological threats through the innovative application of science and technology. DTRA.mil