JSTO in the News

DTRA.mil

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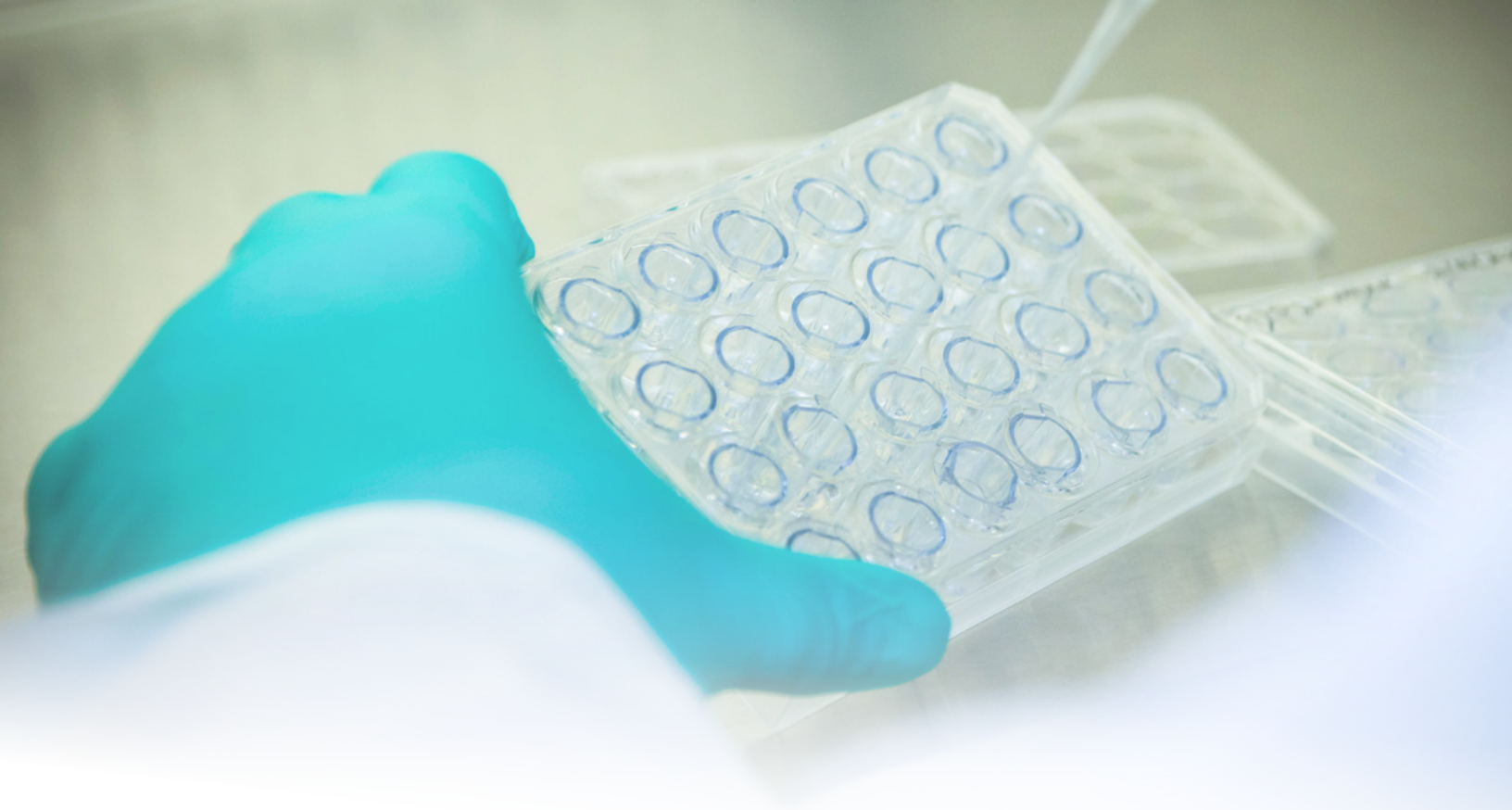
SPECIAL BASIC RESEARCH EDITION

The Ground Floor: Advanced Life-Saving Initiatives Begin With Basic Research.



DTRA MISSION

DTRA provides cross-cutting solutions to enable the Department of Defense, the United States Government, and international partners to Deter strategic attack against the United States and its allies; Prevent, reduce, and counter Weapons of Mass Destruction (WMD) and emerging threats; and Prevail against WMD-armed adversaries in crisis and conflict.

CHEMICAL AND BIOLOGICAL TECHNOLOGIES DEPARTMENT MISSION

Lead DoD science and technology to enable the Joint Force, nation, and our allies to anticipate, safeguard, and defend against chemical and biological threats.

DEFENSE THREAT REDUCTION AGENCY

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Chemical and Biological Technologies Department
Joint Science and Technology Office
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Inside cover: Experimental Therapeutics (ET) is a drug discovery and development enterprise created to protect military personnel from death, disease, and injury and meet DoD mission requirements. While its historical focus has been radioprotection and parasitic disease, ET applies its core competencies of medicinal, synthetic, and analytical chemistry as well as clinical pharmacology to all therapeutic areas within the Medical Research and Development Command's portfolio. ET has a 75-year legacy of excellence in small molecule drug development, with over 65 Investigational New Drug (IND) applications submitted to the U.S. Food and Drug Administrations (FDA). ET is a world leader in malaria drug development—every malaria prophylaxis drug was either created by ET scientists or transited ET test systems on its way to FDA approval. ET recently established a robust antibacterial product development effort mandated by the Presidential Combating Antibiotic Resistant Bacteria initiative. (U.S. Army Photo by Tyra Breaux/Released))

Back cover: Neda Acheampong, a researcher with the Naval Medical Research Center (NMRC), dissects mosquitoes under a microscope in the General Immunology and Parasitology Laboratory to obtain malaria parasites. NMRC's eight laboratories are engaged in a broad spectrum of activity in support of the Navy, Marine Corps, and other Joint Force members, ranging from basic science in the laboratory to field studies in austere and remote areas of the world to cutting-edge research in operational environments. NMRC researchers study infectious diseases, biological warfare detection, combat casualty care, environmental health concerns, aerospace and undersea medicine, medical modeling, operational mission support, and epidemiology. (U.S. Navy photo by Michael Wilson/Released)

THE PIVOTAL ROLE OF BASIC RESEARCH IN FOSTERING *INNOVATION*

Basic research plays a significant role in developing technologies and capabilities to deter, prevent, and prevail against chemical and biological threats for the Joint Force, our nation, and our allies. Investments in basic research by the Defense Threat Reduction Agency's (DTRA) Chemical and Biological Technologies Department in its role as the Joint Science and Technology Office (JSTO) for Chemical and Biological (CB) Defense, an integral component of the Chemical and Biological Defense Program, include developing a highly skilled workforce and infrastructure that enable further research and scientific discoveries. Over the past decade, DTRA JSTO's basic research has led to the discovery of new and often transformative technologies that benefit warfighters.

Probiotics Research Leads to a *Universal* Diagnostics Platform

A DTRA JSTO investment with the Massachusetts Institute of Technology (MIT) that initially explored the potential of creating probiotics as a cure for cholera evolved into developing bioengineered reporter molecules for disease detection. This research led to a rapid, inexpensive, and temperature-stable, paper-based diagnostic platform, which later was extended to rapidly produce drugs on demand. The researchers were able to distinguish between American and African Zika genotypes using Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) editing.

The success of the basic research studies led investigators to form Sherlock Biosciences that produced a CRISPR SARS-CoV-2 diagnostic test kit called SHERLOCK, which was the first CRISPR-based diagnostic technology to receive approval by the Food and Drug Administration (FDA). The transition to DTRA JSTO's applied research program developed a versatile, multiplexed platform technology called Dial-a-Threat (DaT), which could generate assay designs within a day, and produce and test detection assays in months. The program developed a SARS-CoV-2 assay and accelerated DaT technology for military use with Coronavirus Aid, Relief, and Economic Security (CARES) Act funding.

TO LEARN MORE

JSTO in the News, August 2016, Vol. 6, No. 8 article, "Rock, Paper, Zika: Paper Wins as New Detection Tool."

Click here to read the article

JSTO in the News, August 2021, Vol. 11, No. 7 article, "Small. Simple. Sensitive. Specific."

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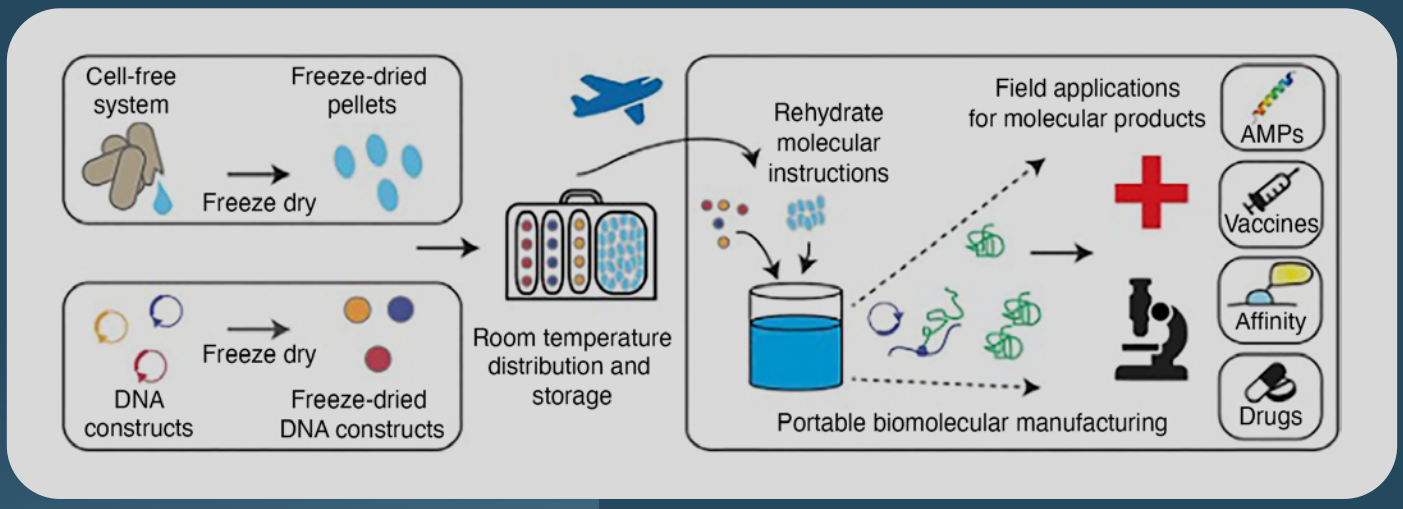

Portable, on-demand biomolecular manufacturing in the field for antimicrobial peptides (AMPs), vaccines, affinity, and drugs. (MIT image)

TO LEARN MORE

JSTO in the News, April 2016, Vol. 6, No. 4 article, "Lethal Weapon 24: Fighting Ebola with Human Antibodies."

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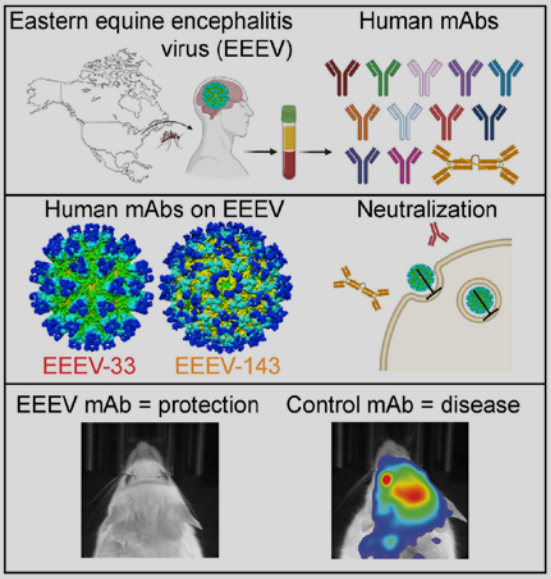
Structural Studies on Viruses *Lead to* Pandemic Panacea

One way the body fights foreign invaders, like bacteria and viruses, is by making antibodies against them. Vanderbilt University explored X-ray crystallography methods to understand the nature of human antibody (huAb) binding to influenza variants leading to neutralization. The studies showed the importance of binding aromatic residues of huAbs in the cavity of the virus receptor sites, and there were later studies on the Ebola and Marburg filoviruses. The methods used in structural studies to isolate antibodies from surviving patients, amplify them, and assay virus neutralization led to developing a versatile platform technology capable of responding rapidly to any future pandemic event.

DTRA JSTO invested with the National Institute of Allergy and Infectious Disease and transitioned Vanderbilt antibodies to Mapp Biopharmaceutical, Inc., to prepare an investigational new drug (IND) application for a broad-spectrum Marburg huAb therapy (Z-Mapp) that, with support from the Biomedical Advanced Research and Development Authority, entered phase I clinical trials in 2022. The Vanderbilt team licensed two huAbs to AstraSeneca, leading to the development of Evusheld, which the FDA approved under emergency use authorization as a therapeutic treatment for SARS-CoV-2 in December 2021. This technology is also being applied to the Eastern Equine Encephalitis and Chikungunya viruses.



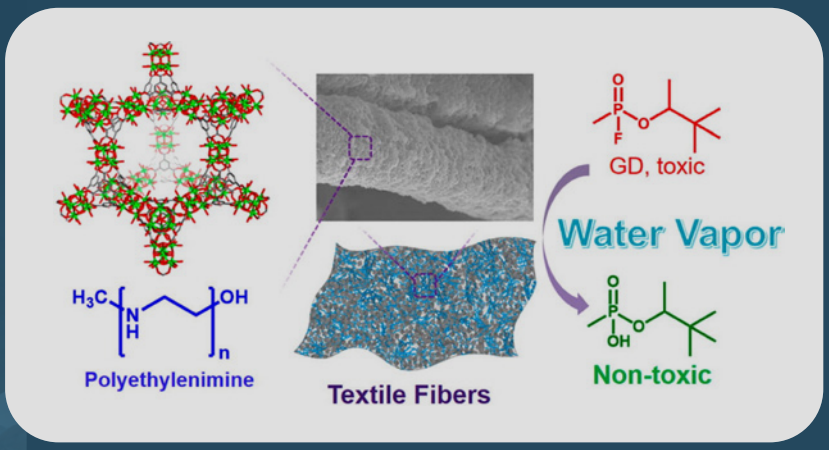
Human antibodies protect against aerosolized Eastern Equine Encephalitis Virus infection. (Image credit Williamson, L.E., et al., Cell 2020)

Research associate Jessica Rodriguez purifies human monoclonal antibodies. (Vanderbilt Vaccine Center, Nashville, Tenn., photo)

Creating a Materials *Pipeline* for Next-Generation CB Protection

Early discovery of new, advanced materials through synthesis, advanced characterization methods, and modeling studies led to the development of catalytic systems that destroy CB agents on contact. Research into new catalytic materials began more than a decade ago at the University of California, Berkeley and at Emory University. A leap forward came with the discovery of zirconium-based metal-organic frameworks (MOFs) at Northwestern University, together with research exploring spectroscopic methods to characterize catalysts under ambient reaction conditions by a collaborative team from Stony Brook University, the U.S. Army Combat Capabilities Development Command, Chemical and Biological Center (DEVCOM CBC), Virginia Tech, Emory University, and the University of North Carolina. DEVCOM CBC is transitioning the various methods to study chemical agents in-house. To perform these sophisticated techniques, DEVCOM CBC hired postdoctoral students and permanent staff who have degrees from their academic partners through DTRA JSTO's Laboratory-Directed University Research Grants Program.

Building on this basic research, DEVCOM CBC is working with Northwestern's NuMat Technologies, Inc., to significantly increase MOF production with support from Small Business Technology Transfer and U.S. Army ManTech programs, and the Rapid Innovation Fund. These materials facilitate advanced development of ultra high-performing filters, protective fabrics, and coatings designed to protect the Joint Force from current and emerging chemical and biological threats. MOF-impregnated JSGPM M61 mask filters exceeded threshold requirements and neared objective requirements, and efforts are underway to create MOF-integrated fabrics into protective scarfs and self-detoxifying suits at the U.S. Army Natick Soldier Research, Development & Engineering Center.



Zirconium-MOF catalysts integrated into textiles are being developed as reactive materials for use in next-generation, self-detoxifying protective suits. (Northwestern University image)

TO LEARN MORE

JSTO in the News, February 2022, Vol. 12, No. 1 article, "Reduce. Reuse. Redefined."

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MOF-based filter prototypes for collective protection and general purpose mask. (NuMat Technologies, Inc., photo)

TO LEARN MORE

JSTO in the News, December 2022, Vol. 12, No. 8 article, "All the Chips on the Table."

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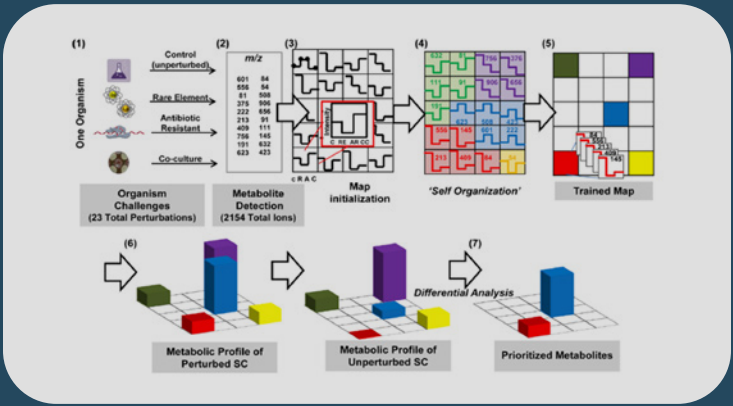


Mapping metabolic profiles on perturbing conditions using self-organizing maps of high-dimensional mass spectrometry data. (Vanderbilt University image)

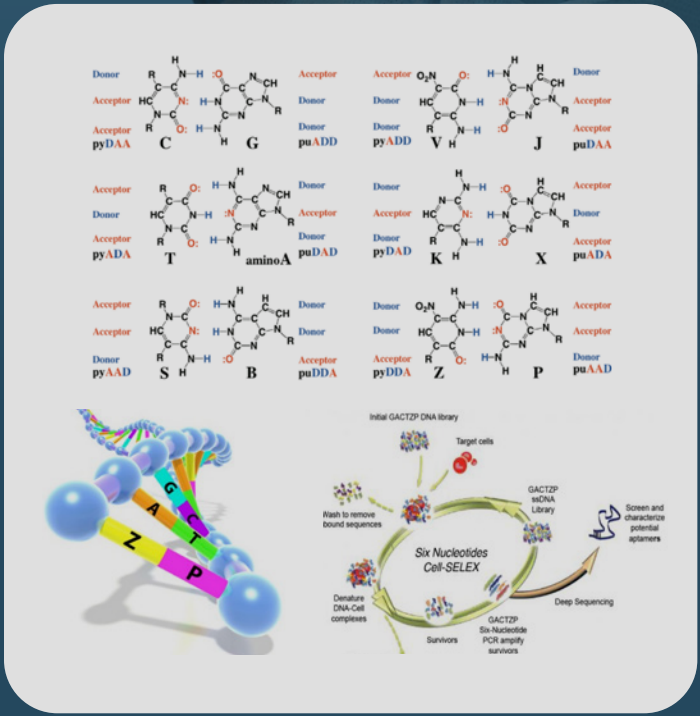
Illuminating Cellular Interactions with Toxic Substances becomes CRISTAL Clear

VIIBRE Pumps and Valves: A decade of experience and steady progress, growing from a DTRA JSTO investment and ending with a commercial drug discovery system interfaced with organ-on-a-chip technology, the CN Bio Innovations PhysioMimix PK (pharmacokinetic) a prototype has been implemented as part of CRISTAL. (CN Bio Innovations photo)

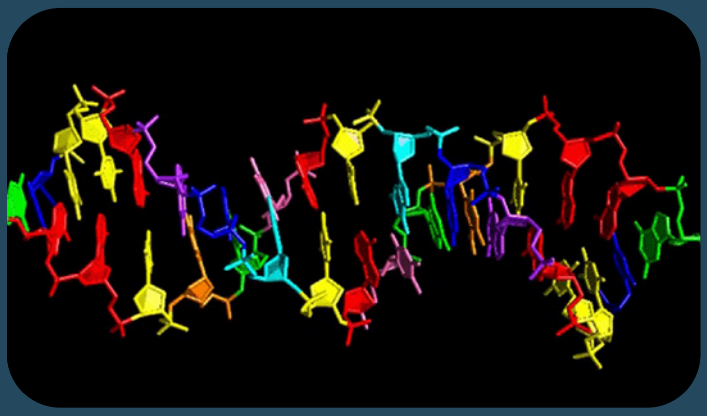
A collaborative team at Vanderbilt University's Institute for Integrative Biosystems Research and Education (VIIBRE) investigated whether they could develop new instrumentation and techniques to advance detection of chemical and biological warfare (CBW) agents and an understanding of how the agents affected biological cells in vitro. The work focused on automated characterization of cellular interactions with toxic agents and demonstrated how a machine-learning algorithm that used genetic optimization could identify a signaling model for a dynamic biological system. The VIIBRE effort also included substantial work to develop tools and techniques to apply ion mobility–mass spectrometry to cellular metabolomics.

This work laid the foundation for developing a multiomics capability for a rapid threat assessment. Multiomics is where the data sets of different omics groups—the comprehensive study of molecules—are combined during analysis. With an investment from DTRA JSTO and the Defense Advanced Research Projects Agency, these technologies were transitioned to DEVCOM CBC, becoming a key component of the Computational Rapid Identification and Scientific Threat Analysis (CRISTAL) program to identify mechanisms of toxicity of CBW agents through automated transcriptomic, metabolomic, and proteomic analyses. The work also has expanded into developing the first compact, self-driving biological laboratory with artificial intelligence/machine learning as a robot scientist that could be implemented in a Biosafety level 4 facility, which has the precautions required to isolate dangerous biological agents in an enclosed laboratory, as well as use in multiple organ-on-a-chip systems.

Expanding the DNA and RNA Alphabet, and Its *Societal Impact*



Expanded DNA alphabet of nucleotide bases. (FfAME image)



Double helix DNA structure incorporating synthetically expanded nucleotide bases. (FfAME image)

The Foundation for Applied Molecular Evolution (FfAME) has a long history in using synthetic organic chemistry to make altered forms of DNA and RNA. DTRA JSTO invested in this project to assess whether a synthetically expanded DNA/RNA alphabet (nucleotide bases) would improve CB detection and diagnostic systems. FfAME demonstrated that these artificially expanded genetic information systems allowed detection without false positives and clean assays.

The advances made though basic research permitted a government-wide emergency response that would have otherwise been unavailable. For example, when the SARS-CoV-2 tests offered by the Centers for Disease Control failed, the chemistry developed by FfAME was able to provide assays that worked.

There are also other rapidly developed detection test kits that manage emerging diseases. The Department of Homeland Security received Zika test kits during the 2016 outbreak in the Americas for diagnosis in 20 minutes at a cost of less than $10 each. The kit is multiplexed to include both dengue and chikungunya and was shipped to the U.S. military base for use in Saudi Arabia. Other work included developing arbovirus detection in trapped mosquitoes in Florida, as well as producing DNA diagnostic tests for HIV and hepatitis C virus by Bayer Diagnostics, LLC.

TO LEARN MORE

JSTO in the News, February 2017, Vol. 7, No. 2 article, "DiagnoSkeeter: Diagnosing Mosquito-Borne Viruses on the Fly."

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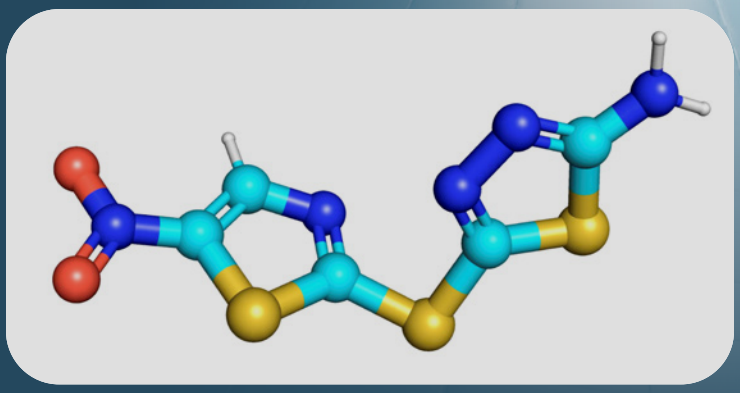
Exploiting Intelligence to *Combat* Drug-Resistant Bacteria

Antimicrobial resistance (AMR) is of major concern today, with a rapidly depleting arsenal of effective antibiotics available. Research at the Massachusetts Institute of Technology (MIT) explored fundamental mechanisms of antibiotic efficacy and eventual AMR using biochemical screening, modeling, and ML methods. The researchers reported evolved cells exposed to high antibiotic concentrations acquire resistance caused by decreased basal metabolic activity. The work took a new direction into antibiotic discovery using deep learning. The team trained a deep neural network capable of predicting molecules with antibacterial activity from a pool of more than 100 million molecules. They discovered a powerful antibiotic called halicin that works against a wide range of bacteria, which is the first in a new class of antibiotics discovered with AI without using any previous human assumptions.

With the DTRA JSTO investments, MIT researchers launched the Antibiotics-AI Project, which is being used to: (1) predict antibiotics from expansive chemical libraries of 1.5 billion existing molecules, (2) design new antibiotics, and (3) identify the molecular mechanisms. These deep-learning approaches led to further development of a rapid platform technology that successfully identified a novel antibiotic against Acinetobacter infections, a common cause of severe disease in troops wounded in Afghanistan and Iraq. MIT was recently awarded a grant to direct their approach to viral infections as part of DTRA JSTO's AI Grand Challenge.



MIT researchers used a machine-learning algorithm to identify a powerful new drug called halicin that kills many strains of antibiotic-resistant bacteria. (MIT image)

TO LEARN MORE

JSTO in the News, February 2023, Vol. 13, No. 2 article, "Docking by Design."

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Sponging *Up* Toxins, Pathogens, and Cytokines

Researchers at the University of California, San Diego (UCSD) envisioned creating nanosponges as potential therapeutic neutralization agents. Nanosponges are made from plasma membranes derived from natural human cells that wrap around a nanoparticle core. The idea was that cellular nanosponges can act as decoys to capture and remove harmful CB threats regardless of structure, thus prevent threats from reaching intended cellular targets. The utility of nanosponges was demonstrated on one of the major virulence factors in bacterial infections, pore-forming toxins (PFTs). Nanosponges recognize and capture PFTs, leveraging that PFTs insert themselves into human red blood cell (RBC) membranes for bioactivity. Cellular nanosponges also show potential as a potent vaccine platform. Toxins detained by nanosponges form a complex that promotes antigen presentation to enhance immune activation. This synergy brings an entirely new dimension to vaccine development against a broad range of toxins and pathogens.

With continued DTRA JSTO support, the repertoire expanded to all types of cells and different nanomaterial cores modified to accommodate almost any payload. This versatility led to effective neutralization of bacterial toxins, chemical toxicants, inflammatory cytokines, pathological antibodies, and viruses, including SARS-CoV-2. Ongoing science exploring formulation of a virus-strain-independent platform technology has the potential as the next panacea for any future pandemic.

Cellics Therapeutics was formed as the science grew from its infancy into a viable platform with broad applicability. Within that enterprise, RBC nanosponges are entering human clinical Phase 1b/2a trials for the treatment of antibiotic-resistant bacterial pneumonia, which heralds a completely different approach from traditional antibiotics. Preclinical and clinical development of macrophage nanosponges for the treatment of sepsis is ongoing as well. A successful outcome would transform the treatment of sepsis in saving lives, which is critical for Joint Force treatment of battlefield injuries.

TO LEARN MORE

JSTO in the News, September 2021, Vol. 11, No. 8 article, "Putting SARS-CoV-2 in a Bind."

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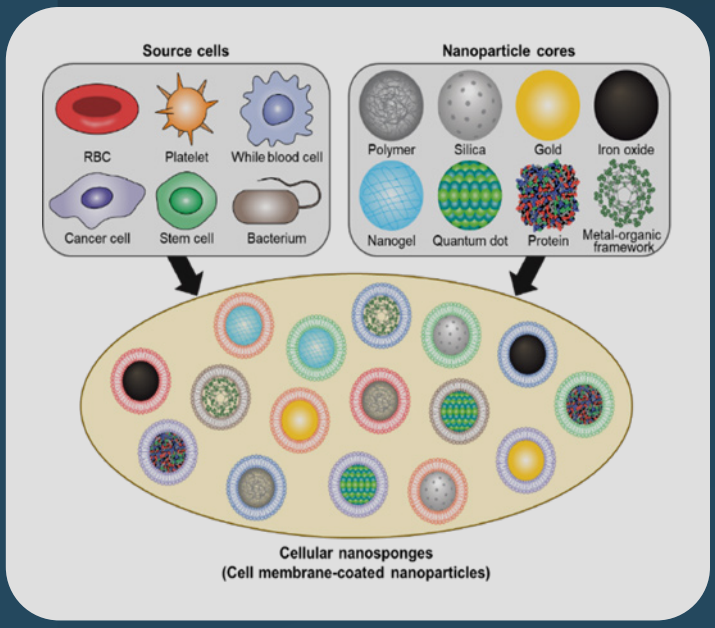
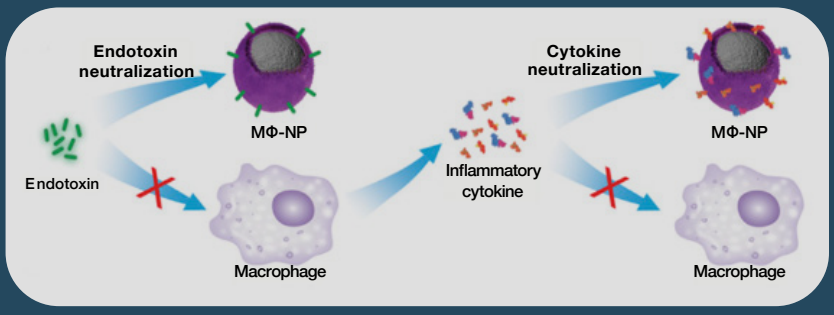


Versatility of nanosponges created from different source cells and nanoparticle cores for therapeutic and prophylactic applications. (UCSD image)



Schematic representation of using nanosponges (MΦ-NPs) to neutralize endotoxins and proinflammatory cytokines as a two-step process for sepsis management. (UCSD image)

TO LEARN MORE

JSTO in the News, June 2022, Vol. 12, No. 4 article, "Brain Games."

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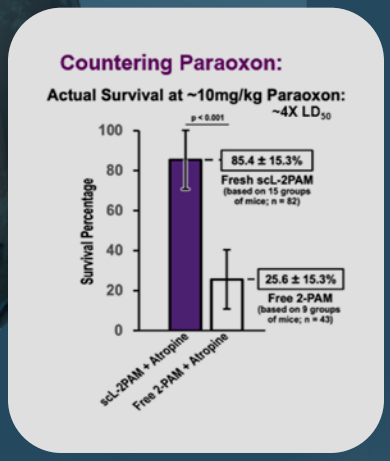
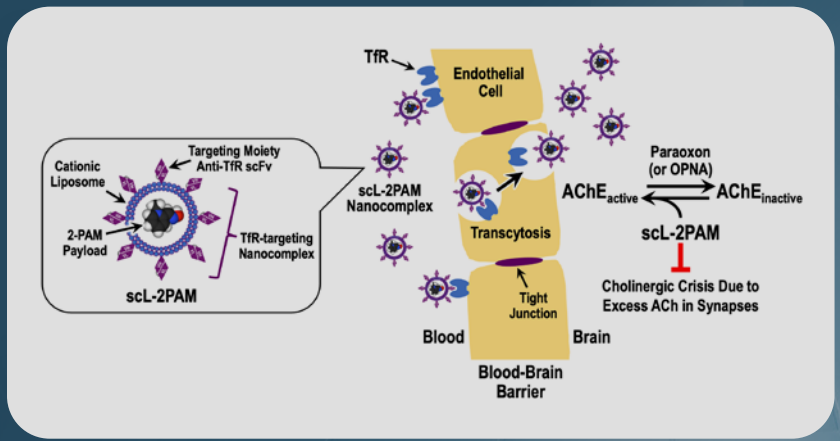
Crossing the Blood-Brain Barrier with Nanotechnology

A grant to SynerGene Therapeutics, Inc., focused on exploring the use of gene therapy for nerve agent prophylaxis employing their proven, single-chain Liposome (scL) nanodelivery system designed to cross the blood brain barrier. SynerGene tests demonstrated this with the encapsulation of an oxime reactivator, 2-pyridine aldoxime methylchloride (2-PAM).

Results from statistically relevant studies validated the superior efficacy of scL-2PAM (85.4%) compared to free 2-PAM (25.6%) against a lethal dose of paraoxon. Based on these initial findings on scL-2PAM, DTRA JSTO invested with SynerGene to work with the U.S. Army Medical Research Institute of Chemical Defense for testing against nerve agents. The results on nerve agents were comparable to those on paraoxon. Optimized lyophilization and reconstitution of scL-2PAM showed 100% biological activity is retained when stored at room temperature for more than 6 months. The contract is moving forward with initial talks with the FDA in expectation for an IND application.



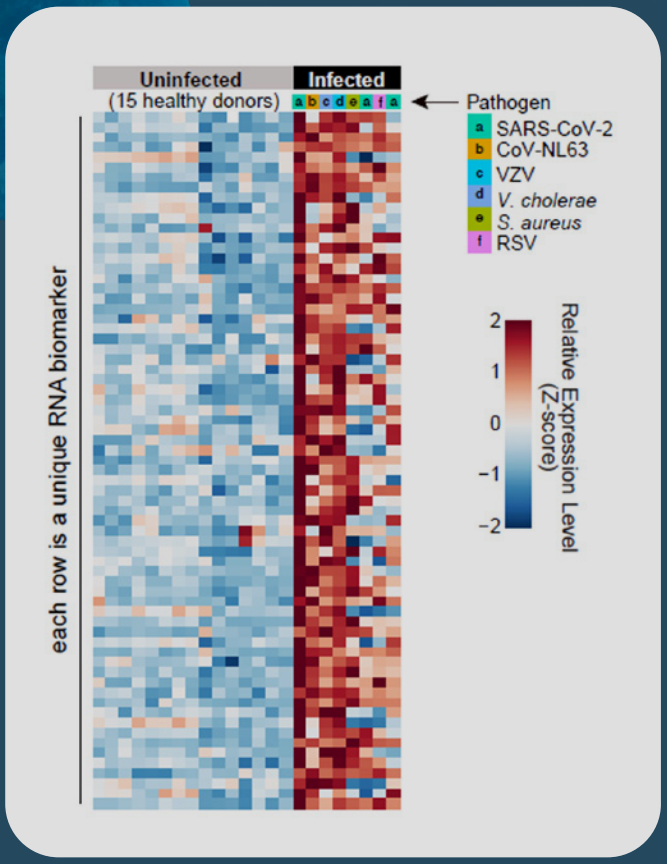
Superiority of scL-2PAM to Free 2-PAM in a model of paraoxon toxicity. (SynerGene image)



Targeted delivery of 2-PAM across the BBB to reactivate OP-inactivated acetylcholinesterase in the central nervous system. (SynerGene image)

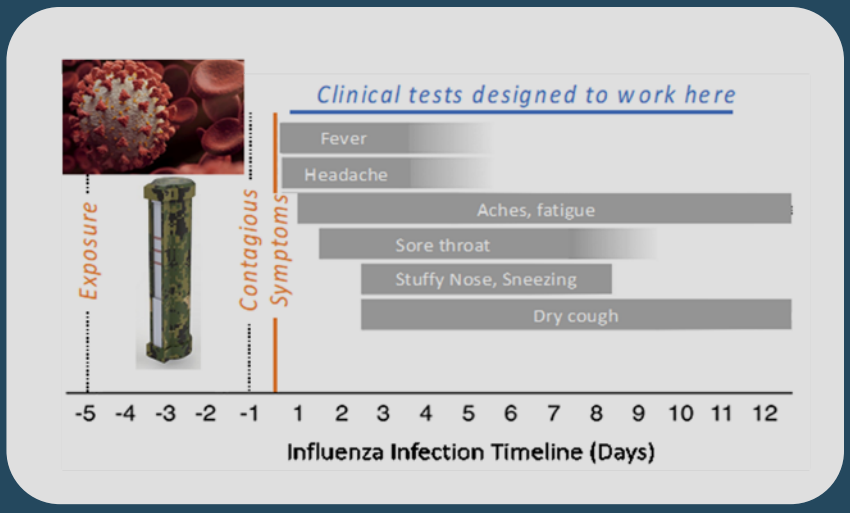
Basic Research on RNA Leads to SickStick: Infection Detection *before* Symptoms Begin

A team of researchers at the University of Colorado Boulder originally proposed to look at RNA species in saliva that might indicate infection in the body. What they found was considerably more than anyone expected: a core set of just 69 human genes that are turned on in humans due to all infections: viral, bacterial, and fungal. Remarkably, the mRNA transcripts of these genes can be detected in human saliva with high fidelity. Through several human studies, the team was able to show that the abundance of these mRNAs in saliva can correctly determine if a person is harboring infection 86% of the time, even when the enrollees were asymptomatic and did not yet know they were sick.

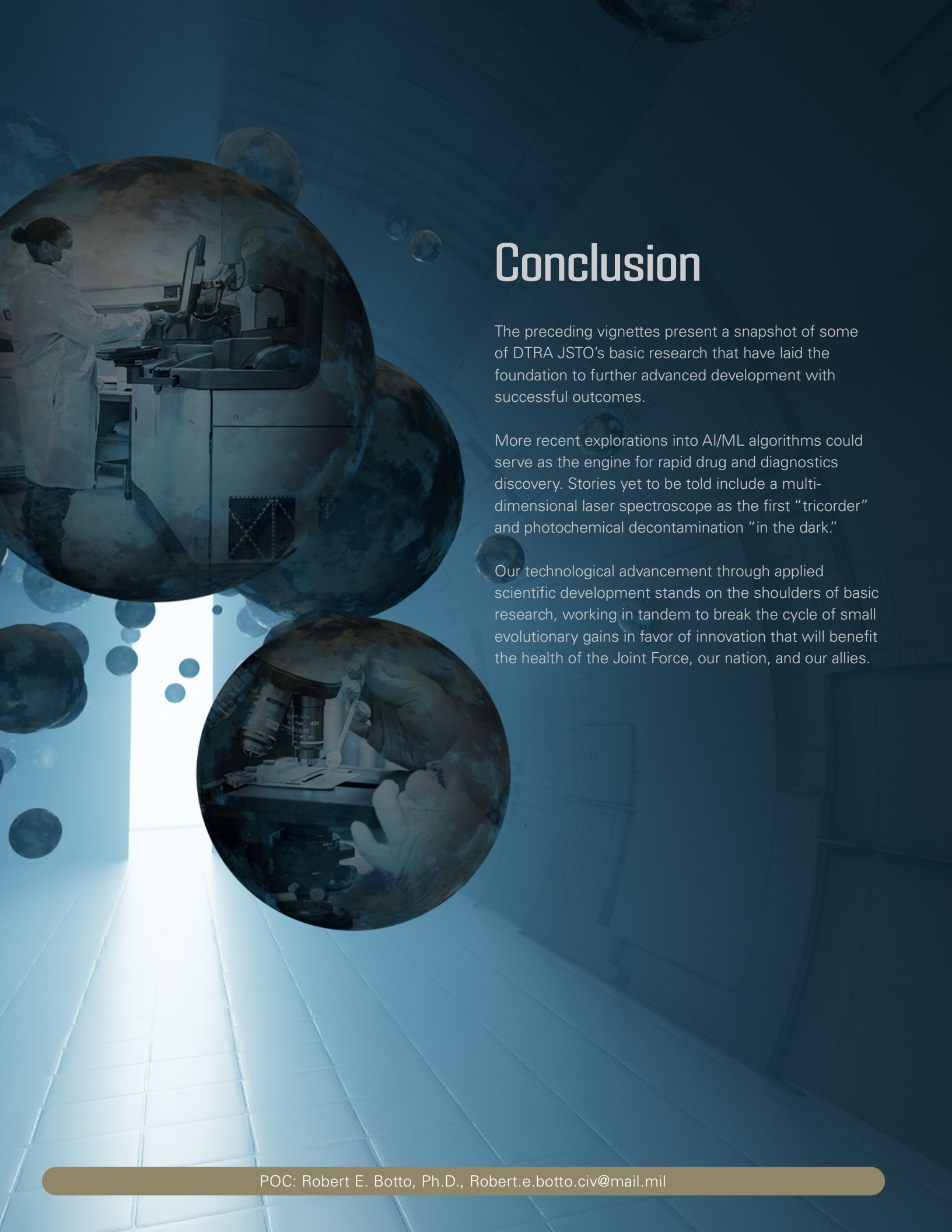


Heatmap showing abundance of mRNA in human saliva can determine whether diverse infections are present in the body. (University of Colorado Boulder image)

The basic research led to several new developments. The University of Colorado Boulder team formed Darwin Biosciences that DTRA JSTO invested with to prepare prototypes of a hand-held device, much like a pregnancy test, which can monitor RNA biomarkers in the field and in real time. This SickStick technology would enhance mission readiness by catching warfighters early in stages of infectious diseases. SickStick has become a premier diagnostic candidate for presymptomatic detection and garners considerable Flag Officer interest as a triage diagnostic. For the Joint Force, this would allow isolation of presymptomatic personnel and preserve unit health status; for civilians, screeners at transit points can test travelers; and for healthcare workers, this would provide the ability to undergo regular testing to prevent healthcare-associated infections. Darwin Biosciences has become one of the first to unleash the deep diagnostic value of saliva with the ability of sensing infection well before the onset of symptoms.



SickStick point-of-care device for presymptomatic diagnosis. (DTRA JSTO image)



Conclusion

The preceding vignettes present a snapshot of some of DTRA JSTO's basic research that have laid the foundation to further advanced development with successful outcomes.

More recent explorations into AI/ML algorithms could serve as the engine for rapid drug and diagnostics discovery. Stories yet to be told include a multi-dimensional laser spectroscope as the first "tricorder" and photochemical decontamination "in the dark."

Our technological advancement through applied scientific development stands on the shoulders of basic research, working in tandem to break the cycle of small evolutionary gains in favor of innovation that will benefit the health of the Joint Force, our nation, and our allies.

POC: Robert E. Botto, Ph.D., Robert.e.botto.civ@mail.mil

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