JSTO in the News

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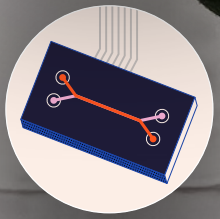
Mixed for the Perfect Match



All the Chips on the Table

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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

Research and Development Directorate
Chemical and Biological Technologies Department
Joint Science and Technology Office for the
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Front cover: Julie Norton, a researcher with the Naval Medical Research Center (NMRC) reviews results from an assay in the Deployment Associated Infections Division (DAID) laboratory. Part of NMRC's Operationally Relevant Infections Department, DAID focuses on the advancement of both prophylactic vaccine and immunoprophylaxis products against Campylobacter, Enterotoxigenic *Escherichia coli (E. coli)*, and Shigella mediated diseases that affect warfighters. (U.S. Navy photo by Michael Wilson/Released)

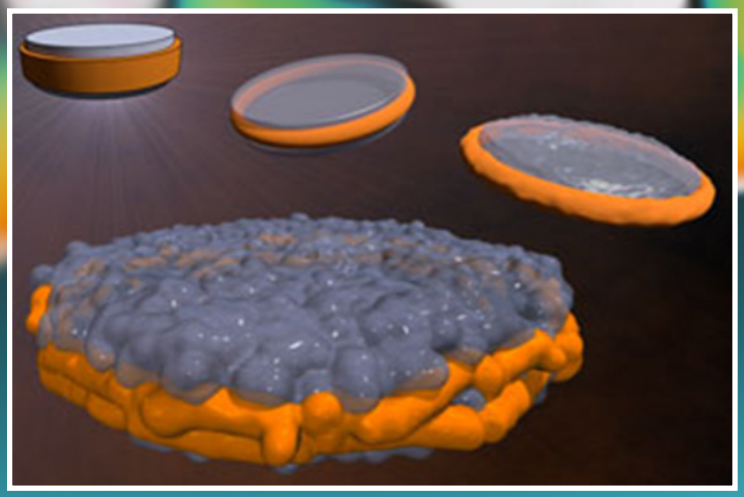
Inside cover: An influenza vaccine being prepared for administration at Moody Air Force Base, Ga. The flu vaccine is an annual requirement for military members to ensure they are deployment ready and able to support the mission. (U.S. Air Force photo by Airman 1st Class Whitney Gillespie)

Back cover: A hospital corpsman draws a typhoid vaccination into a syringe. Typhoid vaccinations can prevent typhoid fever, a life-threatening disease that is common in many regions of the world and includes symptoms such as persistent high fever, weakness, stomach pain, and loss of appetite. (U.S. Navy photo by Mass Communication Specialist 3rd Class Eloise A. Johnson)

MIXED FOR THE PERFECT MATCH

Using a new multipathogen vaccine platform, a single shot can provide the Joint Force with targeted protection against a multitude of individual biological threats.

Harmful biological pathogens, such as viruses, bacteria, fungi, protozoa, and worms, continue to pose a threat to the Joint Force. To combat these natural challenges and better defend warfighters from bioterrorism and biowarfare, the Defense Threat Reduction Agency's (DTRA) Chemical and Biological Technologies Department in its role as the Joint Science and Technology Office (JSTO) for the Chemical and Biological Defense Program collaborated with researchers at Lawrence Livermore National Laboratory (LLNL) to create and evaluate a nanolipoprotein (NLP)-based multipathogen vaccine platform that can be used as a single vaccine against a range of biological pathogens.



The flexible nanolipoprotein vaccine platform offers customization to produce a single vaccine for multiple pathogens. (LLNL image)

Vaccination is perhaps the most effective public health intervention to fight against harmful biological pathogens, and there have been several accomplishments in vaccine development to win the war against deadly bugs. However, DTRA JSTO anticipates emerging threats the Joint Force may face in the future, and it knows there is a continuous confrontation of longstanding, emerging, and possible known and unknown biological threats in the current biothreat platform.

Particularly beneficial to the Joint Force is that researchers have shown NLP subunit vaccines can be freeze-dried, stored for months at room temperature, and rehydrated without losing their potency, making them easy to transport to deployed units in the field. "Subunit" vaccines, also called "acellular" vaccines, do not use the whole pathogen to enhance the protective immune response, but rather the purified part of the pathogens, such as a protein or polysaccharide (several sugar molecules bonded together), that can stimulate immune cells and generate a protective immune response.

The goal is to use the NLP platform to create a single vaccine incorporating antigens from multiple pathogens and protect the Joint Force from several high-priority threats.

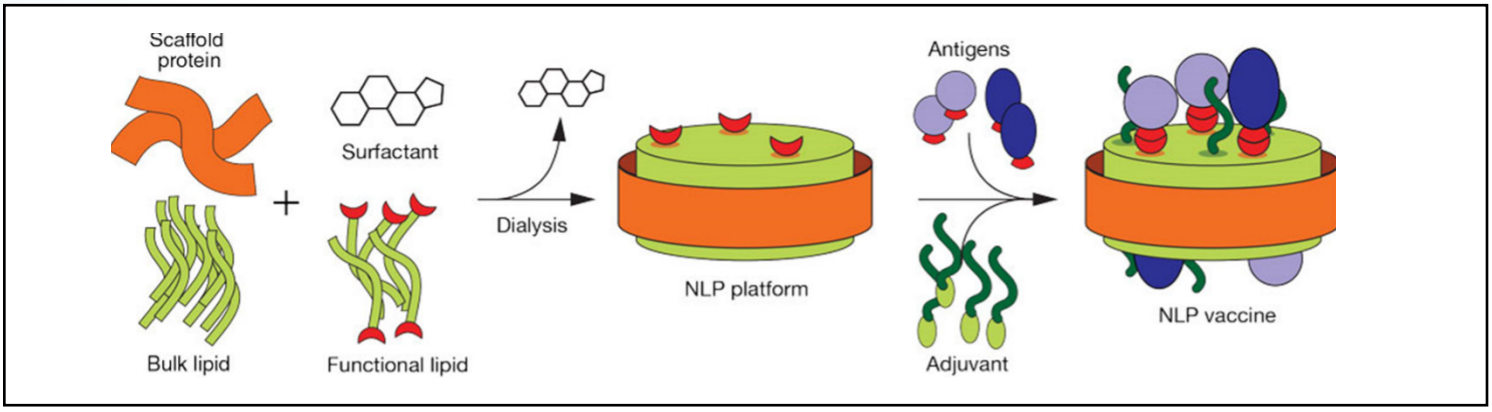
The concept of NLP particles research at LLNL is a breakthrough in vaccine development to protect warfighters and first responders against bioterrorism. The goal is to use the NLP platform to create a single vaccine incorporating antigens from multiple pathogens and protect the Joint Force from several high-priority threats, including *Francisella tularensis* (which causes tularemia, also known as rabbit fever), *Yersinia pestis* (which causes plague), and *Burkholderia pseudomallei* (which causes melioidosis, also known as Whitmore's disease). LLNL with support from DTRA JSTO and researchers at the University of New Mexico Health Sciences Center previously showed the success of this approach against tularemia, which can be deadly if not treated, and this effective NLP-based subunit vaccine will serve as a foundation for enhancing capability and incorporating multiple-antigen targets to develop multipathogen vaccines.

NLPs are water-soluble, biocompatible, nanoscale platforms with favorable features of natural occurrence and structural mimics of cell membranes to connect to other molecules. NLPs are produced by mixing scaffold proteins and lipids with a surfactant that increases its spreading and wetting properties. The proteins and lipids self-assemble into a disk-like structure when the surfactant is removed through dialysis. NLPs allow the targeted delivery of antigens directly to antigen-presenting cells, which then present those antigens to T cells and boost the immune system against the foreign microorganism. This technology can also be used for cancer immunotherapy, which deploys the body's own immune system to fight cancer.

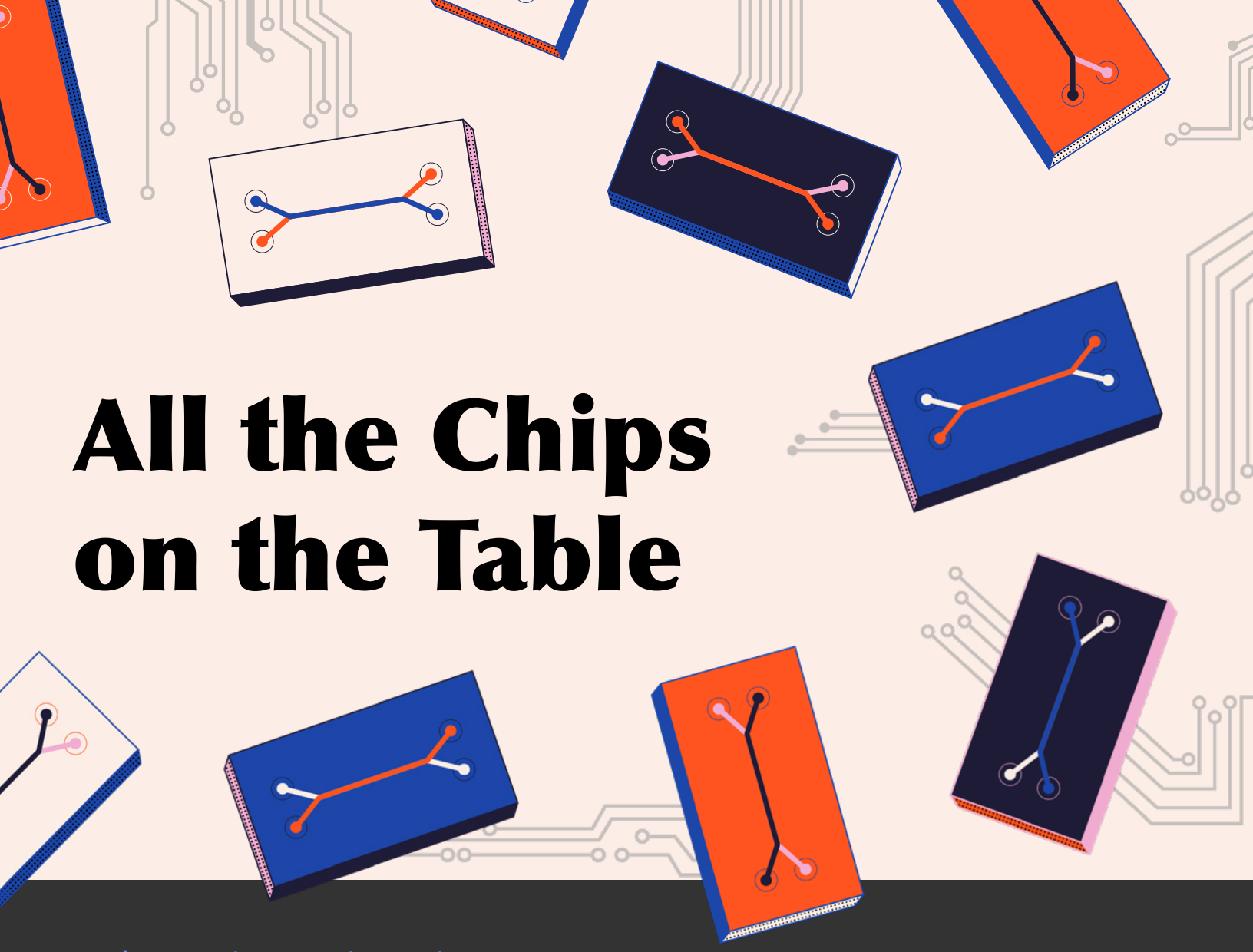
In addition to the use of NLPs against *F. tularensis* and influenza, DTRA and LLNL researchers continue to explore the potential of this platform to customize targeted vaccines for multiple types of pathogens quickly. An LLNL team with researchers at the University of New Mexico found that using a combination of multiple antigen types was critical when single antigens alone provided only partial protection.

The NLP platform can work broadly by providing the foundation to fabricate effective vaccines targeted at multiple biothreats. Since the particles are naturally present in the human body, vaccines produced using the NLP platform are less likely to result in toxicity and will avoid issues associated with current vaccines that involve injecting a live attenuated organism.

The resulting NLP provides a platform for attaching other molecules to produce a potent, safe, and targeted vaccine. Vaccine candidates can be easily incorporated inside lipid complexes, which can be optimized to improve binding, avoid degradation, and improve the release of the therapeutic payload, which will better protect the Joint Force, the nation, and our allies. ●



A nanolipoprotein-based subunit vaccine is produced by mixing scaffold proteins and lipids with a surfactant that increases its spreading and wetting properties. The proteins and lipids self-assemble into a disk-like structure when the surfactant is removed through dialysis. (LLNL image)



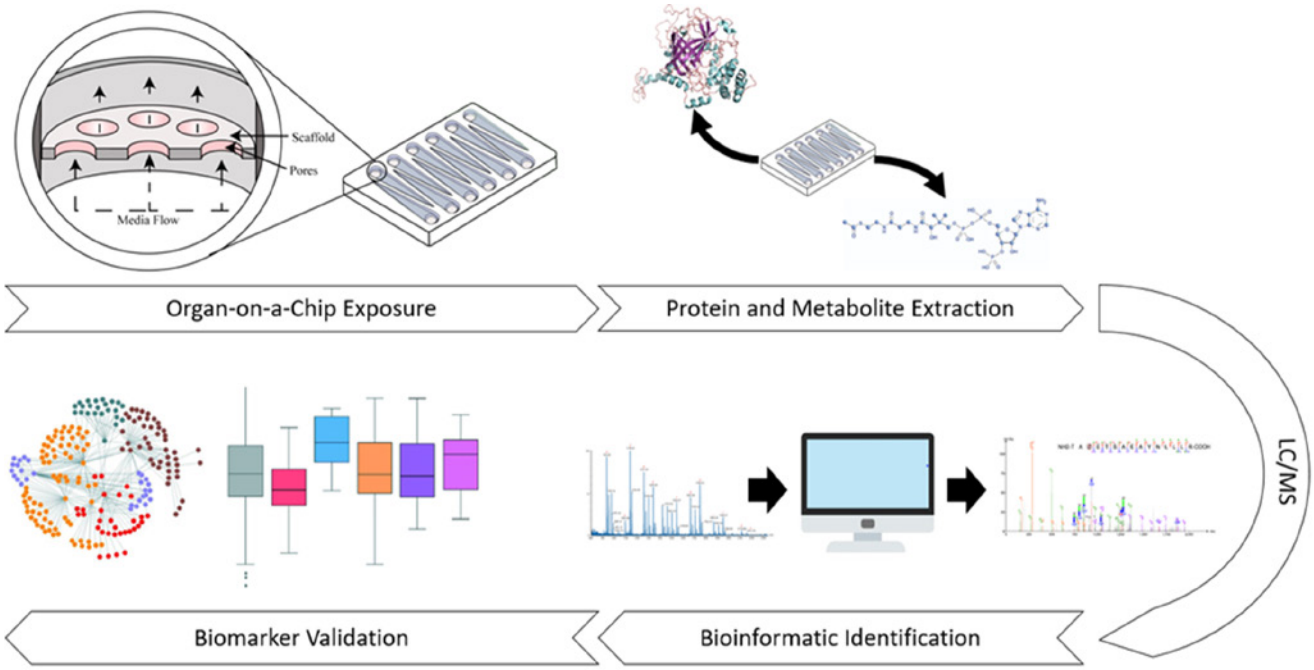
All the Chips on the Table

Lab experimentation using organ-on-a-chip systems proves promising and safe for chemical and biological (CB) warfare agent protection on the battlefield

Current wearable-sensor capabilities have an ability to alert to potential infectious exposure, such as COVID-19 and the flu, 48 hours prior to a positive diagnosis, but this capability has yet to be expanded to a broader spectrum of CB warfare agents of concern. Over the past several years, sensor algorithm research has shown promise in collecting human-exposure data from substitute CB agents such as natural infection of COVID-19, influenza, opioid administration during medical procedures, and vaccine trials.

To determine if these wearable-device algorithms can also alert warfighters to exposure of CB warfare agents, the Defense Threat Reduction Agency's (DTRA) Chemical and Biological Technologies Department in its role as the Joint Science and Technology Office (JSTO) for the Chemical and Biological Defense Program (CBDP) is investing in research with the U.S. Army Combat Capabilities Development Command Chemical Biological Center (DEVCOM CCDC CBC).

DTRA JSTO procured custom multi-organ-on-a-chip technology through DEVCOM CBC to develop exposure studies specific to CBDP interests. Ongoing wearable sensor efforts have identified key physiological features for indicating exposure to CB agents including heart rate, heart rate variability, temperature, and respiratory rate, among others. As a result, the research team customized a multi-organ system that combined cardiac, lung, and skin tissues on a single chip. Researchers



The procedure from organ exposure to CB agents to liquid chromatography–mass spectrometry (LC/MS) analysis of biomarkers. (DEVCOM CCDC CBC image)

correspondingly selected CB agents with exposure routes that affect the lung, skin, and heart, including *Bacillus anthracis*, *Staphylococcal enterotoxin B*, Western Equine Encephalitis Virus, and carfentanil, which is a synthetic opioid approximately 10,000 times more potent than morphine and 100 times more potent than fentanyl.

The researchers conducted the first chip exposures on lung tissue exposed to carfentanil and subsequently collected samples such as metabolomics from all tissues (lung, skin, and heart) to determine the holistic effect from exposure. DTRA JSTO is using the data to inform predictive toxicology models as part of the Computational Rapid Identification and Scientific Analysis (CRISTAL) program and on a large scale will analyze multiomics—the scientific fields associated with measuring biological molecules in a high-throughput way—where the data sets from proteomics (proteins) and metabolomics (metabolites) will be analyzed to inform current work in biomarker-based detection of CB agents. DTRA JSTO also plans to conduct feasibility studies of correlating multiomics biomarkers with physiological response data and compare those to physiological data collected from wearable devices.

DTRA JSTO's research aims to investigate the capability of determining physiological responses to true CB agents of concern from these studies and the capacity to develop vital sign correlations from multiomics data.

The result would ultimately either validate current wearable- based early warning exposure algorithms or inform a need for early warning algorithms specific to each class of agent. This would lead to continued organ-on-a-chip work to conduct exposure studies on a full spectrum of CB agents of concern and at various dosages to develop early alerting algorithms catered to those agents.

DTRA JSTO's research aims to investigate the capability of determining physiological responses to true CB agents of concern from these studies and the capacity to develop vital sign correlations from multiomics data.

This collaboration amongst multiple divisions in DTRA JSTO highlights not only the advancements and possibilities of organ-on-a-chip systems, but the streamlining of DTRA JSTO efforts to build a robust capability through a leaner and more holistic approach to benefit the Joint Force. The perspective from various areas of participation produces a more efficient trajectory of the project and the success of the joint effort to mitigate CB threat exposures more rapidly, with greater sensitivity, and with higher fidelity. ●

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Within the Defense Threat Reduction Agency's Research and Development Directorate resides the Chemical and Biological Technologies Department performing the role of Joint Science and Technology Office for the Chemical and Biological Defense Program. This publication highlights the department's advancements in protecting the Joint Force, our nation, and allies from chemical and biological threats through the innovative application of science and technology.

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