JSTO in the News

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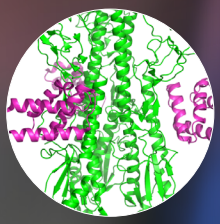
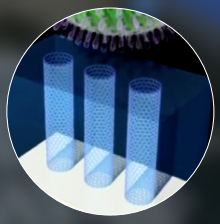
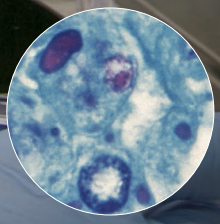


Conquering Viral Threats



Futuristic 'Smart' Uniforms



World's First Ebola Vaccine

Policing Threats through Synthetic Biology

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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On the front cover:
Researchers Eric Meshot, left, and Ngoc Bui evaluate the uniformity of a carbon nanotube array covering the entire area of a 4-inch wafer. Photo by Julie Russell/Lawrence Livermore National Laboratory.

On the back cover:
An Operational Detachment Alpha from 7th Special Forces Group (Airborne) (7 SFG (A)) are lifted off the ground by a CH-47 Chinook helicopter during a training event at Eglin Air Force Base, Fla. Green Berets from 7SFG (A) practice Special Purpose Insertion Extraction (SPIE). SPIEs are used to rapidly insert or extract soldiers from terrain that does not allow helicopters to land. (U.S. Army photo by Spc. Steven Young/Released)

CONQUERING VIRAL THREATS:

NEW PROTEIN DESIGN FOR COUNTERMEASURES

Scientists are seeking to conquer deadly viral threats by using engineered proteins, leading to better protections for warfighters from some of the most dangerous threats they face, including plague and Ebola.

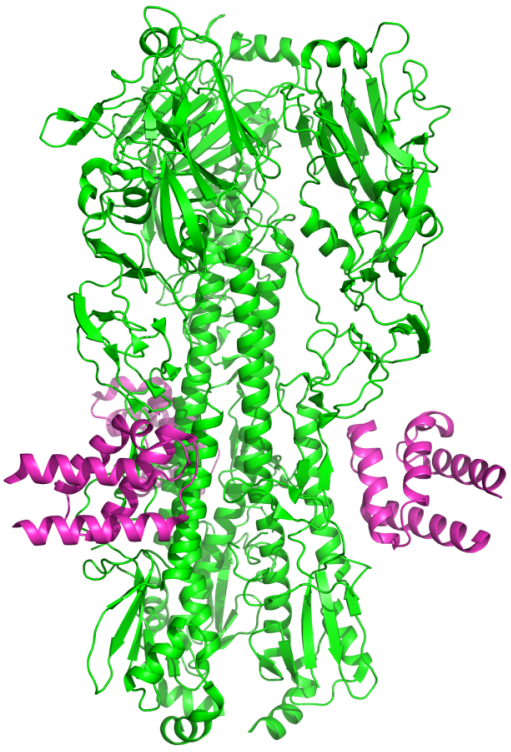
Researchers funded by the Defense Threat Reduction Agency's Joint Science and Technology Office are working to develop new antiviral countermeasures for the warfighter, utilizing the influenza virus. Historically influenza changes its molecular structure rapidly, which makes developing an effective vaccine challenging. While researchers chose to work with the influenza virus, this computational protein design could have broad-spectrum applicability to several viral threats.

New progress in computational protein design demonstrates its vital application in a wide array of countermeasures. Recently published in *PLOS Pathogens* "A Computationally Designed Hemagglutinin Stem-Binding Protein Provides In Vivo Protection from Influenza Independent of a Host Immune Response," scientists report that a computationally designed protein was able to protect against the influenza virus in an animal model.

This JSTO effort is managed by Dr. Ilya Elashvili and led by Dr. David Baker of University of Washington. Dr. Baker's research identifies a small (<100 amino acid) engineered protein that was able to protect mice against diverse influenza virus strains.

As a starting point, the researchers used previously reported computationally designed proteins that showed high affinity and broad specificity towards diverse influenza virus strains. Both studies were previously published in the journals *Science* and *Nature Biotechnology*.

In the current work, Dr. Baker optimized the protein by mutational and selection strategies in order to further improve its neutralizing potency for broad viral influenza strains. The resultant protein was found to be an effective antiviral and protected



Designed anti-influenza protein (magenta) bound to the hemagglutinin from the H1N1 2009 pandemic influenza virus (green). Graphics courtesy of Drs. Merika Koday, Aaron Chevalier and David Baker, University of Washington.

mice against lethal challenge from diverse influenza virus strains when administered as a prophylactic or therapeutic in vivo.

A single intranasal dose of protein (6 mg/kg) prevented viral infection in mice, when administered up to 48 hours before lethal viral challenge. If administered closer to the viral contact (two hours prior), the dosing amounts could be significantly reduced to 0.1 mg/kg.

In the absence of prophylactic treatment, the protein provided complete protection from disease when administered as a single dose (3 mg/kg) two hours after challenge or if administered as a daily therapeutic treatment for four days (once per day) after the challenge.

Importantly, one day post-challenge, a single intranasal dose of the protein substantially outperformed ten oral doses of the leading influenza antiviral, Tamiflu, administered twice daily for five days. The protein was able to provide this protection by binding to a critical part of the viral protein without involving the host's antiviral immune response that is generally invoked by antibodies.

These studies demonstrate the potential of computationally designed binding proteins as a new class of antivirals for prophylactics and therapeutics to protect warfighters from natural or manmade viral threats.

Futuristic 'Smart' Uniforms
TO PROTECT NATION'S TROOPS

In today's changing environment, the next threat our nation's warfighter face may not be on a traditional battlefield. Instead, it may be a chemical or biological attack without notice.

A new project funded by the Defense Threat Reduction Agency's Joint Science and Technology Office and conducted by a team of Lawrence Livermore National Laboratory (LLNL) scientists have created a new material that is breathable and protects against biological and chemical threats. This futuristic material or 'second skin' will offer more protection for our warfighters in contaminated environments by sensing and reacting to chemical and biological threats.

Current protective military uniforms have heavyweight full-barrier protection or permeable adsorptive protection that cannot meet the critical demand of simultaneous high comfort and defense. They also pose a high heat burden to warfighters and do not react to environmental threats. High breathability is a critical requirement for protective clothing to prevent heat-stress and exhaustion when military personnel are engaged in the field.

The JSTO/LLNL 'second skin' offers a 'smart' material that reacts to the environment by blocking chemical agents from penetrating the warfighter's uniform. "Second skin" blocks harmful agents such as sulfur mustard (blister agent), GD and VX nerve agents, toxins such as staphylococcal enterotoxin and biological spores such as anthrax.

The LLNL team, managed by Tracee Whitfield from DTRA, fabricated flexible polymeric membranes with aligned carbon nanotube (CNT) channels as moisture pores. Each pore is less than five nanometers, 5,000 times smaller than the width of a human hair. The new composite material provides high breathability utilizing unique transport properties of these CNT pores. By quantifying the membrane permeability to water vapor, the team found for the first time that, when a concentration gradient is used as a driving force, CNT nanochannels will sustain gas-transport rates exceeding that of a well-known diffusion theory by more than one order of magnitude.

These membranes also provide protection from biological agents due to their minuscule pore size. Biological threats such as bacteria or viruses are typically larger than 10 nm, much larger than the LLNL-designed composite material. Laboratory tests demonstrated the CNT membranes' ability to repel Dengue virus during filtration tests.

This confirms that LLNL-developed CNT membranes provide effective protection from biological threats by size exclusion rather than by preventing wetting. Furthermore, these results demonstrate that CNT pores combine high breathability and bio-protection in a single functional material.

However, chemical agents are much smaller in size and require the membrane pores react to block the threat. To encode the membrane with a smart and dynamic reaction to small chemical hazards, Massachusetts Institute of Technology (MIT) scientists are modifying these CNT membranes with chemical-threat-responsive functional groups.

These functional groups will sense and block the threat like gatekeepers on the pore entrance. Recently, LLNL and MIT integrated actuating polymers with single walled CNTs to demonstrate a chemiresistive dosimetric material. These materials are the foundation of a low cost, passive, wireless hazard badge that will allow detection of nerve agents.

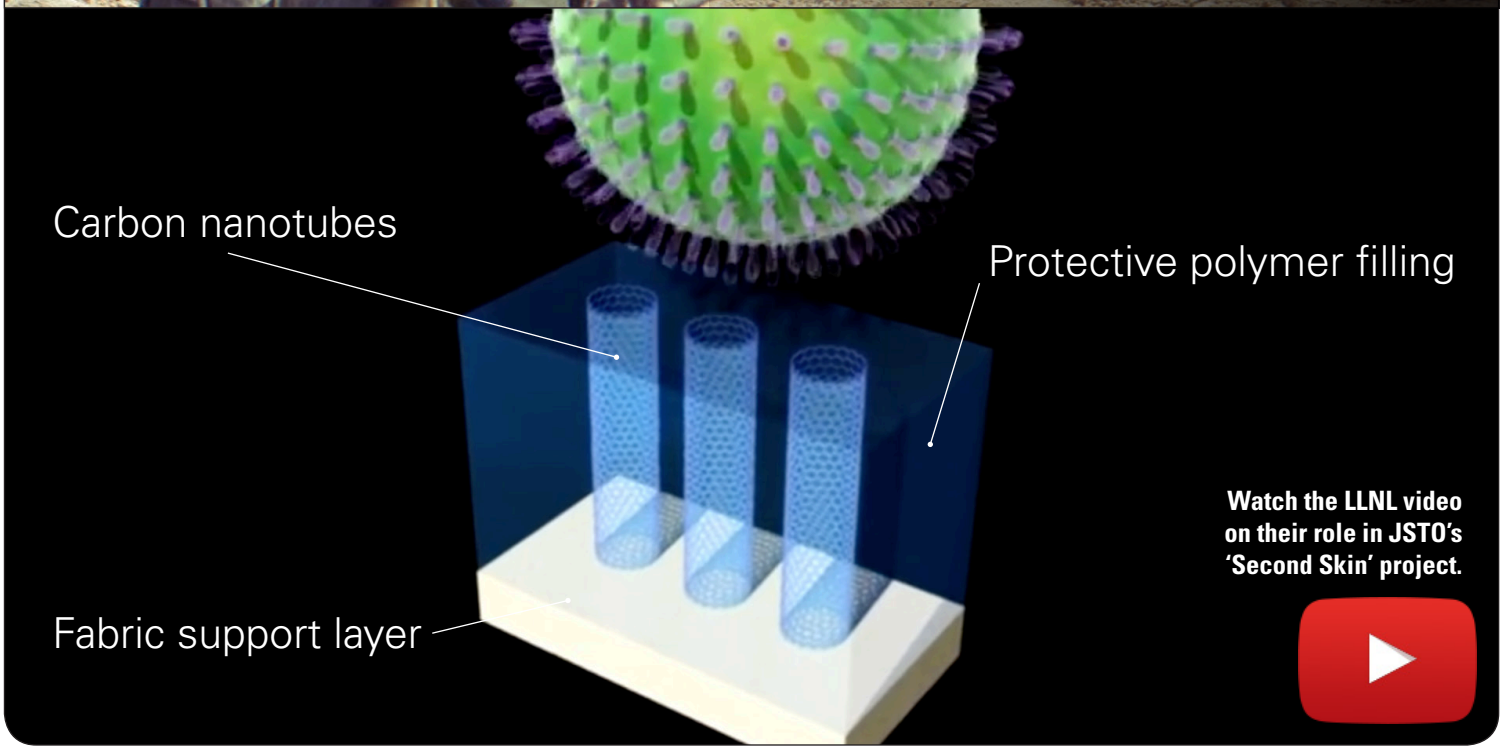
This spin-off technology effort was funded within the 'second skin' project as basic research; however, plans are underway to develop a wireless sensor integrated with responsive protective fabrics for the detection of exposure and material response to chemical warfare agents. This is a paradigm shift from the concept of a deployable sensor that is worn as a badge; as LLNL and MIT would embed sensors in the fabric itself. As the fabric reacts

to provide protection, the physical-chemical change in the fabric can be measured and analyzed. Swatch evaluations will occur in early 2018 to demonstrate the concept of 'second skin,' a major milestone that is a key step in the maturation of this technology. The new uniforms could be deployed to the field in less than 10 years.

For more information on the research conducted, see "Carbon Nanotubes: Ultrabreathable and Protective Membranes with Sub-5 nm Carbon Nanotube Pores," in *Advanced Materials* and "Wireless Hazard Badges to Detect Nerve-Agent Simulants" in *Angewandte Chemie International Edition*.

Building Breathable and Protective Fabric

Watch JSTO's 'Second Skin' video to learn more.



Watch the LLNL video on their role in JSTO's 'Second Skin' project.

World's First Ebola Vaccine *Closer to Being* LICENSED

The unprecedented Ebola epidemic in West Africa first broke out in Guinea in March 2014, and quickly spread to neighboring countries of Liberia and Sierra Leone. In all, the epidemic spread to nine countries resulting in more than 27,000 confirmed cases and 11,000 deaths.

The deadly virus not only continues to pose a threat to West African citizens, but to medical staff and warfighters deployed to the region. The Defense Threat Reduction Agency's Joint Science and Technology Office led basic research for the first Ebola vaccine, which was granted emergency use authorization and deployed within the affected area.

Recently, DTRA's JSTO-funded Merck Ebola Vaccine, designated V920, moved closer to becoming a licensed vaccine available to protect the warfighters. The U.S. Food and Drug Administration (FDA) granted the vaccine breakthrough therapy designation, and the European Medicines Agency (EMA) provided the vaccine PRIME (PRIority MEdicines) status.

The FDA's breakthrough therapy designation accelerates development and review of a drug candidate planned for use, alone or in combination, to treat a serious or life-threatening disease or condition when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints.

Similarly, PRIME is an approach from the EMA to enhance support for the development of medicines that target an unmet medical need. PRIME is intended to optimize development plans and speed up evaluation so these medicines can reach patients quicker. This special status focuses on medicines that may offer a major therapeutic advantage over existing treatments or benefit patients without any other treatment options. To be accepted for PRIME, a medicine has to show its potential to benefit patients with unmet medical needs based on early clinical data.

V920 was engineered by scientists from the Public Health Agency of Canada and subsequently licensed to a subsidiary of NewLink Genetics Corporation. DTRA funded NewLink Genetics to develop the vaccine, including funding critical animal efficacy studies, vaccine production and a human safety study at Walter Reed National Military Medical Center in Bethesda, Md. Merck then licensed V920 from NewLink Genetics to accelerate the development, licensure and availability of the vaccine.

Since that time, the vaccine began a clinical development program with funding from the U.S. Government, including DTRA and the Biomedical Advanced Research Development Authority among others.

Although research evaluating V920 is ongoing, data from a 2015 study conducted in Guinea by the World Health Organization, the Health Ministry of Guinea, Médecins Sans Frontières (Doctors Without Borders), Epicentre and the Norwegian Institute of Public Health reported 100 percent efficacy (95 percent confidence interval: 74.7- 100 percent efficacy; p=0.0036) following vaccination with a single dose in vaccinated individuals.

The study also reported that all vaccinated individuals appeared to be protected against the Ebola virus infection within six to 10 days of vaccination.

The FDA breakthrough therapy designation and the EMA PRIME status will streamline the licensing of the world's first vaccine for Ebola. The DTRA-funded V920 vaccine will then be available to protect warfighters and our allies from future Ebola endemics whether natural or weaponized.

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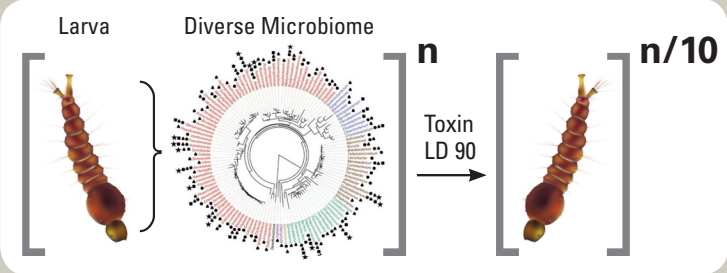
Policing Chemical and Biological Threats through SYNTHETiC BIOLoGY

The Defense Threat Reduction Agency's Joint Science and Technology Office is now a leader in the synthetic biology and gene editing community due to a series of initiatives spearheaded by JSTO scientist Dr. Brian Pate. These efforts helped create a safer operating environment for our warfighters and address challenges posed by chemical and biological weapons.

One of Dr. Pate's initiatives focuses on exploring the microbiomes of mosquito larvae to identify genetic traits that confer resistance to deadly nerve agents. Performed at the U.S. Air Force School of Aerospace Medicine, this work leverages a novel method of microbiome manipulation known as "pawnobiome evolution" to clarify the causal connection between the microbiome and the host phenotype. Specifically, the research explores the genetic changes of the microbiome that confer pesticide resistance to the mosquitos. Scientists will then consider which of these strategies to introduce the identified microbiome genetic traits into naïve bacteria strains relevant to protect warfighters from nerve agents.



Scientists will purchase thousands of mosquito larvae and expose them to high doses of toxins, such as organophosphates. Surviving larvae will have their microbiome isolated and transferred into new larvae. Scientists will repeat the process and compare the genetic results to identify microbiome genetic traits in bacteria relevant to protecting warfighters. Image courtesy of MAJ Jameson Voss, Air Force Research Laboratory.

A second effort under Dr. Pate's management, performed at the Edgewood Chemical Biological Center and the U.S. Military Academy (West Point), strives to understand the response of skin microbiomes to chemical and biological agents. The team will select appropriate candidate organisms native to the human skin microbiome to serve as hosts for genetic modification to introduce protective responses. The goal is to modify the bacteria living on the skin of warfighters so they can police the skin's surface for chemical and biological agents. If a harmful agent is detected, the modified organism will release an appropriate countermeasure or wound-healing growth factor.

JSTO's broader synthetic biology program also includes an effort performed at the Naval Research Laboratory and the U.S. Naval Academy. This activity, which spans multiple departments at both institutions, explores the response of the microbiome within the respiratory tract to marine toxins, as well as how the human respiratory microbiome can be modified to introduce resistance to toxin-based weapons.

A midshipman from the U.S. Naval Academy works at the Naval Research Laboratory as part of a team that will compete at the 2016 DTRA Syn Bio Academies Challenge. Photo courtesy of Joel Golden, Naval Research Laboratory.

Recently several groups of Naval Academy midshipmen collaborated with students from the California Institute of Technology, George Mason University, University of Maryland and Naval Research Laboratory scientists. The teams utilized molecular modeling to clarify the time-dependent gating of ion channels that are the target of certain marine toxins and predicted the amount of time available to cells to respond to these toxins. They then cloned two-component voltage sensors into a vector to be introduced into cells. This will allow the cells the ability to sense the presence of toxins that target ion channels. The project aims to modify the microbiome of the human respiratory tract to make it capable of sensing toxins that target ion channels and providing a countermeasure response.

DTRA's efforts also include fostering a deeper understanding of synthetic biology for future warfighters. The DTRA Syn Bio Academies Challenge is a pilot program where cadets and midshipmen compete for an annual prize while exploring the field of synthetic biology.

In addition, Mr. Dale Taylor and Dr. Ashley Triplett, also from JSTO, recently mentored students in synthetic biology at the 2016 Joint Science and Technology Institute. DTRA's initiatives for current and future warfighters continue to position JSTO as a leader in synthetic biology.

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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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