

Winter 2011 Vol.1 No. 2



JSTO SCIENCE AND TECHNOLOGY UPDATE



A Publication of the Defense Threat Reduction Agency &
STRATCOM Center for Combating WMD, Research and Development Enterprise,
Chemical/Biological Technologies Directorate (DTRA/SCC-WMD(RD-CB))



Director's Message

By Dr. Alan S. Rudolph

Welcome to the second edition of the Joint Science and Technology Office (JSTO) Science and Technology Update and the first since my arrival last fall as the new JSTO director. I want to first thank you for taking the time to read this issue, and I pledge to you that this is just one of the many ways we intend to communicate in the future with our myriad stakeholders around the world.

This winter's issue is dedicated to articles and coverage of the 2010 Chemical and Biological Defense Science and Technology Conference that JSTO hosted in Orlando last November. With more than 1,500 attendees from industry, government, and academia, the conference was a tremendous opportunity to continue to network and collaborate with the goal of providing our warfighters the protection they need to survive and thrive on today's battlefields. It also brought together senior thought leaders across government, industry, and academia, creating a vibrant community focused on discussion and debate on key issues we face in protecting the nation from biological and chemical threats.

As we move forward in 2011, we are instituting a number of changes at JSTO. These changes are aimed at ensuring that JSTO is capitalizing on the best available science and technology solutions to fill the critical capability gaps facing our warfighters and to transition these solutions to production as quickly and efficiently as possible for defense and national security needs. To that end, we will also be focusing our efforts on new strategic thrusts and enabling capabilities that will provide knowledge creation and knowledge translation from our enterprise. We will articulate this new vision over the coming months. We are committed to making JSTO both innovative and relevant in providing real capability and product solutions to the warfighter and for national security needs. This will require new efforts to avoid surprise from fast-moving dynamic scientific disciplines, while creating consortia of active performers that mix academic, industry, and national laboratory assets. We also recognize that we need to be more agile in our business practices, and we are working hard at JSTO to develop new

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Dr. Alan S. Rudolph,
director of the Chemical &
Biological Technologies Directorate

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and improved business methods that allow us to move more quickly from sourcing good ideas to initiating action through contract award.

It is imperative that we have access to the best and most cutting-edge science and technology ideas. I am empowering my science and technology managers (STMs) to use all means necessary to proactively reach out to the S&T community and identify new S&T ideas and solutions that can bring revolutionary capability to our mission. Whether through informal workshops, seminar presentations, site visits, professional meetings, or collaboration at our annual conference, our STMs will be scouring the globe for revolutionary science and technology. If they can't find you, don't hesitate to reach out to them and engage. They are charged with building new programmatic visions through focused program announcements that are integrated with our strategic plan and provide exciting new thrusts that translate into

real solutions for chemical and biological defense. If I can assist in helping to make these connections, please contact me.

Finally, I would like to remind everyone of our next conference. The 2011 CBD S&T Conference is scheduled for November 14–18 in Las Vegas; and, if you attended our 2010 event, you know what a great opportunity this is to meet not only your government partners, but people from all parts of the S&T community. The conference continues to grow both in numbers and importance and has quickly become a can't miss event. We are also in the process of planning next year's meeting, and we encourage you to actively engage with us on building the program.

I look forward to meeting with many of you in the coming year and wish you only the best.



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DTRA/SCC-WMD(RD-CB)

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Hundreds Attend Chem-Bio Defense Conference in Florida

More than 1,500 representatives from the military, government, research, industry, and academia converged in Orlando, FL for the 2010 Chemical and Biological Defense Science and Technology Conference, November 15–19.

Dr. Alan Rudolph, director of Chemical and Biological Technologies in the Defense Threat Reduction Agency, hosted the conference. The annual event brought members of the medical and physical science communities together to identify and examine the new, dynamic developments in basic and applied research within the chemical and biological defense landscape.

In addition to Dr. Rudolph, the event included appearances by Dr. Richard Danzig, chairman for the Center for a New American Security and former Secretary of the Navy; 2005 Nobel laureate Dr. Robert H. Grubbs; Dr. David J. Galas, senior vice president of the Institute for Systems Biology; Dr. Tara O'Toole, under secretary for science and technology at the Department of Homeland Security; Mr. David Hoffman, Pulitzer Prize winning author; and Mr. Jason Rao, senior policy advisor for Global Science Engagement in the White House Office of Science and Technology Policy.

In his opening remarks, Dr. Rudolph welcomed and challenged conference attendees on what he called the three C's:

See Chem-Bio Defense Conference page 3

create, collaborate, and communicate. He urged the audience to help DTRA RD-CB respond to that simplest of questions, "What if we could?"

Dr. Rudolph also promised that the Joint Science and Technology Office will work to improve collaboration and communication with the physical and medical science communities to promote open innovation and develop communities of action. The director added that DTRA was exploring ways to enhance its internet capabilities to become more responsive to incoming ideas from the field.

Over the five-day conference, attendees would hear dozens of speakers during panel, keynote, and parallel sessions speak on the scientific and technical advances made that may both lead to a safer battlefield and be applicable to civilian populations around the world.



Dr. Richard Danzig, chairman of the Center for a New American Security, addresses attendees of the 2010 Chemical and Biological Defense Science and Technology Conference in Orlando on November 18, 2010

the urgency to transition these advances to capabilities.

The evening ended with the presentation of conference awards by Dr. Rudolph and Thomas McMahon, director at CUBRC, which sponsored the dinner.

The following 2010 Chemical and Biological Defense Science and Technology Conference awards were presented for scientific achievement, collaboration, and conference platform and poster presentations.

See Chem-Bio Defense Conference page 4



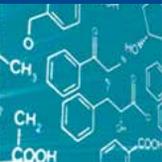
Maj. Gen. John Howlett, deputy director of the United States Strategic Command Center for Combating Weapons of Mass Destruction, and Mr. Doug Bruder, associate director for research and development, Defense Threat Reduction Agency meet with two international attendees during a break in the proceedings at the 2010 Chemical and Biological Defense Science and Technology Conference

The conference culminated with an awards ceremony and dinner featuring remarks by Dr. Richard Danzig who recently returned from interviewing members of the Japanese religious cult Aum Shinrikyo, best known for their sarin gas attacks on the Tokyo subway system in 1995. What struck him most about what he learned from these interviews was how easily this small group was able to conduct the science to achieve the purity levels needed to make sarin an effective weapon.

According to Dr. Danzig, it is this ability to cheaply and quickly develop chemical and biological weapons that makes the advances of today's scientists and biotech industry critical to our future security and that drives

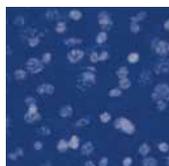


Thomas McMahon (L), director of CUBRC, and Dr. Alan Rudolph, director of the Chemical and Biological Technologies directorate at the Defense Threat Reduction Agency (R), present the Outstanding Scientific Achievement award to Justin Skoble of Aduro BioTech at a ceremony at the 2010 Chemical and Biological Defense Science and Technology Conference



2010 Chemical and Biological Defense Science and Technology Awards

Category	Winner	Organization	Abstract Title	Topic
Outstanding Scientific Achievement	Justin Skoble	Aduro BioTech	Listeria monocytogenes-Based Tularemia Vaccines	Novel Vaccine Technologies
Outstanding Collaboration	Marc Mathews	Natick Soldier Research Development and Engineering Center	Future Chemical/Biological (CB) Ensemble Ground Soldier System (GSS) Technology Demonstration	Preparing for Technology Transition - Advanced Development and Demonstration of CB Defense Technologies
Outstanding Platform Presentation	Emily English	Johns Hopkins University/Applied Physics Laboratory	Methods for Evaluation of Organophosphate Biochemical Targets	Chemical and Biological Agent Characterization
Outstanding Platform Presentation	Kimberly Bishop-Lilly	Naval Medical Research Center	Linking Phenotype to Genotype by Whole Genome Pyrosequencing: Deciphering New Pathways to Ciprofloxacin and Phage Resistance in Bacillus anthracis	Pathogen Characterization, Identification and Evaluation: Linking Phenotype to Genotype
Outstanding Platform Presentation	Brett Martin	Naval Research Laboratory	Controllable Chemical Protection Based on Electroactive Tethered Membranes – Impedance Spectroscopy and Vapor Testing	Novel Materials for CB Protection
Outstanding Platform Presentation	Shane Mueller	Applied Research Associates	Assessing the Cognitive Impact of Chemical Protective Gear and Heat Stress	Human Performance in a CBRN Environment
Outstanding Platform Presentation	John North	Inimex Pharmaceuticals, Inc	Innate Defense Regulators: Host-Directed, Broad-Spectrum Drugs for Pre- and Post-Exposure Prophylaxis and Therapy of Infection	Host-Directed Therapeutics and Immunomodulation
Outstanding Poster Presentation	Tom Ding	Walter Reed Army Institute of Research	Cellular and Serum Screening Antigen Array of Brucella Suis for Vaccines and Diagnostics	Novel Vaccine Technologies
Outstanding Poster Presentation	Patrick Iversen	AVI BioPharma	Rapid Response Therapeutic for Pandemic (H1N1-SOIV) and Seasonal Influenza	Pathogen-Directed Therapeutics
Outstanding Poster Presentation	Monica Borucki	Lawrence Livermore National Laboratory	Understanding the Role of Genetic Drift and Shift in RNA Virus Host-Switching Events	Pathogen Characterization, Identification and Evaluation: Linking Phenotype to Genotype



Chem-Bio Defense Conference Poster Winners

Understanding the Role of Quasispecies in Interspecies Transmission Events



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ABSTRACT

Recently LLNL bioinformatic capabilities were used to better understand how current circulating influenza strains could evolve into a new pandemic strain. Influenza proteomes from distinct viral phenotype classes were searched for class specific amino acid mutations conserved in past pandemics, using reverse engineered linear classifiers. Thirty-four amino acid markers associated with host specificity and high mortality rate were found. The study concluded that evolutionary pathways involving H1N1 human and swine strains mixed with avian strains show the potential to acquire the pandemic markers with a double reassortment and one or two amino acid mutations (Allen et al., 2009).



This project aims to build on these data, by defining genetic mutations associated with a host-switching event for two different medically significant groups of RNA viruses: (1) lyssaviruses and (2) coronaviruses. In each case ultra-deep genome sequencing will be combined with advanced computational analysis to allow characterization of genomic changes that characterize host-switching events. Additionally, current sequencing technologies will be compared for ease of use, error rate and sequence bias, and depth of coverage.



EXPERIMENTAL APPROACH

Development of methods to predict the potential of a particular pathogen emerge:

- Ultra-deep genome sequencing will be combined with advanced computational analysis to characterize genomic changes and host-switching events.
- Initial experiments were conducted using Illumina ultra-deep sequencing to determine amount of sequence coverage necessary to identify rare variants in mutant spectra.
- Next generation sequencing platforms will be compared by sequencing a subset of samples using the 454, SOLID and Illumina technology. Advanced pattern recognition and other bioinformatics techniques will be used to mine sequence data and provide information on how much sequencing is needed to capture the genetic viral diversity, the potential for re-occurring selective sweeps, and the potential for within host genetic shifts.
- Data generated from *in vitro* and *in vivo* studies are being used to define the genetic mutations associated with a host-switching events:
 - Identify genetic mutations associated with a recent and naturally-occurring rabies virus host-switching event.
 - Identify the role of genetic drift and genetic shift (recombination) in the generation of bovine coronavirus variants that are able to adapt to human cell lines.



Preliminary Data: Ultra-deep sequencing of naturally infected samples

Samples tested:

- One naturally-infected bovine nasal swab
- Two samples from rabies virus infected foxes
- Two plasmid controls were generated (pCR4.0 with a 1 kb insert from the polymerase gene)

Controls: The sequence of the control insert was determined for each control using Sanger sequencing. These data were used to determine the error rate due to the processing of samples for Illumina sequencing.

Amplification: 14-16 degenerate primer pairs were designed to sequence approx. 10 kb of each genome.

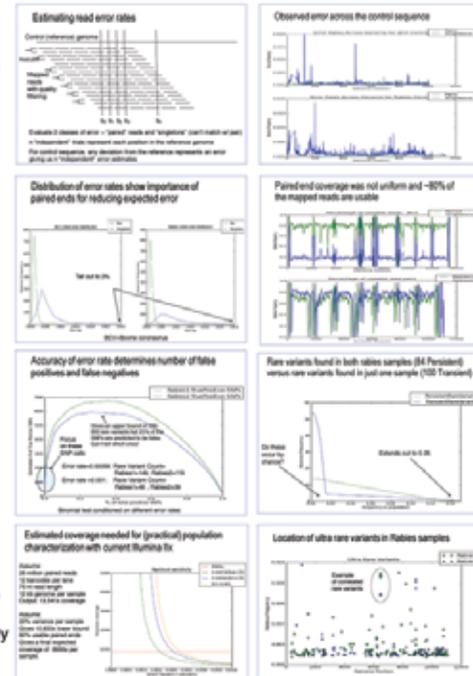
Sequencing: One lane of paired-end sequence data was generated for each sample using Illumina Ix.

Preliminary Results: Average of 2 x 112 paired-end reads generated per sample

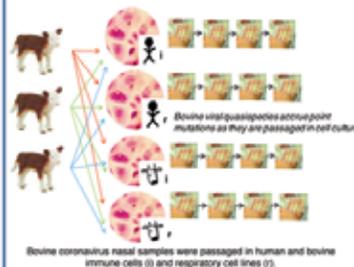
- Control – 6.3 gb, 2 x 29,325,049 reads
- Bovine coronavirus – 6.1 gb, 2 x 27,231,827 reads
- Rabies 1 – 6.06 gb 2 x 27,063,566 reads
- Rabies 2 – 6.06 gb 2 x 27,051,934 reads
- ~85% of reads mapped to reference
- ~490,000x total coverage for each sample.
- Primer regions ignored from analysis

Conclusions:

- Paired-end reads are much more stable as compared to single reads.
- Important to use adequate coverage to capture diversity of the virus population
- Ultra rare variants (<1%) appear to be less likely to persist in population



Identification of point mutations that are uniquely present in bovine coronavirus variants that have acquired the ability to multiply in human cell lines



Methods: Collected >200 nasal swabs from area calves and identified over 20 samples infected with bovine coronavirus via RT-PCR. Twelve samples were passed serially in human and bovine cells (macrophage and lung cell lines). Passage attempts in lung cell lines (A549 and EBL) were unsuccessful for natural isolates.

Preliminary Results: Ability of a sample to be passed serially appears to be related to titer of starting material and cell type used for viral passage

- Bovine coronavirus samples were most readily amplified and passed in bovine macrophages (BOMAC) and human macrophages (THP-1) as compared to bovine lung cells (EBL) and human lung cells (A549).
- We are currently amplifying the genomes of passaged and unpassaged virus for ultra-deep sequencing.

LLNL-POST-480471

This work was performed under the auspices of the U.S. Department of Energy by Lawrence Livermore National Laboratory under Contract DE-AC02-07NA27344. Funding was provided by the Transformational Medical Technologies Initiative and LLNL LDRD 10-LW-026.

Rapid Response Therapeutic for Pandemic (H1N1-SOIV) and Seasonal Influenza



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¹AVI BioPharma, Bothell, WA, and Corvallis, OR, USA, ²Tulane Medical Center, New Orleans, LA, USA, ³Burleson Research Technologies, NC, USA

ABSTRACT

Objective: Emergence of novel influenza viruses including the recent pandemic H1N1 strain presents a new challenge to the human population. An exercise was initiated to identify an effective therapeutic for design to synthesize in one week.

Methods: Conserved influenza A genome sequences were identified by extensive alignment using the NCBI Influenza database. Potential homologs with human genome sequences were excluded using BLAST for expressed sequences. Twelve active candidates and three inactive sequences were prepared and evaluated in a mouse influenza infection model with A/Puerto Rico/08/09 H2N1 infection with endpoints of lung viral titer and preservation of body weight. Lead candidates were then evaluated in a non-adapted H1N1 (SOIV) ferret infection model with endpoints that include clinical signs, nasal wash viral titer and lung viral titer. Pilot toxicology studies were conducted in the rat and studies to evaluate sequence-specificity, CC50, and CC50 were conducted in cell culture.

Primary Results: The H2N1 infected mouse model led to identification of a PMOPlus oligomer (AVI-7100) targeting a viral segment transcription start site as a lead candidate. The reduction of viral titer was dose dependent over a range of 2 to 8 mg/kg by the intraperitoneal route and greater than 10 mg/kg continuous positive control. This lead compound also demonstrated significant reduction in viral titer, improvement in clinical signs and reduction in inflammatory cells in the H1N1 ferret model at a dose of 10 mg/kg by the intraperitoneal route. Pilot toxicology studies indicate AVI-7100 is well tolerated at doses over 150 mg/kg in the rat. Inhibition of viral titer is sequence specific, the CC50 is greater than 1500nM, and the inhibition of virus is proportional to the oligomer concentration in rats.

Primary Conclusions: A rapid response to the pandemic H1N1 influenza was accomplished in less than two weeks. The studies identified AVI-7100 which appears to have a broad safety margin and is effective in both mouse and ferret influenza models challenged by H2N1 and H1N1, respectively.

Potential Impact: Rapid therapeutic antiviral design for influenza represents a template for therapeutic design for emerging infectious disease or engineered bioterror agents.

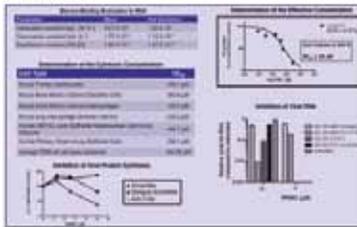
INTRODUCTION

Influenza A, a member of the Orthomyxoviridae family, is composed of a negative-sense, single-stranded and segmented RNA genome. The virus is enveloped in a lipid membrane derived from the host cell which is embedded with viral hemagglutinin (HA), neuraminidase (NA), and M2 proteins. A matrix (M1) protein is found just below the lipid envelope and the core is made of the eight RNA segments, the polymerase proteins (PB1, PB2 and PA) and the nucleoprotein (NP). Two nonstructural proteins are also present internally. The virus particle is composed of approximately 1% HA, 5% NA, 20% NP, and 70% protein.

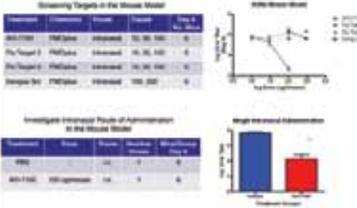
A triple-reassortant influenza A (H1N1) virus has been circulating since 1998 with segments from pigs (HA, NP, NA, M and NS), humans (PB1, and PB2 and PA). A newly described and novel swine-origin influenza A (H1N1) virus (SOIV) is a triple reassortant virus that includes genetic elements of this prevailing virus that reassort with the neuraminidase (NA) and matrix (M) segments of a Eurasian swine virus. The previous influenza A (H1N1) triple-reassortant virus was occasionally transmitted to humans but not spread efficiently from human-to-human but the new SOIV is very efficient in human-to-human transmission.

While the SOIV is currently sensitive to the neuraminidase inhibitors oseltamivir and zanamivir, seasonal influenza has previously been documented to evolve mutations that confer neuraminidase inhibitor resistance. WSN SOIV replace the human H2 as the seasonal influenza virus or WSN SOIV resistant with yet another strain of influenza to create another new variant? WSN is avian to become more lethal? These uncertainties are compounded by the time interval from the identification of a new virus to the manufacture and distribution of a new vaccine. Further, a sufficiently novel viral hemagglutinin antigen may necessitate the use of large doses of immunogen and a prime boost schedule, posing practical difficulties for mass vaccination campaigns that must promptly elicit protective immunity. In view of these considerations, there exists an urgent need to create novel forms of prophylaxis and therapy for SOIV in particular, ideally with broad activity against various influenza viral strains, subtypes and types.

I. In Vivo Studies



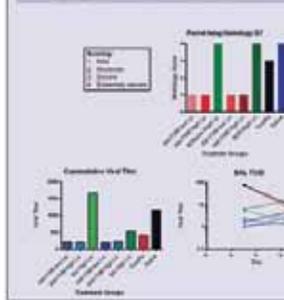
II. MOUSE STUDIES (H2N1 Port Chimeres)



III. Ferret Studies

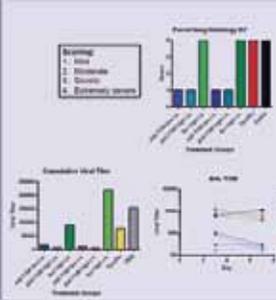
Ferret Study 1 with H1N1 SOIV

Group	Agent	Chemistry	Dose (mg/kg)	Route	Schedule	Day	Day
1	AVI-7100	PMOPlus	10	i.p.	-4h, 12, 24, 36, 48, 60	0	0
2	AVI-7100	PMOPlus	30	i.p.	-4h, 12, 24, 36, 48, 60	0	0
3	SOIV	PMOPlus	30	i.p.	-4h, 12, 24, 36, 48, 60	0	0
4	AVI-7100	PMOPlus	10	i.p.	-4h, 12, 24, 36, 48, 60	0	0
5	SOIV	PMOPlus	10	i.p.	-4h, 12, 24, 36, 48, 60	0	0
6	SOIV	PMOPlus	10	i.p.	-4h, 12, 24, 36, 48, 60	0	0
7	Saline	-	-	-	-	-	-
8	Saline	-	-	-	-	-	-
TOTALS						24	24



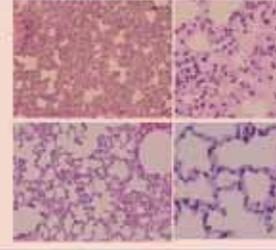
Ferret Study 2 with H1N1 SOIV

Group	Agent	Chemistry	Dose (mg/kg)	Route	Schedule	Day	Day
1	AVI-7100	PMOPlus	10	i.p.	-4h, 12, 24, 36, 48, 60	0	0
2	AVI-7100	PMOPlus	30	i.p.	-4h, 12, 24, 36, 48, 60	0	0
3	SOIV	PMOPlus	30	i.p.	-4h, 12, 24, 36, 48, 60	0	0
4	AVI-7100	PMOPlus	10	i.p.	-4h, 12, 24, 36, 48, 60	0	0
5	SOIV	PMOPlus	10	i.p.	-4h, 12, 24, 36, 48, 60	0	0
6	SOIV	PMOPlus	10	i.p.	-4h, 12, 24, 36, 48, 60	0	0
7	Saline	-	-	-	-	-	-
8	Saline	-	-	-	-	-	-
TOTALS						24	24



Ferret Study with Oseltamivir resistant H1N1 (SOIV)

Group	Treatment	Dose (mg/kg)	Route	Schedule	Recovery	Recovery
1	Oseltamivir	0	i.p.	-4h, 12, 24, 36, 48, 60	0	0
2	AVI-7100	30	i.p.	-4h, 1, 2, 3, 4, 5, 6	0	0
3	AVI-7100	10	i.p.	-4h, 1, 2, 3, 4, 5, 6	0	0
4	Saline	-	-	-	-	-
5	Oseltamivir	0	i.p.	-4h, 12, 24, 36, 48, 60	0	0
6	AVI-7100	70	i.p.	-4h, 1, 2, 3, 4, 5, 6	0	0



Conclusions:

- Multiple oligomers were evaluated in a mouse model to identify AVI-7100 as an effective target and a single dose by the intranasal route is effective.
- AVI-7100 is a 20-mer containing three PMOPlus cationic linkages. AVI-7100 prevents viral titer expansion in cell culture and reduction in targeted viral protein synthesis.
- AVI-7100 is active against fully virulent and non-adapted pandemic H1N1 virus in the ferret model.
- AVI-7100 is effective against non-adapted H1N1 followed intraperitoneal or (i.p.) intranasal (i.n.) delivery in the ferret.
- AVI-7100 protects against viral damage in the lung caused by Oseltamivir resistant H1N1-SOIV.

Screening Immunogenicity of *B. Suis* Protein Array for Vaccines and Diagnostics

Tom Ding¹, Stephen Boyle², Edward Young³, Jie Feng¹, Richard Borschel¹, Haijing Hu¹, and David Hoover¹,
¹Division of BRD, Walter Reed Army Institute of Research, Silver Spring, MD, ²Virginia Tech University, VA, ³Baylor College of Medicine, TX.

Abstract

This abstract describes the development of a protein array of conserved *B. suis* proteins using the high throughput screening and detection system (HTS) in this study. The protein array contains 2000 spots of *B. suis* proteins and is used to screen for antibodies against *B. suis* antigens. The array is used to identify potential vaccine candidates and diagnostic markers. The array is used to screen for antibodies against *B. suis* antigens. The array is used to identify potential vaccine candidates and diagnostic markers. The array is used to screen for antibodies against *B. suis* antigens. The array is used to identify potential vaccine candidates and diagnostic markers.

Table 1: Whole genome for identification of *B. suis* genes

Gene ID	Gene Name	Accession
WRAIR_0001	WRAIR_0001	WRAIR_0001
WRAIR_0002	WRAIR_0002	WRAIR_0002
WRAIR_0003	WRAIR_0003	WRAIR_0003

Background: *B. suis* is a zoonotic pathogen that causes brucellosis in humans and animals. The disease is caused by the bacterium *B. suis*, which is a member of the *Brucella* genus. The disease is characterized by fever, joint pain, and fatigue. The disease is caused by the bacterium *B. suis*, which is a member of the *Brucella* genus. The disease is characterized by fever, joint pain, and fatigue.

Results

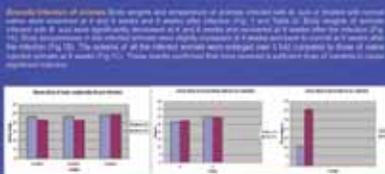


Fig. 1: Mouse body weight, temperature and spleen weight after 8-week infection.

Table 2: Mouse body weight, temperature and spleen weight after 8-week infection.

Day Post-Infection	Body Weight (g)	Body Temperature (°C)	Spleen Weight (mg)
0	20.0 ± 0.5	37.0 ± 0.2	10.0 ± 0.5
7	20.5 ± 0.5	37.5 ± 0.2	15.0 ± 0.5
14	21.0 ± 0.5	38.0 ± 0.2	20.0 ± 0.5
21	21.5 ± 0.5	38.5 ± 0.2	25.0 ± 0.5

Methods: The protein array was developed using a high-throughput screening and detection system (HTS). The array contains 2000 spots of *B. suis* proteins. The array is used to screen for antibodies against *B. suis* antigens. The array is used to identify potential vaccine candidates and diagnostic markers.

Conclusions: The protein array is a valuable tool for identifying potential vaccine candidates and diagnostic markers. The array is used to screen for antibodies against *B. suis* antigens. The array is used to identify potential vaccine candidates and diagnostic markers.

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Table 3: Identification of *B. suis* genes

Gene ID	Gene Name	Accession
WRAIR_0001	WRAIR_0001	WRAIR_0001
WRAIR_0002	WRAIR_0002	WRAIR_0002
WRAIR_0003	WRAIR_0003	WRAIR_0003

Table 4: Characteristics of *B. suis* proteins and conserved proteins

Protein ID	Protein Name	Accession
WRAIR_0001	WRAIR_0001	WRAIR_0001
WRAIR_0002	WRAIR_0002	WRAIR_0002
WRAIR_0003	WRAIR_0003	WRAIR_0003

Table 5: Reactivity of *B. suis* proteins with anti-*B. suis* antibodies

Protein ID	Reactivity
WRAIR_0001	High
WRAIR_0002	Medium
WRAIR_0003	Low

Conclusions

The protein array is a valuable tool for identifying potential vaccine candidates and diagnostic markers. The array is used to screen for antibodies against *B. suis* antigens. The array is used to identify potential vaccine candidates and diagnostic markers.

Acknowledgments

The authors thank the following individuals for their contributions to this project: Tom Ding, Stephen Boyle, Edward Young, Jie Feng, Richard Borschel, Haijing Hu, and David Hoover.

Interagency Biological Restoration Demonstration (IBRD) Concludes

By Katie Crockett

The Interagency Biological Restoration Demonstration (IBRD) concluded with a Capstone Exhibition held in Seattle, WA, September 22 to 24, 2010. During the exhibition, products developed over the course of the program were showcased through panel presentations and discussions, as well as in posters. Keynote speakers at the event were Mr. Andy Weber, ATSD(NCB); Judge Alice Hill (Ret.), Senior Counselor to the Homeland Security Secretary; and Mr. Tim Manning, Deputy Administrator for Protection and National Preparedness, Federal Emergency Management Agency.

The following federal, state and local stakeholders also sent representatives to the IBRD:

- Joint Project Manager Guardian (JPMG)
- Joint Project Manager Decontamination (JPM Decon)
- Joint Requirements Office (JRO)

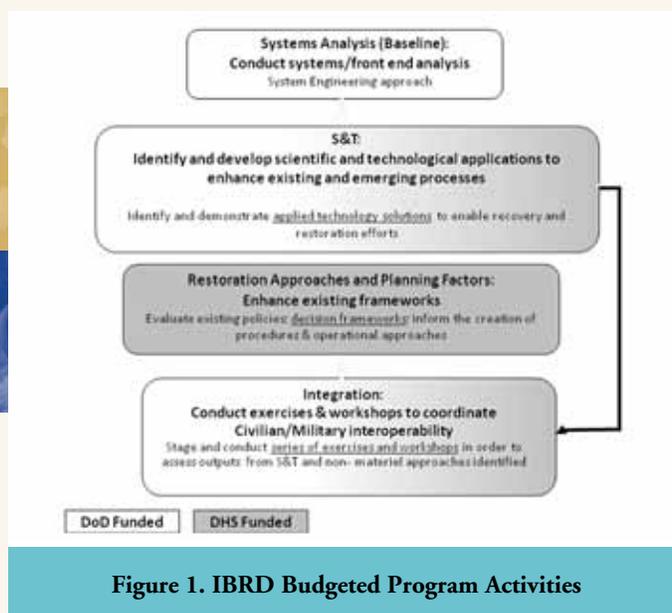


Figure 1. IBRD Budgeted Program Activities

- Joint Base Lewis-McChord (JBLM) Office of Emergency Management
- Seattle Urban Area Security Initiative (UASI) participant offices of emergency management, first responders, and public health
- Environmental Protection Agency (EPA)
- U.S. Departments of Homeland Security (DHS), Health and Human Services (HHS), and State (DOS)

The IBRD Capstone Exhibition was the culmination of a four-year program jointly managed and funded by DoD through the Defense Threat Reduction Agency (DTRA) and DHS's Science and Technology (S&T) Directorate. This program addressed recovery from a biological event specifically in a wide urban area, which was the scenario presented in National Planning Scenario #2 (Biological Attack–Aerosol Anthrax). Recognizing the increasing role DoD plays in domestic incident consequence management and the fact that an intentional biological agent release near a military installation will not be bound by any fence, DTRA and DHS S&T took the innovative approach of jointly sponsoring the IBRD so that the departments could collaboratively address the issue, ultimately improving the nation's ability to recover from any such event. For example, in 2005, according to "Military First Response:

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Sampling Demonstration – A CST member presents the CST capabilities



JHU APL demonstrates sample collection technologies



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Lessons Learned from Hurricane Katrina 2007,” the U.S. Armed Forces and National Guard deployed 72,000 troops to the affected area following Hurricane Katrina, making it the largest military deployment within U.S. borders since the Civil War.

Program Structure

Across the Interagency, consequence management activities have focused primarily on the response phase of an incident, with recovery being largely ignored—specifically how to remediate a large urban area following a biological agent release. This is especially disconcerting in light of the anthrax release in 2001, in which an estimated few grams of anthrax resulted in costing hundreds of million dollars and several years to clean up. The first building discovered to be contaminated—the American Media, Inc. building in Florida—reopened after more than five years. In recent years, several studies have been conducted on how to remediate a single facility, but virtually nothing existed on how to assess and remediate an outdoor environment. Therefore, the goal of the IBRD was to reduce the time and resources associated with recovering and restoring a wide urban area following the release of a biological agent.

The following were specific objectives of the program:

- Understand the social, economic, and operational interdependencies, both past and present, that affect recovery and restoration actions
- Establish long-term, formal coordination between DoD and DHS, and determine how this level of coordination can be optimized for stakeholder’s use at the state, regional, and local levels
- Develop strategic restoration plans for DoD and DHS and decision frameworks that can be used in other parts of the nation
- Identify and demonstrate technologies that support recovery and restoration operations
- Exercise restoration activities and available technology solutions using national planning scenarios

Each department provided a program manager and half of the roughly \$34 million program budget that was used to fund the activities identified in figure 1.

Early on in the program, the co-program managers realized the importance of having the EPA represented on the program management team. Each agency brought strengths to the team: DTRA’s S&T expertise in decontamination, sampling, and sample processing when combined with DHS’s knowledge of urban consequence management and EPA’s history in long-term environmental effects of contamination resulted in a truly interagency effort.

The IBRD program partnered with the Seattle urban area, working through the Seattle UASI, to provide operational input. The Seattle urban area was selected as the program partner in part because it contains critical assets such as Seattle-Tacoma airport and the ports of Seattle and Tacoma. In addition, major corporations such as Microsoft, Costco, Amazon, and Boeing are headquartered in the region. Finally, the area contains major military facilities such as JBLM and Madigan Army Medical Center. In fact, roughly 70% of the military population at JBLM lives off base in the surrounding counties, meaning that an event in the area would have a profound effect on the operation of the base and those stationed there.

IBRD Outcomes

The first year of the program was spent conducting a front-end systems analysis that identified the then current baseline of wide area recovery capabilities as well as the gaps and chokepoints in those capabilities. These gaps were then aligned with federal interagency needs and investment priorities. Additionally, the identified gaps and chokepoints were cross-walked with gaps noted by the White House Homeland Security Council (now part of the National Security Council), DHS Universal Task List, and the DoD JRO Passive Defense Capability Assessment. Based on intra- and interagency input, the following areas were selected for IBRD investment.

- Outdoor decontamination strategies, methods, and materials
- Method for outdoor characterization of affected area (including sampling and sample processing)
- Risk-based approach to determining the health risk associated with agent re-aerosolization
- Methods and standards for outdoor clearance

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- Agent fate and transport in the environment
- Method to characterize buildings as requiring fumigation, partial fumigation, or surface decontamination

Nonmateriel solutions developed to begin to address some of these gaps focused on a national-level consequence management planning template (which included the development of decision frameworks) that was then used to draft the Seattle region Recovery Framework for a Biological Attack, and on the facilitation of relationship building between relevant military and civilian personnel. For example, IBRD and JPMG cosponsored workshops for the Military-Civilian Coordination Advisory Group in Tacoma, WA; San Diego, CA; and San Antonio, TX. The purpose of these workshops was to build or strengthen relationships between military installations and civilian emergency management organizations that are in close proximity with each another. Further, after-action reports from several program-sponsored and moderated workshops on topics such as Community Resilience, Anthrax Contaminated Waste Disposal, Civilian and Military Responsibilities, and Defense Support to Civil Authorities are also included in the nonmateriel program deliverables.



IBRD Program Managers Ryan Madden (DTRA) and Chris Russell (DHS S&T) listen to a demonstration by JHU APL on sample analysis technologies



Mr. Andy Weber, Mr. Lance Brooks (DHS S&T), and Dr. Alan Rudolph listening to keynote speaker Judge Alice Hill at the IBRD Capstone

Science and technology solutions developed by IBRD fell into four primary categories:

- Biological sampling approaches and methods
- Decontamination technologies and procedures
- Decision support tools
- Agent fate and transport

The following are descriptions of a sampling of IBRD S&T efforts.

BIOLOGICAL SAMPLING APPROACHES AND METHODS

One of the observations of the front-end systems analysis was that significant and obstructive variability exists between DoD and civilian operations and protocols, such as during sample collection. The DoD/Civilian Sampling Methods Compatibility Study identified all current, in-use DoD and Interagency biological sampling and laboratory sample processing capabilities. Further, it assessed the compatibility of military and civilian capabilities and provided recommendations for how to make these capabilities more compatible.

Another conclusion of the front-end systems analysis was that diminished or overwhelmed laboratory sample processing capacity is likely to be a significant chokepoint during response and recovery from a biological event. In response, IBRD funded a project that developed and evaluated high-throughput sample processing and rapid viability-analysis protocols



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using Rapid Viability-PCR. The High-Throughput Sample Process for Outdoor Environment Media Study was particularly germane because assessed the processing of environmental samples and surface samples containing outdoor debris and demonstrated that it was possible to significantly scale up the robotic platform, which enabled expanded sample processing with low impact on laboratory technicians. Furthermore, automated processing and analysis minimizes risk by reducing exposure of personnel to pathogen-containing samples and reduces repetitive injury strain on laboratory personnel.

In July 2010, IBRD held the Sample Strategy, Collection, and Analysis Demonstration in the Seattle region. The purpose of this demonstration was to improve the understanding of sampling methodologies, strategies, and plans by way of demonstrations and discussions of related topics. Over two days, participants demonstrated a variety of topics associated with biological sampling, such as building triage, the use of decision support tools on sample strategy development, outdoor sample strategies, and DoD Weapons of Mass Destruction Civil Support Team (CST) sample collection techniques.

DECONTAMINATION TECHNOLOGIES AND PROCEDURES

In 2007, DTRA issued a Request for Information (RFI) to identify decontamination technologies and application devices appropriate for further development. Responses to the RFI were then reviewed by an independent panel comprising subject matter experts in relevant fields for concept of employment, compatibility with existing systems, and product efficacy and maturity. Selected technologies were primarily small- and medium-scale application devices that could be used for specialized and hard-to-reach areas, and ranged from systems mounted on heavy vehicles for delivery and large-scale decontaminant application to methodologies assembled from resources likely to be easily obtainable at the local level.



In addition, IBRD leveraged the results of a study conducted by the EPA that assessed the performance of liquid and foam decontamination technologies. Decontaminant technologies were tested on coupons prepared with B. anthracis (Ames strain) on typical surfaces found in outdoor urban environments and residential buildings such as stainless steel, ceramic, glass, granite, concrete, brick, asphalt, wood, and rubber. In addition to decontamination efficacy, the effect of decontamination on the materials was also evaluated.

Recovery of a facility or outdoor area that has been contaminated with a highly persistent agent such as anthrax is a complex process. Numerous variables, such as size of contaminated area, materials in the contaminated area, and availability of remediation resources, must be considered when selecting the appropriate remediation approach for a specific facility or area. IBRD therefore developed a Decontamination Trade-Off Tool to aid decision-makers in selecting the appropriate technology and strategy. The tool provides a systematic process for evaluating a wide range of approaches, including volumetric and surface decontamination, natural attenuation, and seal and abandon. The process includes a trade-off analysis to help decision-makers understand the costs and benefits of the various decontamination methods for the particular facility or area needing treatment, whether alone or as part of a larger decontamination effort. Because the state of decontamination knowledge and technology continues to evolve rapidly, the process is designed to accommodate new strategies, materials, and changing information.

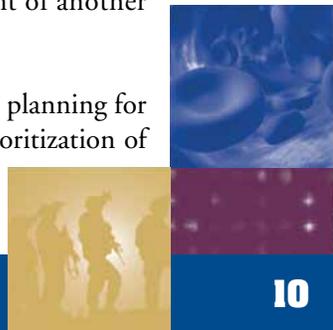
Finally, in August 2010, equipment designed to disseminate the decontamination solution in an outdoor urban environment was demonstrated in the Seattle area. Technologies demonstrated consisted of systems currently in use by the DoD, systems developed by industry, and technologies being evaluated by the S&T community. In addition to demonstrating technologies, attendees were given the opportunity to use and evaluate the equipment themselves.

DECISION SUPPORT TOOLS

One of the most well-received outcomes of the IBRD program was the development of two automated decision-support toolsets. What would eventually become the Prioritization Analysis Tool for All-Hazards (PATH)/Analyzer for Wide Area Restoration Effectiveness (AWARE) tool was originally created as a means to help performers with their analysis. Once the utility of the tool in other applications was realized, IBRD went on to fund its development (and the development of another support tool).

PATH/AWARE is an analysis and decision-support toolset to aid emergency managers and policy-makers in planning for recovery activities in an outdoor environment. PATH/AWARE includes a module that can assist in the prioritization of

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critical infrastructure for clean up. PATH/AWARE injects objectivity and transparency into resource allocation decisions and helps estimate time and cost for each phase of remediation.

Automated Decision Visualization and Information System for Emergency Response/Recovery (ADVISER) is a comprehensive decision framework that addresses everything from notification through first response, initial characterization and planning to site-specific remediation and restoration of an outdoor urban environment. In addition, planners can perform what-if assessments to see how resources are affected.

AGENT FATE AND TRANSPORT

Currently, there is little real-world outdoor data on the fate and persistence of *Bacillus* species in the outdoor environment. Additionally, there is no validated method for how to conduct environmental sampling over a wide area. Little data exists on the movement of biological aerosols in an urban setting or their ability to infiltrate fixed facilities. To address these issues, IBRD funded studies on the fate and transport of *B. thuringiensis*, an organism that shares many biological and physical properties with *B. anthracis*. During these studies (which piggy-backed on already scheduled outdoor, urban releases of *B. thuringiensis*), it was concluded that—

- *B. thuringiensis* persists in the environment for at least four years
- It is predominantly detected in soils and less so in foliage, grass, and water
- Viable agent was observed in 24-hour integrated air samples for up to 48 weeks post-release
- Agent does transport into buildings and was detected in buildings two months post-release

This information, which will be further addressed subsequent programs, may be used to optimize remediation efforts in the event of a persistent biological agent release.

In order to ensure that IBRD products did not simply become shelfware, a technology transition agreement (TTA) was drafted for DoD operators. (While DHS does not have as formal a policy on the transitioning of program products, agreements have been established with the EPA and DHS's Office of Health Affairs.) A TTA was established with JPMG and JPM Decon; and within each JPM, specific programs of record were identified into which IBRD products would transition. For example, products will transition into the CSTs through JPMG's support of the National Guard Bureau,

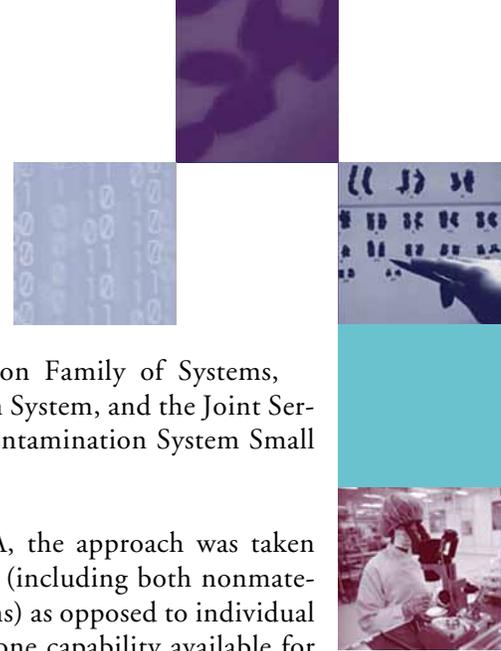
the Common Analytic Laboratory System, and the Installation Protection program. Capabilities developed by IBRD will also transition into the Decon Family of Systems, the Joint Materiel Decon System, and the Joint Service Transportable Decontamination System Small Scale/Large Scale.

When drafting the TTA, the approach was taken to transition capabilities (including both nonmateriel and materiel solutions) as opposed to individual products. For example, one capability available for transition was "Outdoor Sample Processing and Analysis Methodology." The purpose of this capability was to provide consistent sample results across the DoD/Interagency. Several studies conducted by the program, such as the "DoD Sample and Sample Processing Study," the "Sample Method Efficiency for Dirty Surfaces," and the "Outdoor High-Throughput Sample Processing and Analysis Study," contributed to this capability.

Next Steps

Not surprisingly, the success of IBRD spawned independent follow-on efforts for both DTRA and DHS S&T. Though the role each agency will play in the other's follow-on effort is not known at this time, both DTRA and DHS S&T are committed to continuing close coordination and substantive participation in the other's respective programs. Both projects will leverage the products and lessons learned from IBRD but take them to the next level of development or apply them to new scenarios. DHS will kick off its Interagency Chemical Biological Radiological Restoration Demonstration program in FY11 that will test the transportability of the tools (materiel and nonmateriel) developed in IBRD to another U.S. region (Denver, CO) and expand to include chemical and radiological restoration.

DTRA will begin funding the Transatlantic Collaborative Biological Resiliency Demonstration (TaCBRD) in FY12 that will extend beyond recovery and will develop and demonstrate DoD's resiliency to a wide-area biological event that affects civilian and military key infrastructure within the European Command (EUCOM) area of responsibility. TaCBRD will look at the operational interdependencies that may affect resiliency and will work to resolve or at least improve identified technology gaps. In addition to continuing its relationship with DHS, the Department of State and the United States Agency for International Development will play significant roles in program planning and execution. EUCOM has already signed on as the Operational Manager for the program and JPMG has been identified as the Transition Manager.



Individual Protection Advanced Technology Demonstration: Providing Protection Without Raising the Thermal Burden

By LTC Kelly Crigger*

In September 2010, the Defense Threat Reduction Agency (DTRA), in conjunction with the Natick Soldier Research Development and Engineering Center (NSRDEC) and the Joint Program Executive Office for Chemical and Biological Defense (JPEO-CBD), culminated a three-year, advanced-technology demonstration (ATD) that provided the Joint Project Manager for Individual Protection (JPM-IP) with four novel chemical and biological protective systems, two integrated mask and helmet designs, and a new chemical, biological, radiological, and nuclear (CBRN) networking capability to improve the warfighter's situational awareness.

The goal was simple—provide chemical and biological protection without raising the thermal burden on the soldier—but the solution was complicated. Using the thermal properties of the Flame-Resistant Army Combat Uniform (FRACU) as the independent variable, we wanted to know what level of chemical protection was possible. We wanted to identify the tradespace between protection and heat stress and provide the JPM with data to assist in the decision-making process.

The problem is the standard to which the current CB protective uniforms are tailored to meet. A longstanding requirement of 10 grams per square meter of chemical protection

“DTRA set out to develop thinner, lighter uniforms with integrated CB protection that soldiers could wear on a daily basis without raising their thermal burden.”

has forced the uniforms to be thick, which raises the heat stress on soldiers to levels that cause heat exhaustion. As a result, field commanders accept the risk of not taking their CB protective uniforms with them into combat operations because they don't see the payoff in carrying a thick, hot uniform for a low-probability threat. So DTRA, along with NSRDEC acting as the technology manager and JPEO-CBD acting as the transition manager, set out to develop thinner, lighter uniforms with integrated CB protection that soldiers could wear on a daily basis without raising their thermal burden. The basic question was, “If thermal burden is the independent variable that does not change, then what kind of protection can we provide the warfighter?”

A philosophical issue had to be resolved immediately. When a group of government personnel and their civilian contractors sit around a table and talk about deliverables for an acquisition program, the discussion gravitates toward requirements. Require-

ments, however, are a core element of programs of record, not ATDs—where the focus is on the technology and the capability it provides instead of performance requirements. We decided that, for this ATD, we would ask, “What can we do,” instead of “What must we do?”

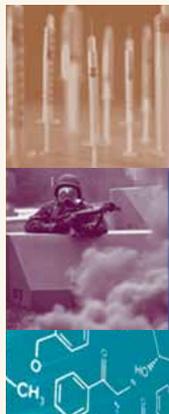
The main goal of every ATD is reducing risk for the JPMs. An ATD shows requirements writers (in this case JPEO-CBD and its subordinate JPMs) which technologies are available and which concepts are possible so they can write a feasible, achievable Initial Capabilities Document and Capability Development Document. By showcasing and testing the latest and greatest technologies in individual protection, we reduce the risk of the JPMs writing unattainable performance parameters for materiel solutions.

An ATD can be executed unilaterally by a single organization; but gathering a coalition of other stakeholders certainly increases the potential for success. The planning for this ATD included the customer in the process from the first meeting. The JPM-IP in Stafford, VA was the logical choice since we wanted to transition our technologies to that office for their Uniform Individual Protective Equipment (UIPE) program of record. It made sense to bring them in early and get their opinions on the program so we could execute parallel design, development, and testing. This was important in the test and evaluation (T&E) phase of the operation because, if we conducted our T&E plan correctly, we would end up saving them a great deal of funds. We also included the Program Executive Office–Soldier (PEO-Soldier) from the beginning so this ATD would not be a CBRN-only project. Any piece of equipment attached to the warfighter's body is managed by PEO-Soldier, and so we targeted its Nett Warrior program for transitioning our technologies.

Success can be measured only if there is a baseline metric for comparison; so one of our team's first tasks was to determine the baseline measurements for the independent variable of thermal burden. Rather than the Army Combat Uniform (ACU), we chose a more practical uniform, the FRACU, as the candidate for our baseline reading. The FRACU had not been fielded at that time, but it would be the duty uniform of the near future. Using the thermal manikin chamber at the U.S. Army

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*Since this article was written, LTC Crigger has retired from the military and DTRA RD-CB.





Institute for Environmental Medicine, we collected the FRACU's baseline thermal performance and heat stress data and used it as our threshold target for improvement.

Although three years sounds like a long time in the life of an ATD, it is not. However, we realized we did not have the time or resources to develop new systems for every soldier on the battlefield and had to choose a certain mission set to tailor the demonstration toward. There was one variable that stood out and made the decision easier—time.

Time is a key element in CBRN protection. If warfighters have enough time to change their clothes before becoming contaminated, they can wear a higher level of protection than soldiers who suddenly find themselves in a contaminated environment and must fight in the uniforms they are wearing. Likewise, a soldier who purposefully ventures into contamination for a long period of time to accomplish a specific task (such as decontamination of buildings or retrieving a contaminated sample) needs a higher protection level than a soldier whose focus is only to exfiltrate a contaminated area as soon as possible. Infantrymen who kick in doors need immediate CB protection for short periods of time, while CBRN soldiers who perform missions in contaminated areas have the luxury of changing into CB protective uniforms and staying in the contamination area longer. To complicate matters more, there are many personnel who wear one-piece uniforms in combat, such as aircrews and combat vehicle crews.

We could not make new uniforms for every skill set in the armed services. We had to choose one and focus our efforts on that mission set. Since the ground warfighter was the focus of the programs of record that we wanted to transition our technologies to (e.g., PEO-Soldier's Nett Warrior and JPM-IP's UIPE), we decided to focus on that skill set—the combat soldier who needs immediate CB protection for a short duration.

Another difficult decision was that of launderability and durability: “How long will the CB protection last if these are soldiers’ duty uniforms that they wash at home?” To the end, we decided this was a technology demonstration aimed at proving that lighter, thinner materials could be used for CB protection without raising the thermal burden. The logistics equation of the materials was outside of the scope of the demonstration; so we decided to focus on the science of the systems and gather as much data on that as possible. That decision was not without its criticisms, but DTRA’s responsibility is the science and technology aspects of a certain capability, not the logistics of it.

“For infantrymen, managing their thermal burden was the most important factor; but for chemical soldiers, communication was the highest priority.”

The primary program that would provide a materiel solution for the thermal burden was the Integrated Protective Fabric System, a government-funded research project through NSRDEC in Natick, MA, to develop permeable and semipermeable membranes with CB protection. However, we knew that it would be necessary to solicit materiel solutions from industry as well, so at the end of the first year of the program, before beginning system design, we put out a Request for Information to industry and received 44 submissions. Most surprising were the number of undergarments proposed by industry, which threw a wrench into our planning, as undergarments were not part of the ATD.

Bringing industry in, however, has its own complications, as industry-submitted test data can have uneven test methodologies with the possibility of skewed data. Testing has to be on a fair and even playing field, which means using standardized test methodologies and purchasing products for testing to keep the results fair. Donated products can create the perception of favoritism, so the program’s budget has to account for the purchasing of industry materials.

One of the drawbacks to being in the research and development field is the lack of direct contact with the warfighter and subsequent decrement in operational experience, which is a nice way of saying scientists sometimes invest in technologies that have little to no practical application. So we went straight to the troops and asked for their feedback on our work. With the help of Matt Kramer of NSRDEC’s Human Factors Lab, we developed a pair-wise comparison questionnaire and took it to three separate Army installations to survey 100 soldiers on their likes and dislikes of protective clothing. The results were somewhat surprising.

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We learned that each skill set has a different priority while in a CBRN protective posture. For infantrymen, managing their thermal burden was the most important factor; but for chemical soldiers, communication was the highest priority. Soldiers who are in a protective posture for long periods of time are more concerned with the ability to communicate with each other than with staying cool. Another aspect that helped focus the team's efforts was feedback on the general concepts of each uniform, such as the benefits of an undergarment versus a duty-uniform type garment.

A benefit of technology demonstrations is the freedom to include new technologies that might not seem to have a direct link to the program of record that the ATD is tied to. Technology demonstrations give the government an outlet to develop more capabilities than a single-source technology program. Our demonstration's goal was to reduce the thermal burden on the warfighter, but that didn't limit us to garments and uniforms only. In fact, it allowed us to explore possibilities in air filtration, helmet-mask interfaces, and situational awareness because we were not tied to requirements. It also allowed us the latitude to pick and choose technologies to demonstrate, such as the eGlove.

The eGlove is a product of the Space and Naval Warfare Systems Command that enables warfighters to use hand gestures to send messages to their terminals. It is one of the few technologies focused on conveying information from humans to their computers instead of vice versa using a glove wired with accelerometers. It wasn't something we thought we would use in this demonstration, but the applications and the potential were there for the warfighter. Including it in the demonstration gave us a new capability to make the warfighter a more complete system. Without having the latitude of being an ATD where we sought to push the boundaries of the possible, we could not have done that.

About a year before the final demonstration, we had to make another series of decisions. We had too many technologies and not enough time to develop them into full prototypes, so we had to decide on which technologies would go forward. Since these were immature technologies, our selection criteria were subjective and came down to the potential for the warfighter. We had to take a hard look at the products on the table and decide which ones had the most promise.

The line between those that went into further development for operational prototyping and those that did not left a few concepts that were good, but not great. Since we didn't want to leave them out, we decided on a different venue to showcase them—an alternative technologies demonstration that

would be held in parallel to the main operational demo to show some of the thought processes that went into these technologies. For example, during the concept exploration phase, we envisioned a body armor vest that held CBRN-protective sleeves rolled up inside the torso of the vest, which would deploy by being unrolled when the warfighter needed them. It wasn't a fully mature concept, but we felt it had enough merit to show off during the VIP days of the demonstration when the CBRN community came to see our work.

The T&E plan is a critical part of the ATD process and has to be planned out early in the project. In particular, it is imperative that the plan receive input from the JPMs to reduce their risk when it comes time for these offices to select their final candidates for any programs of record that the ATD feeds. Having the T&E plan directed by a neutral third party is also critical to maintain impartiality, especially since our demonstration would use both government and industry solutions whose test data would be scrutinized closely. The Army Test and Evaluation Command and its subordinate unit, the Aberdeen Test Center, were chosen for their expertise in T&E to write and implement the test plan, which was then approved by NSRDEC and DTRA.

But any test plan, no matter how well thought out it is, must be adapted to the environment if something seems unfeasible or unrealistic. We targeted September 2010 to execute the operational test plan with soldiers from Fort Leonard Wood, MO and Fort Benning, GA. After the first day, we identified flaws in the test plan and adjusted accordingly. For example, we first envisioned a one-mile road march in a baseline FRACU configuration and then in a closed configuration, Mission Oriented Protective Posture 4 equivalent, to gauge the difference in data points. That sounds great in a briefing, but in reality is unnecessary roughness on the troops. There was no need to march them for one mile just to get objective performance and subjective comfort data. In essence, we were wearing them out too fast, so we adjusted the T&E plan by shortening the road march to a quarter mile in each configuration for the next five days of testing.

During the operational demo, we received great feedback from the soldiers on everything from the network solutions, to the passive cooling measures of the uniforms, to the "I'll never use this" factor. This live feedback was invaluable and certainly one of the greatest lessons learned from this program. In the end, it is the warfighter whose combat capability we are trying to improve and who benefits from the research and development community pushing the boundaries of possibilities.

Improving Ion Mobility Spectrometry Detection Capabilities Using a Theoretical Quantum Chemistry Approach

Douglas S. Burns, Marshall G. Cory, Jeffrey J. Piotrowski, Richard R. Thomas, and Joseph L. Vasey

Overview



Ion Mobility Spectrometry (IMS) is an analytical technique used to separate and identify ionized molecules in the gas phase based on their ion mobility in a carrier gas. The technology has been modified and improved since it was first developed in the 1950s, and IMS remains a work horse for chemical agent detection in today's battlefield. In fact, the U.S. Army has fielded over 50,000 IMS-based units. Its user friendliness, ruggedness, and rapid detection capability make IMS-based detectors extremely attractive for operators in the field. Two popular IMS-based detectors are the M22 Automatic Chemical Agent Alarm (ACADA) and the M4 Joint Chemical Agent Detector (JCAD), which are used to detect and identify blister and nerve agents. Despite their prevalence and popularity, however, there are drawbacks to this technology that can severely limit their effectiveness in the field, including excessive false-alarm rates and their adaptability to new and emerging threats.

ENSCO, Inc. is taking a fresh approach to solving these challenges through modeling and simulation. Our goal is to demonstrate how existing fielded IMS detectors can be modified to meet both current and future detection requirements thus eliminating the need for some new and expensive acquisition programs to build next generation detectors to meet the detection needs of the future. Indeed, our approach is in keeping with the theme of this year's Chemical Biological Defense Program APBI, "do more, without more."

Our approach to solving IMS's most difficult detection problems is to develop a semi-empirical (parameterized first-principles) model to predict the drift times of chemical ions in any detector configuration and operating condition, and calculate the resulting spectra. We apply state-of-the-art quantum chemical (QC) methods to generate the critical environmentally dependent chemical data that drives the thermodynamic, kinetic, and classical dynamics models that are used to calculate the drift time and number density of the ion. QC calculations are used to predict molecular interactions within the IMS detector that facilitates the determination of the size and shape of the ion-neutral chemical structures, a critical parameter for predicting how rapidly the ion cluster travels in the drift tube under the conditions of the IMS detector.

Our model provides insight into the effect of varying system parameters on the detection of a target molecule that, in turn, helps drive the modifications needed in existing IMS-based detector systems to meet new and emerging detection requirements. This first-principles predictive methodology—quantum chemistry, which is embedded in a larger scale engineering model—Synthetic IMS (SIMS), will provide the community with a rapid-evaluation tool suitable to triage a large matrix of instrument parameters that can be modified and optimized to allow for detection of other or new compounds of interest, such as explosives, new, and nontraditional chemical agents.

Components of the SIMS Model

There are three main components to the SIMS model. First, we calculate which chemical compound will be ionized preferentially over other chemicals present in the sample. Second, QC calculations are made to determine the size and shape of the clusters that form from the ionized compounds. Finally, we apply kinetic, thermodynamic, and classical dynamics models to calculate how rapidly these clusters travel in the drift tube when subjected to an electric field. In the following paragraphs, we will elaborate on each of these modeling components.

Which compound is preferentially ionized? A critical aspect of IMS is the ionization of the sample.¹ Therefore, the first step in our model is to determine which chemical will be ionized preferentially over other compounds in the sample. Depending on the mode of operation of the IMS instrument, this may involve calculating the tendency of the chemical to take on an electron (negative ion mode) or a proton (positive ion mode). For IMS instruments run in negative ion mode, a measure of the tendency to take on the electron is the Electron Affinity (EA) of the chemical and for instruments run in positive ion mode a measure of the tendency to take on a proton is the Proton Affinity (PA) of the chemical. Nerve agents and nerve agent simulants, for example dimethyl methylphosphonate (DMMP), are organophosphorus compounds that have high proton affinities and are typically analyzed in positive ion mode. In contrast, blister agents, like sulfur mustard, typically contain halogen atoms and tend to cluster with negative ions and are analyzed in negative ion mode.

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We previously demonstrated a quantum chemistry approach for predicting PAs for a wide variety of compounds.² An example of the output from these calculations is shown in figure 1. The relative order (highest proton affinity to lowest proton affinity) of a variety of toxic industrial compounds (TICs) and potential interferent compounds are graphically represented in this figure. Compounds to the left in figure 1 have a greater proton affinity than compounds to the right, and thus are more likely to take the available charge. The importance of ordering compounds in this manner is to show which chemicals might interfere with the ability of the IMS instrument to detect a target compound. In general, a chemical with a proton affinity greater than the target compound will preferentially be ionized, leaving the target compound unchanged (neutral) and likely undetected.

What are the sizes and shapes of the ion clusters that form? A critical step in the modeling effort is to calculate the size and shape of the ion clusters that form in the IMS ionization chamber. The mass and morphology of these clusters will ultimately determine how rapidly they travel down the IMS drift tube. There are two competing pathways that must be modeled in this step: the ability to form an ion cluster and the breakdown or fragmentation of the ion cluster once formed. As illustrated in figure 2, modeling the protonation of isobutane resulted in the formation of fragmentation products as well as protonated isobutene. Since the mass and morphology of the resulting ions are different, the mobility of these ions will also be different.

The goal of this step is to first physically and chemically understand the target chemical compound and then, using this knowledge, optimize its detection in an IMS device. Given a set of arbitrary ambient conditions, we will use chemical theory to predict which of the possible gas-phase complexes will actually form, the morphology of the complexes that are formed, and the charge distribution of those complexes. We then use this QC-supplied microscopic data to drive our classical dynamics calculations that model the effect of temperature (collisional processes), pressure, and humidity on the complexes and the resulting chemistry that occurs in both the reaction and drift regions of an IMS instrument. The QC-obtained fundamental data can be readily applied to any relevant conditions, including the temperatures of the ambient, ionization, and drift regions of the system. Furthermore, it can be used to determine the optimal operating conditions of the IMS system; for example, should the drift tube temperature be raised and how much should it be raised.

This is accomplished through our application of QC methods that we use to calculate the probability distribution of possible molecular conformations, which we then use to obtain thermodynamic information, principally the Gibbs Free Energy, ΔG . We use this information to determine what complexes are possible and which of their conformations are

most probable for the temperature and pressure conditions under which the IMS system was operated. These data are used to determine the equilibrium between competing complexes, for example, $(\text{NH}_4^+)(\text{H}_2\text{O})_2 + \text{H}_2\text{O}$ in equilibrium with $(\text{NH}_4^+)(\text{H}_2\text{O})_3$ again as a function of temperature and pressure. Figure 3 illustrates these data for $(\text{NH}_4^+)(\text{H}_2\text{O})_{i=1-3}$. In general, as the system temperature is lowered, the lowest energy conformation becomes significantly more favored and the ratio changes accordingly.



How rapidly do these ion clusters travel down the IMS drift tube? The following equation describes the mobility (K) of an ion moving through a gas under the influence of an electric field (Mason and McDaniel³) where—

- e is the charge
- N is the number concentration
- μ is the reduced mass of the ion and neutral (i.e., atmosphere)
- k is Boltzmann's constant
- T_{eff} is the effective temperature of the ions
- Ω_D is the effective collision cross section of the ion and the neutral

$$K = \left(\frac{3e}{16N} \right) \left(\frac{2\pi}{\mu k T_{\text{eff}}} \right)^{\frac{1}{2}} \left[\frac{1}{\Omega_D (T_{\text{eff}})} \right] \quad \text{Equation 1}$$

Once we calculate which clusters can form and the probable conformations, we are able to determine how these ion clusters move in the electric field. The result of the QC modeling also yields information concerning the dynamical process, for example, morphology, centers of mass, and charge distribution within the system. Such information is important when modeling the collisional process in the drift region. It is used to understand how, on average, the system will orient with respect to the applied field, which will allow for the average volume swept out by the complex per unit time to be determined, which, in turn, is directly related to the collision-induced drag acting to retard the motion of the complex in the drift region. This information is directly related to the observed K_0 .

The difficulty in evaluating Equation 1 lies in obtaining a physically descriptive Ω_D , which in turn requires the use of a physically faithful ion-neutral interaction potential in its evaluation. Various potential models exist that describe the ion-neutral interaction, which account for the attractive and repulsive interactions between the ion and neutral. The important QC-derived data includes the binding energy (ϵ_0) of the ion-neutral complex (taken as the difference between the energy of the cluster and the energies of the ion and neutral at infinity), as well as an estimate

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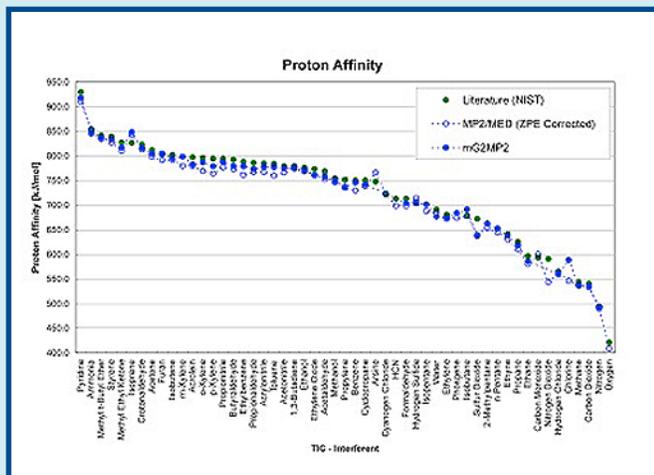


Figure 1. Theoretical and Experimental PAs for 53 Analytes

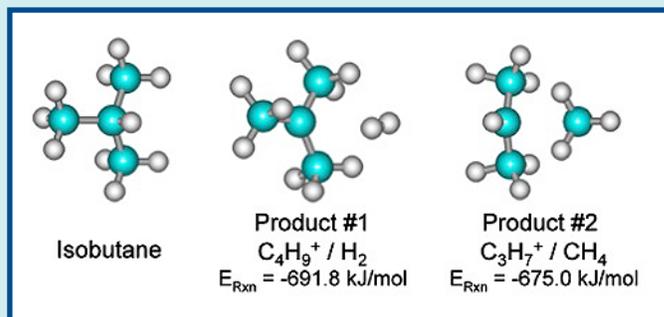


Figure 2. MP2/6-311++G** optimized structures for Isobutane, a C₄⁺ fragmentation product and a C₃⁺ fragmentation product

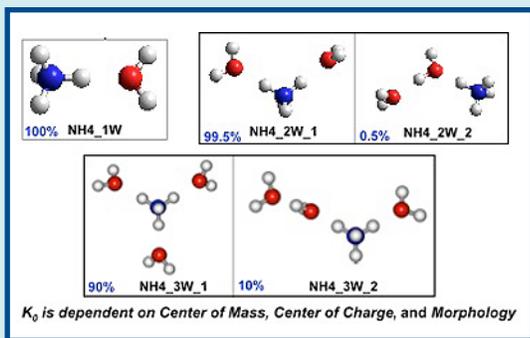


Figure 3. Optimized structures and Boltzmann weighted relative number concentrations for (NH₄⁺)(H₂O)_{i=1-3} at T = 300 K

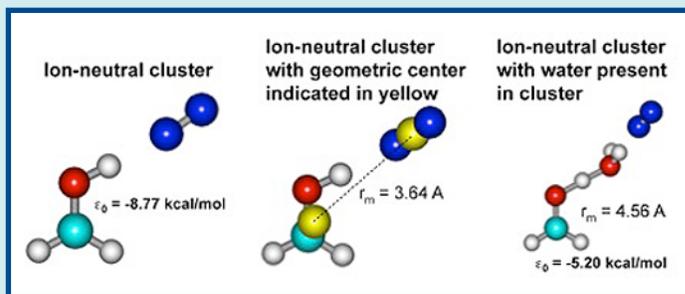


Figure 4. Example of binding energy and size terms

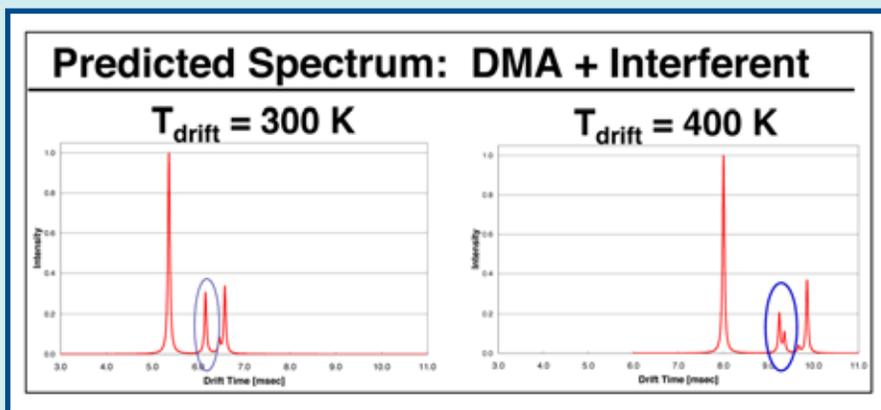


Figure 5. Predicted Ion Mobility Spectra for separating dimethyl amine and an interferent



of the cluster size. Figure 4 is an example of a QC-generated protonated formaldehyde (ion) cluster in N_2 (neutral) showing the computed binding energy (ϵ_0) and radial size taken from the centers of geometry of the ion and neutral.

Once the theoretical model has been built for a particular chemical compound and it is able to predict the observed mobility constants for that compound, the methodology can be embedded in a larger scale engineering model, such as SIMS, to predict drift times as a function of system parameters. The SIMS application can be used to triage a large matrix of instrument parameters that may be modified and optimized to detect different or new and emerging chemical compounds than the instrument was not originally designed to detect. For example, figure 5 shows how the model was used to separate dimethyl amine (DMA) and an interferent by rationally changing the drift tube temperature. In this case, DMA and the interferent have the same drift time when $T_{\text{drift}} = 300$ K, but different drift times when $T_{\text{drift}} = 400$ K.

Discussion and Benefits of Modeling

Increased Probability of Detection. A fundamental model of the chemistry in an IMS detector facilitates an increase in the probability of detection. Developers can rationally adjust instrument conditions to maximize the detection of threat materials. Simultaneously, the response to potential interferent compounds can be reduced by identifying through modeling the chemical modifiers and/or dopant mixtures that will preferentially interact with target compounds of interest.

Reduced False Alarm Rates. False alarm rates can be reduced through an understanding of the influence of environmental parameters like temperature or humidity on the ion chemistry in the detector, such as knowing how much the size of the target ion cluster increases at higher moisture levels. Larger ion clusters with greater mass result in slower drift velocities leading to longer drift times that are outside of the preprogrammed detection window. Detection algorithms can be enhanced to account for ion drift times that under certain environmental conditions can shift outside of the current detection window.

Reduced Test and Evaluation Costs. The CBD community has the daunting task of testing and evaluating both existing and newly developed equipment over a large parameter space, which includes (1) the ability to detect a large number of threat compounds, (2) the ability to detect these threat compounds in the presence of a large number of potential interferent compounds, (3) concentration effects, such as being able to detect at the PEL or LD50 levels, and (4) testing in a wide range of environmental conditions, including indoor and outdoor temperature, humidity, and air pressure. Theoretical modeling facilitates the ability to rap-

idly evaluate this parameter space and to focus the limited time and financial resources on important experiments.

Respond Rapidly to New Threats. The ability to reliably predict the drift time of a new threat allows vendors to more rapidly develop new detection algorithms. Upon identification of a new threat, modeling can be used to assess its ability to be detected using IMS to understand which interferent compounds present challenges and to identify chemical modifiers to enhance the signal of the threat material. Modeling can resolve issues such as the following:

- If the drift time will shift if $[H_2O]$ is present in the system and by how much
- If the presence of an interferent will influence a plasmagram
- If the interferent will preferentially take the charge
- How much an interferent will modify K_0 (drift time)
- How the instrument conditions (T , P , $[H_2O]$, residence time) can be changed to strategically alter K_0

The authors wish to acknowledge partial funding from the Science and Technology Directorate of the U.S. Department of Homeland Security (DHS S&T) contract HSHQDC-08-C-00110, and Dr. Angela Ervin of DHS S&T. While this research has been funded by this agency, the results and content of this publication do not necessarily reflect the views and opinions of the funding agency. In addition, we wish to acknowledge ENSCO, Inc. for funding the majority of the model development under an ENSCO Internal R&D effort.

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Gamma-Tocotrienol as a Novel Radiation Countermeasure Agent

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Background: Threat of radiological and nuclear weapons

In the context of the 2010 nuclear summit in Washington, DC, President Obama said, “If there was ever a detonation [of nuclear weapons] in New York City or London or Johannesburg, the ramifications—economically, politically and from a security perspective—would be devastating.”

Nuclear and radiological weapons are the most insidious among the four weapons of mass destruction and disruption: chemical, biological, radiological, and nuclear (CBRN). Table 1 shows several scenarios where radiation exposure can occur.

Based on the energy yield of the radiological/nuclear device ranging from 0.01 to 10,000 kilotons, light destruction is possible within 0.4 to 10 miles from the epicenter of the explosion.¹ In addition to the larger issues of economical, political, and security ramifications, exposure to these scenarios would lead to acute radiation syndrome—resulting in immediate lethality—and long-term consequences like cancer and pulmonary fibrosis, depending on the radiation quality, dose, and dose rate. Above all, an explosion of even a very-low energy yield, improvised nuclear device (a “dirty bomb”) could create devastating chaos and psychological fear in “worried well” people.

Immediately after their discovery, radiological substances were hailed as the miracles of medicine; but the inventors—Marie Curie, Irene Curie, and Frederick Joliot-Curie—were probably the first victims of an unintentional radiation accident. In modern times, the Chernobyl accident is probably the most studied nuclear accident.² There was no adequate protection for the first responders, except for the time-distance-shielding concept. Birth defects were later reported because of the lack of protection.³ In other major nuclear accidents, like Goiânia⁴ and Tokai-mura,⁵ there were only limited options to protect the victims. In the Tokai-mura criticality, the sole survivor has long-term effects of cataract and subclinical hypothyroidism.⁶ These unfortunate accidents indicate the potential dangers and consequences that can be unleashed by terrorist use of nuclear weapons or improvised nuclear devices. The ease in procuring radiological materials by terrorists has increased these potential radiological and nuclear threat scenarios.

Radiation countermeasures (radioprotectants) for first responder operations in the context of nuclear/radiological terrorism—an unmet end-user need

These accidents illustrate the urgency to develop a countermeasure that can protect first responders in a radiation exposure field for both rescue and military operations. This unmet end-user need in the field and the scarcity of prophylactic radiological medical countermeasures are critical issues for commanders in planning and executing military operations. Several books are devoted to

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Table 1. Radiation Exposure Scenarios

Terrorist threat

- Radiological dispersal device (dirty bomb)
- Attack or sabotage of a nuclear facility
- Use of nuclear weapons

Accidents

- Nuclear power generators
- Medical radiation therapy
- Industrial radiator
- Lost/stolen medical or industrial radioactive sources

Extended space travel

disaster management including radiation,⁷⁻⁹ but safe and effective radioprotectants are still not available.^{10,11} Thiols and nonthiols-cytokines,¹² prostaglandins,¹³ steroids,¹⁴ antioxidants,¹⁵ and nutraceuticals¹⁶⁻¹⁹ were proposed as potential radioprotectants, but none have been approved by the Food and Drug Administration (FDA). Amifostine, a sulphhydryl compound, was approved for clinical use in conjunction with cisplatin toxicity and for patients in radiotherapy for head and neck cancer,²⁰ but it was not accepted and approved as a choice radioprotector for military personnel. Moreover, it may not be useful for first responders because of its performance-degrading toxicity²¹ and hypocalcaemia.²²

Emerging role of tocals as potential radiation countermeasure agent

Tocols are a family of naturally occurring antioxidants existing as four isoforms of tocotrienols and tocopherols. The difference between tocopherols and tocotrienols is the presence of three double bonds in the side chain of tocotrienols.²³ Tocols have different antioxidant properties and tocotrienols generally are superior antioxidants.

Srinivasan et al.²⁴ reported that alpha-tocopherol (AT) diminishes radiation-induced delayed-type hypersensitivity in mice and improve the survival of lethally irradiated mice. An improved formulation of AT resulted in better protection.¹⁷ Our later studies showed that one of the tocotrienols, gamma-tocotrienol (GT3), is not only a superior antioxidant but also a potent radioprotectant.²⁵ Studies by other investigators revealed that delta-tocotrienol and a hemisuccinate of AT-tocopherol succinate also provide similar degrees of radioprotection. This update will focus on the development of GT3 as a radiation countermeasure.

Biochemistry of radiation damage

Exposure to radiation initiates free radical formation by two different pathways: direct and indirect.²⁶ In the direct pathway, critical target biomolecules, such as proteins, nucleic acid, and cell membrane components, are ionized directly by radiation creating the respective free radicals. In the indirect pathway, free radicals, such as superoxide, hydroxyl radical, and aqueous electrons are produced by the radiolysis of cellular water. These radicals attack critical biomolecules. In both pathways, free radicals of cellular components are formed that initiate cellular dysfunction and ultimately death or mutation of the cell through DNA damage, membrane damage, and damage to mitochondria. These molecular and cellular events lead to radiation-induced, multiorgan dysfunction syndromes (MODS) in vital tissues like bone marrow, gastrointestinal tract, spleen, lungs, and the central nervous system.²⁷ These reactions are shown in figure 1. Depending on their free radical potential, antioxidants interrupt one or more reactions (indicated by stars) and protect the organism from lethality.

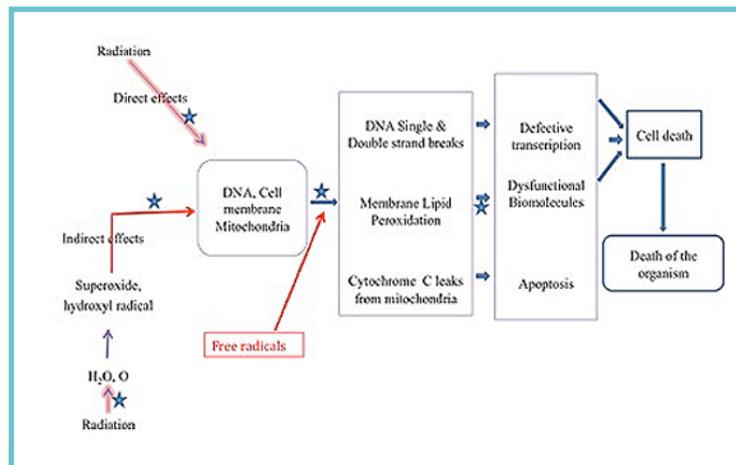


Figure 1. Radiation-Induced Free Radicals

Experimental animal model and techniques to evaluate radioprotective efficacy of GT3

Adult male CD2F1 mice were injected with 200 mg/kg GT3 subcutaneously 24 hours before irradiation at specified radiation doses at a dose rate of 0.6 Gy/min. Several endpoints were monitored to evaluate the efficacy of GT3: (1) protection of bone marrow as measured by histopathology of bone marrow at different days post-irradiation, number of hematopoietic stem cells, and blood elements; (2) protection of gastrointestinal tract as measured by mucosal surface area and survival at higher radiation doses; and (3) 30-day survival to determine if GT3 protect the animal from lethality. (See figure 2.)

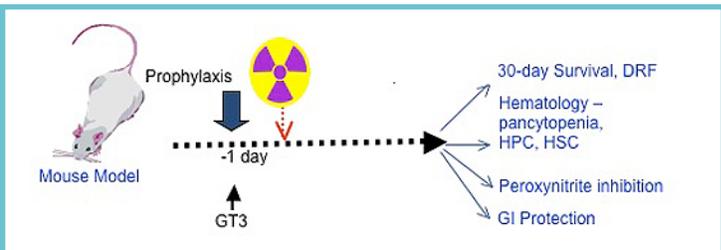


Figure 2. General Experimental Schedule

Results

Protection of Bone Marrow: Histopathology

Sternal bone marrow from vehicle (excipient)-treated mice irradiated at 7 Gy and stained with hematoxylin on day 13 after irradiation showed extensive depletion of cells as shown in

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figure 3. But the bone marrow from mice treated with GT3 and irradiated indicated almost complete recovery to normalcy.

Protection of hematopoietic stem cells

Hematopoietic stem cells (HSC) are the source for peripheral blood cells. HSC are early targets for radiation damage, and depletion of HSC will result in peripheral blood pancytopenia. As a result, radiation-induced infection and hemorrhage may happen, ultimately leading to the death of the organism. Figure 4 shows that the percentage of HSC in bone marrow from naïve, unirradiated, vehicle-treated, and GT3-treated mice vary from 1 hour to 13 days after irradiation.

Upon irradiation at 7 Gy, the HSC in vehicle-treated mice continuously decrease until 4 days and continue to stay at that level at 13 days postirradiation. When the animals were treated with GT3, HSC were elevated at an early time of 1 hour after irradiation, but continued to fall like the vehicle-treated animals until day 4 after irradiation. But on days 7 and 13 after irradiation, the HSC increased by 2.5-fold and 3.5-fold, respectively, as compared to the vehicle-treated and irradiated group. These studies clearly demonstrate that HSC are protected by GT3.²⁸

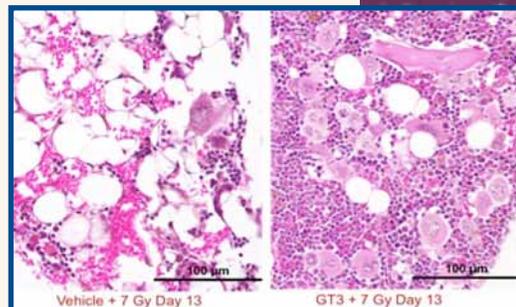


Figure 3. Protection of bone marrow by GT3 given 24 hours before radiation

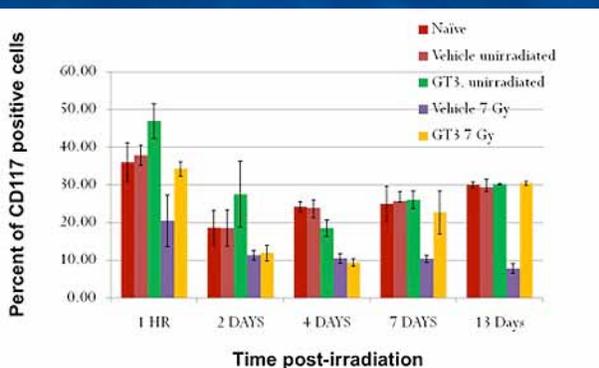


Figure 4. Protection of Hematopoietic Stem Cells by GT3 Given 24 Hours Before Irradiation

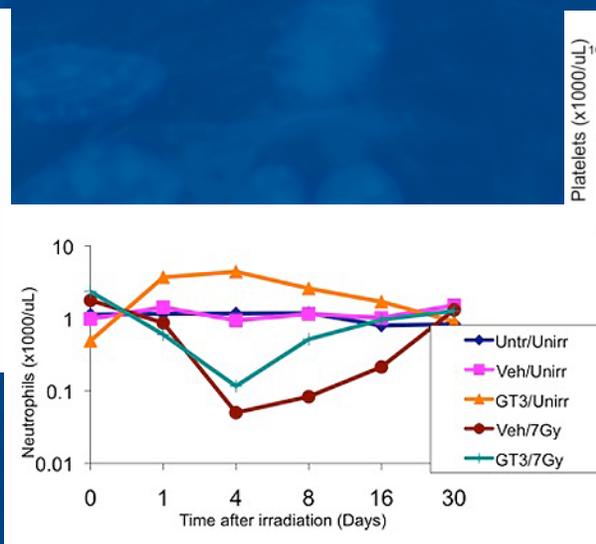


Figure 5. GT3 Pretreatment Enhances Recovery of Neutrophils after Radiation

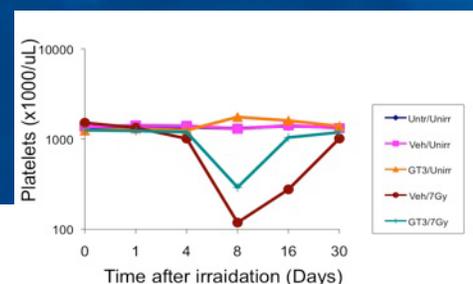


Figure 6. GT3 Pretreatment Enhances Recovery of Platelets after Radiation

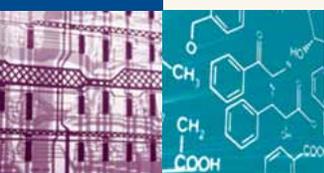
Prevention of peripheral blood pancytopenia

If the HSC are protected by GT3, it will be followed by the accelerated recovery of blood cells specifically neutrophils (figure 5) and platelets (figure 6). When the peripheral blood neutrophils (involved in infection) and platelets (involved in hemorrhage) were done, we found that the levels of these cells become very low in 4 days in mice that did not receive GT3 before irradiation.

When GT3 was administered before irradiation, although the cell counts decreased to a low level on day 4, thereafter the recovery was very rapid. At the end of 30 days, both vehicle- and GT3-treated mice showed similar counts. These studies were done by Kulkarni et al.²⁸ and Ghosh et al.²⁹

Gastrointestinal Protection

Other than bone marrow, gastro-intestinal tract is another tissue susceptible to radiation. Radiation-induced damage to the intestinal mucosa may lead to the translocation of intestinal microbes into blood and other tissue and initiate opportunistic infection. Figure 7 shows that, in irradiated mice, mucosal surface area is significantly reduced in vehicle-treated mice in a time-dependent manner.



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When mice were treated with GT3, there was a significant increase in the mucosal surface area. When mice were exposed to higher radiation doses that are known to cause damage to the intestine, the mice treated with GT3 survived longer than the vehicle-treated mice, as shown in figure 8.

Survival of Mice Exposed to Radiation: Ultimate Test for the Efficacy of GT3

The ultimate test of the efficacy of any putative radioprotectant is the ability of the drug to protect animal from lethality. In the case of GT3, survival efficacy was done in two steps: survival protection at various doses of GT3 and determination of dose reduction factor.

Survival protection at different doses of GT3

Mice were given various doses (50, 100, 200, and 400 mg/kg) of GT3 and exposed to supralethal dose of 11 Gy of Cobalt-60 (gamma) radiation. After exposure to radiation, mice were returned to their cages and monitored for 30 days for survival. The results are shown in figure 9.

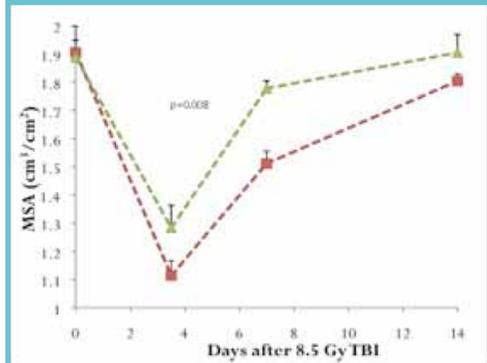


Figure 7. GT3 Confers Protection Against Intestinal Injury as Measured by Mucosal Surface Area

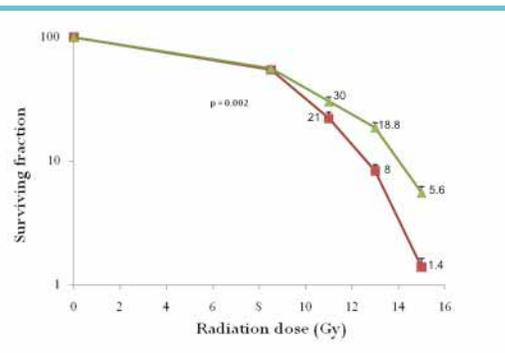


Figure 8. GT3 Confers Protection Against Gastrointestinal Death

The LD50/30 radiation dose for this strain of mice is 8.5 Gy. GT3-protected mice exposed to 11 Gy depending on the dose of GT3 used. None of the vehicle-treated mice survived after 17 days; 94 percent died by day 14 after exposure. Even at the lowest dose of GT3 tested (50 mg/kg) about 20 percent of mice survived. At higher doses of GT3 (100, 200, and 400 mg/kg) 80 to 100 percent of mice survived radiation exposure. A dose of 200 mg/kg was taken as the optimum dose since 100 percent of irradiated mice survived.

Dose reduction factor (DRF) of GT3

Lethality protection of different radiation countermeasures are compared by determining their dose-reduction factors. DRF is defined as the ratio of LD50/30 radiation dose for the drug to the LD50/30 radiation dose of the vehicle. The DRF for GT3 was determined by Ghosh et al.²⁹ and was found to be 1.29 (1.27–1.32, 95 percent confidence intervals). See figure 10.

Advanced development of GT3: Prospects for FDA approval

The FDA “two-animal rule” requires that the efficacy and safety must be “demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans.”³⁰ Based on the ongoing radiation countermeasure efficacy and mechanistic studies in mice (see references in this paper and other references),³¹⁻³⁶ GT3 has been approved for testing efficacy in nonhuman primates. These studies will be started soon after the completion of com-

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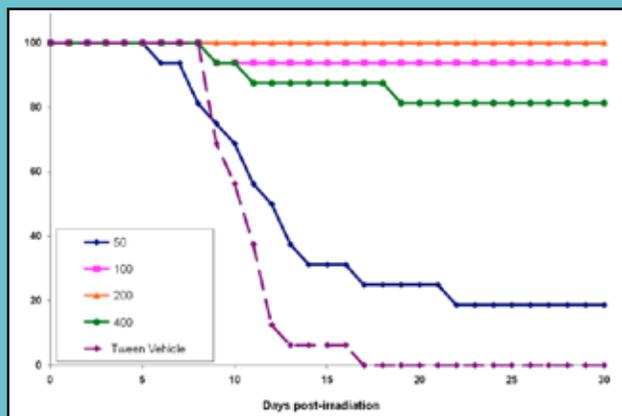


Figure 9. Radiation Protection by Various Doses of GT3

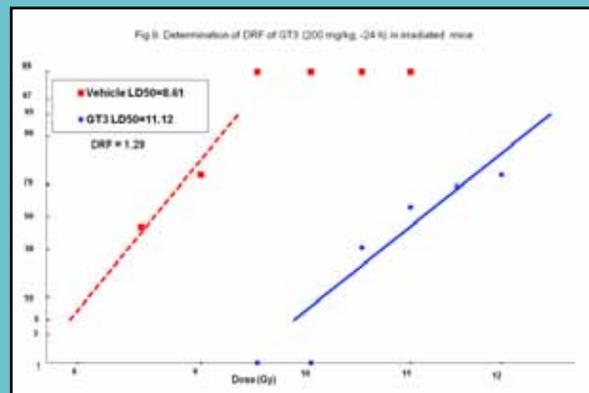


Figure 10. Determination of DRF of GT3 (200 mg/kg, -24 h) in Irradiated Mice

parative toxicity studies with other tocotols under a grant from DTRA.

Summary

Gamma-tocotrienol is a novel, potent, radiation-countermeasure agent. Efficacy studies in mice indicate that even a low dose of 50 mg/kg provides some degree of protection at a superlethal radiation dose of 11 Gy. We observed 100 percent protection with 200 mg/kg drug dose, and so this dose was used for further studies. DRF for GT3 was 1.29. GT3 protected mice from hematological and gastrointestinal damage and from lethality. Based on these studies, GT3 is slated to advance to efficacy studies in nonhuman primates. Mechanistic studies will continue in the meantime.

Financial support for these studies was provided by the Defense Threat Reduction Agency to Dr. K. Sree Kumar in AFRR (grant #s H.10027_07_AR_R and CBM.RAD.01.10.AR.005), and to Dr. Martin Hauer-Jensen in UAMS (grant # HDTRA 1-07-C-0028)

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Controllable Chemical Protection Using an Electroactive Membrane with Tethered Charges

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Standard chemical protective equipment (CPE), such as clothing and suits, have been improving for decades and can provide highly effective protection from chemical and biological (CB) agents. However, wearing CPE at its full protective capability can quickly diminish the combat performance of soldiers because it is cumbersome and cannot readily dispel body heat. It can also cause difficulties in communication, sensory perception, and physical coordination. So CPE is carried as an auxiliary and is only worn if threat is imminent or already present. This action usually requires from 4 to 8 minutes, and personnel are at risk of exposure to the agent during this time. Also, it is necessary that personnel keep CPE close at hand. If protective equipment could be made so that it can be worn at all times and does not degrade

have a high permeability to water vapor in the open state, which provides breathability and is comfortable for the wearer. However, if a chemical warfare (CW) agent appears, the application of the small voltage will rapidly switch the material to the closed state. When closed, the clothing will block transport of the agent. When the threat is removed, a second voltage application will revert the clothing to its open, breathable state. Both the open and closed states have long-term environmental stability.

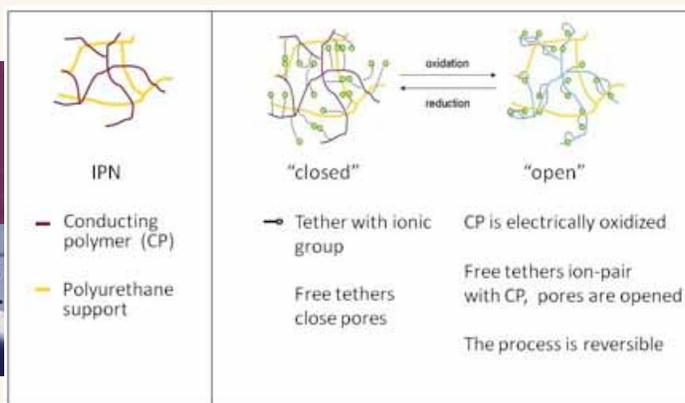


Figure 1. Depiction of the Electrically Conductive, Tether-Containing IPN Material

combat performance, these drawbacks could be eliminated. One can envision a clothing material that is comfortable to the wearer in the absence of CB agents but is able to be switched to a protective, impermeable state if an agent is present.

Our group at the Naval Research Laboratory in Washington, DC (Brett D. Martin, Ph.D.; Banahalli Ratna, Ph.D.; Martin M. Moore; Jawad Naciri, Ph.D.; Teresa Mazure; and Gusphyl Justin, Ph.D.) recently developed a membrane material composed of soft polyurethane interspersed with a conducting polymer network that can be reversibly switched between two conducting states by the application of about 1 volt. The conducting polymer network contains molecular tethers that each have a charged terminus. When the network is switched, the moveable tethers respond by forming complexes that either increase or decrease the material's porosity. The material has an open state with a high porosity and a closed state with a lowered porosity. Protective clothing or clothing sections formed from this material will

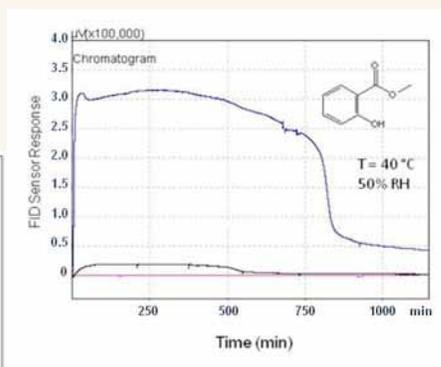


Figure 2. Passage of methyl salicylate simulant through an expanded Teflon control (blue), the open IPN (black) and the closed IPN (pink). The experiment was performed at 40 °C with 50% relative humidity

The conducting polymer network and the polyurethane support are present as a molecular blend of polymer chains that are cross-linked. The material can be described as an interpenetrating network (IPN) and is shown in figure 1. The tether chains, which have a negatively charged terminus, are attached to the conducting polymer main chains. They are highly flexible and can adopt many configurations. It is thought that this enables them to fill the interstitial nanoscale spaces between the conducting polymer main chains and the polyurethane chains, effectively blocking permeation of agent molecules. This is when the IPN is in its closed, protective state. When the threat agent is removed, the application of a small oxidizing (electron-removing) voltage transforms the conducting polymer to its positively charged oxidized form. In our paradigm seen in figure 1, the negatively charged tethers respond by forming ion-pairing complexes with the conducting polymer main chains. The nanoscale spaces between the main

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chains and the polyurethane chains become vacated, and the IPN enters its open state. Here, the material has a higher porosity and it is able to rapidly transport water vapor and air molecules. It is then breathable and comfortable to the wearer.

The IPN can be returned to its closed state by applying the voltage again, this time with a reducing (electron-supplying) polarity. The electrons enter the conducting polymer main chains and return them to their initial, electrically neutral state. The negatively charged tethers are released and reenter the nanoscale spaces between the main chains and the polyurethane chains, and the IPN will once again block permeation of agent molecules. The material can be cycled repeatedly through this open-close process.

The moveable tethers are based on short chains of polyethylene glycol (PEG), which are highly flexible and are known to facilitate ion transport. The PEG serves two purposes: first, its flexibility allows the tethers to adopt many configurations, which helps them to block transport of agent molecules; second, PEG assists in charge transport processes that are necessary for the material to be electrically switchable from the open to the closed state and vice versa.

The IPN material is made by dissolving its molecular precursors into a solvent mixture, casting them into a nylon filter, and heating it to 75 °C. The precursors include the compounds that polymerize to form the conducting polymer

portion of the IPN, an iron-containing compound that catalyzes this polymerization, and a type of ether-based polyurethane. After the IPN is formed within the nylon support, the iron catalyst is easily removed by extraction with hot water, and the material is allowed to dry. The final weight ratio in the IPN of conducting polymer to polyurethane is about 50:50. The final nylon-IPN composite material is mechanically rugged and electrically conducting.

Electrical and electrochemical characterization of the material has shown that the electrical impedance of the closed state is about 10-fold higher than that of the open state. This is thought to be because the closed form of the material slows the migration of ions, which lowers the total current that can be passed through the material in a given time. Using software, we modeled the

material as an electrical circuit using resistors and capacitors. We found that the closed state behaves as a circuit with a capacitor and resistor in parallel, whereas the open state acts much like a resistor alone.

The plot in figure 2 shows the different permeabilities of the IPN in its open (black) and closed (pink) states compared with an expanded Teflon (ET) membrane (blue).

ET is used in breathable sports clothing. The materials were challenged using vapor from the CW agent simulant methyl salicylate (MS). The chemical structure is shown in figure 2, and the challenge amount was 3.1 mg MS per cm² membrane. The amount of MS that passed through each material was absorbed into an air stream and then quantified by a standard flame-ionization detector. The ET (blue trace) clearly allows much more MS to permeate than either the open or the closed state of the IPN. After approximately 11 hours, the open state passes only about 6% of the amount that the ET does during that time. Most importantly, the closed state allows virtually no detectable amount of simulant to pass even after 18 hours of MS exposure. This result is significant because of the long amount of time elapsed with no breakthrough in the closed state and because MS is a relatively small molecule, having a lower molecular weight (152 daltons) than most mustard, V- and G-agents. Similar results were obtained when the IPN was challenged with vapor from chloroethyl ethyl sulfide (a mustard gas simulant), benzene, and liquid with dissolved methyl parathion (a V-agent simulant). In these challenges, the closed IPN state permitted very small amounts of the compounds to permeate, but still dramatically less than that permitted by the open IPN state or the ET control.

The moisture vapor transport (MVT) capability of a material is a key parameter that determines whether it is breathable and comfortable to wear. In our studies, MVT measurements were performed by using each sample as a partition that was sealed into a two-chambered permeation cell. The relative humidity (RH) in the first chamber was subjected to step changes of 25% to 30%, and the RH of the second chamber was recorded as a response over time. The experiment was performed at final RH settings of 25%, 50%, and 80% in the first chamber. This procedure allowed quantification of how well the sample was able pass water vapor. In figure 3, the y-axis represents this value in terms of the change in RH in the second chamber, per unit time.

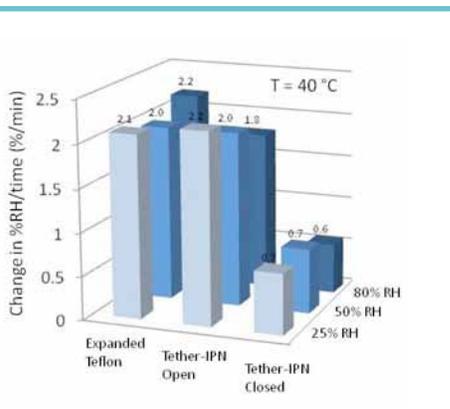


Figure 3. Moisture Vapor Transport through an Expanded Teflon Control

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The MVT behavior of the open and closed IPN states is shown along with that of an ET membrane for comparison. The open IPN allows MVT at nearly the same rate as that of the ET. Using several types of test apparatus, other groups have found that ET transports water vapor at very high rates compared to other clothing materials. Our results for the open IPN suggest that it will also compare favorably to the other materials in the different test apparatus. The closed IPN allows much less MVT, as expected, since it blocks transport of diverse types of small molecules.

The IPN membrane material provides breathability for comfort while in the open state and the desired protective capability while closed. In continuation of our studies, we are determining how (or if) simulant transport rates change as a function of RH and temperature. We are also investigating material responses in AVLAG-type challenge configurations involving convective flow normal to the sample surface, responses to V-series simulants such as alkyl phosphates, and MVT studies using dual convective flow.



This project, Electroactive Tethered Membrane for Controllable Chemical Protection, is sponsored by DTRA (project BA07PRO01).

News and Information Resources

Office of the Deputy Assistant to the Secretary of Defense for
Chemical and Biological Defense Programs (OATSD(CBDP))
<http://www.acq.osd.mil/cp/index.html>

Joint Program Executive Office for Chemical and Biological
Defense (JPEO CBD)
<http://www.jpeocbd.osd.mil/packs/Default2.aspx?pg=0>

Chemical, Biological, Radiological, & Nuclear Defense
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<https://mrmc-www.army.mil/>

U.S. Army Medical Research Institute of Infectious Diseases
(USAMRIID)
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U.S. Army Medical Research Institute of Chemical Defense
(USAMRICD)
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Walter Reed Army Institute of Research (WRAIR)
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<http://www.ecbc.army.mil/>

U.S. Army Natick Soldier Systems Center (NATICK)
<http://www.army.mil/info/organization/natick/>

Air Force Research Laboratory (AFRL)
<http://www.wpafb.af.mil/AFRL/>

Navy Medical Research Center (NMRC)
<http://www.med.navy.mil/sites/nmrc/Pages/index.htm>

National Defense Industrial Association (NDIA)
<http://www.ndia.org/Divisions/Divisions/ChemicalBiologicalDefense/Pages/default.aspx>

University of Pittsburgh Medical Center (UPMC) Center for Biosecurity
http://www.upmc-biosecurity.org/website/biosecurity_briefing/index.html

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<http://www.fbresearch.org/aboutfbr/tabid/423/default.aspx>

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<http://www.netsci.org/Science/index.html>

Science-Business eXchange
<http://www.nature.com/scibx/index.html>

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<http://www.technologyreview.com/>



DOING BUSINESS WITH DTRA

Doing Business with the Defense Threat Reduction Agency/United States Strategic Command Center for Combating Weapons of Mass Destruction, Research and Development Enterprise, Chemical and Biological Technologies Directorate (DTRA/SCC-WMD RD-CB)

The mission of the Chemical/Biological Technologies Directorate, Research & Development Enterprise at the Defense Threat Reduction Agency & STRATCOM Center for Combating WMD is to manage and integrate the discovery, development, demonstration, and transition of chemical and biological defense solutions for the Department of Defense. The Directorate serves as the focal point for Science & Technology expertise and provides state-of-the-art defense capabilities to permit U.S. military forces to mitigate the threat of chemical and biological weapons of mass destruction and, if necessary, to operate and successfully complete missions in chemical and biological warfare environments. For additional details regarding the Chemical/Biological Technologies directorate, see: www.dtra.mil/missions/missionshome.aspx

DTRA provides notification of business opportunities through a variety of websites. These include the Agency's website (www.dtra.mil), see "Doing Business with Us." Additionally, competitive solicitations are posted to the Federal Business Opportunities website (www.fbo.gov). Federal Grants of financial assistance are posted to the Grants.gov website (www.grants.gov).

For the small business community, DTRA participates in two of the Department of Defense's Small Business Innovation Research (SBIR) programs. The DTRA SBIR program and the Chemical and Biological Defense (CBD) SBIR program announcements and corresponding solicitation dates can be seen at the DoD SBIR Resource Center (www.dodsbir.net). To participate in any DoD SBIR program, register your small business at the DoD SBIR Resource Center website.

METHODS OF SOLICITING BUSINESS

The Defense Threat Reduction Agency frequently uses Broad Agency Announcements (BAAs) and Request for Proposals (RFPs) to solicit proposals for new business opportunities to include Research & Development.

All proposals are submitted electronically. Offerors must strictly follow the instructions presented in the individual solicitation. Registration is required to participate in a solicitation. Depending on the solicitation, there may be unique registration and proposal upload websites specific to the opportunity. Carefully read the solicitation instructions and abide by the specific due dates/times. Do not assume anything. When responding to a U.S. Government business solicitation, it may be helpful to be aware of the Federal Acquisition Regulations (FAR), available through Acquisition Central (www.acquisition.gov/far), in addition to the Defense Federal Acquisition Regulation Supplement (DFARS); see Defense Department Acquisition and Policy (www.acq.osd.mil/dpap).

Did you know?

Flu breakthrough promises a vaccine to kill all strains.

<http://www.guardian.co.uk/society/2011/feb/06/flu-universal-vaccine-test-success>

The city of Rajkot, India will host an important scientific and industry-related international conference bridging gaps in discovery and development.

<http://timesofindia.indiatimes.com/city/rajkot/City-to-host-intl-meet-on-science/article-show/7158740.cms>

Researchers at the University of Hawaii and a Honolulu start-up company have developed a hyperspectral sensor system that may be able to detect harmful substances, including those involved in biological and chemical weapons.

<http://www.bioprepwatch.com/news/225442-hawaiian-professor-develops-new-bioweapon-sensor>

A new class of sensors able to detect multiple biological and chemical threats simultaneously with unprecedented performance may soon be within reach, thanks to the establishment of a multimillion-dollar research center led by Georgia Institute of Technology engineers.

<http://www.photonics.com/Article.aspx?AID=45181>

Researchers have found a chemical that lengthens the circadian rhythm, which could mean possible drugs to reset the biological day clock of humans who do shift-work, suffer from jet lag, or have circadian rhythm-related disorders.

<http://content.usatoday.com/communities/sciencefair/post/2010/12/chemical-could-reset-circadian-clock/1>

An abandoned chemical weapons plant has been overrun with fluffy bunnies.

<http://www.wired.com/dangerroom/2010/12/bunnies-frolic-on-japans-old-chem-weapons-site/>

Nearly two-thirds of the world's chemical warfare materials have been destroyed.

http://www.globalsecuritynewswire.org/gsn/nw_20101213_7964.php

Pulmatrix, a Lexington, MA-based company, is developing inhaled therapeutics for respiratory infections caused by airborne agents to create a field-deployable drug/device combination to protect the warfighter and civilians against an array of airborne threats including anthrax, tularemia, and different strains of influenza.

<http://www.genengnews.com/gen-news-highlights/pulmatrix-wins-5-7m-darpa-funding-to-develop-host-targeted-inhaled-therapies/81244380/>

Researchers at MIT and the University of Albany have now discovered one way that cells boost production of proteins that perform critical tasks, such as repairing DNA, when they are exposed to life-threatening stresses, including exposure to toxic chemicals and radiation.

<http://web.mit.edu/newsoffice/2010/cell-stress-1217.html>

The Obama administration has become so concerned about the slowing pace of new drugs coming out of the pharmaceutical industry that officials have decided to start a billion-dollar government drug development center to help create medicines.

<http://www.nytimes.com/2011/01/23/health/policy/23drug.html>

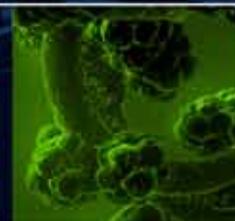


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