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CONTRACTING ORGANIZATION:

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14. ABSTRACT Scientific investigations, product development, and response to threats of endemic diseases and emerging pathogens are undertaken to reduce the risk of infection and lessen the impact of naturally occurring or man-made pathogens to humankind. If, however, proper precautions are not taken and safe practices are not utilized there is a risk that these interventions could contribute to increase the potential exposure of individual scientists and technical staff, as well as surrounding communities, to dangerous infectious diseases. The threat is perhaps greatest within the international laboratory community where these dangerous pathogens are routinely manipulated and investigated. This award supports critical training and hands-on experience to predominantly international scientists working with especially dangerous pathogens that require special biocontainment facilities for their safe and secure handling.					
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INTRODUCTION

Perhaps at no time in recent history has it been so evident that the study of infectious diseases, naturally-occurring agents and emerging pathogens is needed. Recent events have also underscored the need for rigorous training of professionals who work in modern biocontainment laboratories where this type of research takes place. Scientific investigations, product development, and response to threats of endemic diseases or bioterrorism are critically important on a global scale. To do the work required to increase scientific and medical understanding and to develop the diagnostics, therapeutics, and vaccines necessary to combatting disease and other threats, scientists and technical staff must be specially trained in proper precautions, safe practices, personal protective barriers, standard operating procedures, laboratory design, facility operations and more.

The threat is perhaps greatest within the international laboratory community where these dangerous pathogens may be routinely manipulated and investigated under less than ideal conditions by individuals who may lack adequate training or experience. While historically, this work was concentrated in a small number of research or government facilities where a limited number of highly trained investigators worked within appropriately equipped laboratories, today this type of investigation, research and development has become a global enterprise. Unfortunately, some of the individuals and their parent organizations attempting to conduct this work do not have in place adequate facilities, nor the training and administrative oversight to ensure the safety of the investigations, protection of the personnel, and the safe evaluation of the projects underway.

Through the aims identified below, we are sharing the valuable experiences we have gained at the Galveston National Laboratory (GNL) with others throughout the world who are involved in laboratory research. Our state-of-the-art facilities and the experience and knowledge we have gained from years of biocontainment laboratory operations have led to the development of thorough training programs that have been successfully implemented with our own scientists and personnel. We are pleased to share our expertise with biocontainment laboratory scientists and program directors around the world through the National Biocontainment Training Center's (NBTC) expanded scope of work.

The progress reported here complements activities summarized separately in a companion project (Award Number W81XWH-09-2-0053, also titled National Biocontainment Training Center). Together these awards support a coordinated effort to provide critical training and hands-on experience to U.S. and international scientists working with especially dangerous pathogens that require special biocontainment facilities for their safe and secure handling.

BODY

Research accomplishments associated with each specific aim are summarized on the following pages. This report covers July 2013 – July 2014.

Staffing - The NBTC draws upon the expertise of a number of professionals who work at the University of Texas Medical Branch. The professionals listed below have been integrally involved in some aspect of fulfilling the NBTC's mission during the last 12 months.

James W. LeDuc serves as principal investigator for the training center and is responsible for oversight of program initiatives, fiscal management and progress reporting.

Dennis Bente is directly involved in mentoring and supervising the research of international research fellows whose work takes place in the biocontainment laboratories.

Anne-Sophie Brocard is the LBTP director, manages the training facility, develops training programs for the NBTC, and is involved in training on-site at the NBTC, at conferences, and at collaborative partner locations around the world.

Christopher Gibbs assists in the training of building engineering fellows and provides hands-on guidance, especially in the care, maintenance and certification of the biological safety cabinets used in virtually every laboratory that handles pathogens.

Miguel Grimaldo directs the building engineering fellowship and provides lectures and hands-on guidance to fellows within the program. He also represents the program at meetings and events dedicated to biocontainment engineering.

Connie Holubar assists in the preparation of reports, organization and implementation of guest lectures, and general communications of program activities. She also monitors relevant policy issues and communicates those throughout the system.

Aaron Miller assists with the efforts to address Aim 4, to develop and implement training opportunities that focus on the safe and secure operations of novel laboratory instrumentation being introduced into the biocontainment laboratory environment.

John Morrill provides assistance in the training of students in the care, use and handling of laboratory animals within BSL-3 and BSL-4 biocontainment laboratories.

Ronald Veselenak also works to address Aim 4, to develop and implement training opportunities that focus on the safe and secure operations of novel laboratory instrumentation being introduced into the biocontainment laboratory environment.

Sheri Leavitt assists senior trainers with the training of students specializing in in-vivo techniques at ASBL-2 and assists the in-vitro trainers.

Mary Milazzo assists in the mentored training of students and staff in the BSL-4 biocontainment laboratory. She also assists in mentored training and the administration of tracking the status of approved users in the BSL-4 containment laboratories.

Belinda Rivera is a senior trainer who provides biosafety training for specializing in in-vivo techniques at ABSL-2 to ABSL-4, and she is involved in training on site, at conferences, and at collaborative partner locations around the world.

Nathaniel Schueller assists senior trainers with the training of students specializing in in-vivo techniques at ABSL-2 and assists with other training as needed.

Dee Zimmerman is the Biosafety Officer and Director of the Environmental Health and Biosafety Regulations and Requirements Core at UTMB. She oversees all aspects of safety training and is a member of the newly appointed external laboratory safety group advising the CDC.

Specific Aims

Aim 1. To provide standards-based biological containment laboratory safety knowledge to international partners.

Background

There continues to be a huge need for training in biosafety and biosecurity on an international level. To address this need and to reduce the potential impacts on national security, we continue to successfully expand our efforts to engage international partners in educational programs that are structured around the same principles and practices we use at the National Biocontainment Training Center at the University of Texas Medical Branch in Galveston.

Our focus is on identifying and providing training to personnel from international biocontainment facilities that are involved in the diagnosis and/or research and development of infectious diseases. Over the last year our international training efforts have continued to expand and grow, with many of our efforts extending beyond a specific quarter as collaborations evolve. The training of individuals from around the world is conducted both in Galveston and at international locations where it can be tailored to meet the facility's specific environmental, capacity and staff needs. In addition to providing individual training, we focus on opportunities to "train the trainer," leveraging our efforts as our students return to their countries to provide training within their own facilities and beyond.



We continue to work with a growing network of national and regional organizations that are focused on biosafety, biosecurity and related fields of interest, providing our leadership and expertise, in conjunction with other professional groups, to expand collaborative efforts that enhance training efforts. Through this aim we are providing standards-based biological containment laboratory safety knowledge in a hands-on manner with international scientists and laboratory personnel. Our efforts are focused on enhancing this important aspect of public health, safety, research and development as relates to infectious diseases.

Progress

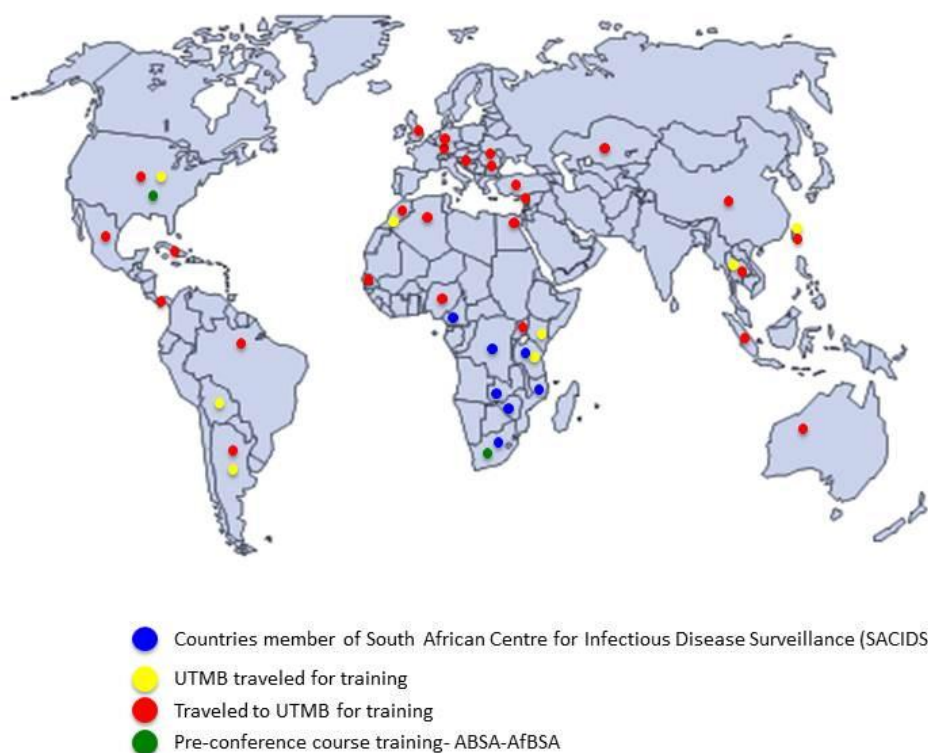
We are building collaborative working relationships with professional organizations throughout the world. As the map below shows, we continue to expand our biosafety training in response to growing needs and the international recognition of our unique abilities. We not only seek opportunities but also respond to requests for assistance to ensure that biosafety personnel around the world are professionally and thoroughly trained and that those with responsibility for training others have the tools and education they need.

BSL2-BSL3-ABSL3-BSL4

Training

Algeria
Argentina
Australia
Bolivia
Brazil
Bulgaria
Cameroon
China
Cuba
Egypt
Hawaii
Israel
Kazakhstan
Kenya
Mexico
Morocco
Mozambique
Nigeria
Panama
Romania
Senegal
Singapore
Slovenia
Switzerland
Taiwan
Tanzania
Thailand
Turkey
Thailand
Uganda
Ukraine
United Kingdom
USA
Zambia
Zimbabwe

International Training 2006 – July 2014



Biocontainment Engineering Working Group, International Federation of Biosafety Associations (IFBA). In an ongoing effort, Mr. Miguel Grimaldo, a GNL biocontainment engineer with the training center, continued this year to participate in the development of risk-management based guidelines for biocontainment laboratories as a member of the Biocontainment Engineering Working Group of the International Federation of Biosafety Associations (IFBA). These guidelines will eventually be endorsed by international organizations such as World Health Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO) and the Office International des Epizooties (OIE), the World Organization for Animal Health.

Central American Regional Biosafety Group. Mr. Grimaldo participated in a biosafety meeting for the region encompassing Central America, South America, the Caribbean and Panama in August 2013. The purpose was to discuss the creation of a Regional/Sub Regional biosafety association. More than 40 individuals from 13 countries participated in the planning and assessment meeting. Throughout the year, Mr. Grimaldo has continued to participate with this group and has lent his biocontainment engineering expertise to efforts to build a formal association. This participation has also led to training sessions with contacts made, both at the NBTC and abroad.

American Biological Safety Association. The 56th Annual meeting of the American Biological Safety Association (ABSA) conference was held in Kansas City, Missouri, October 17-23, 2013. NBTC trainers facilitated sessions during the event and also presented pre- and post-conference educational sessions that were attended by both domestic and international conference attendees. Presenters included:



- Ms. Belinda Rivera taught an eight-hour class entitled “Advanced Principles and Practices of Working in an ABSL-3.” The course provided information to individuals that are currently working in, plan on working in, or who audit ABSL-3 facilities. The course covered the unique hazards of working in an ABSL-3 facility and covered personal protective equipment (PPE), animal handling procedures, husbandry procedures, caging options, waste management, and emergency response procedures. Institutions with ABSL-3 facilities need to involve safety personnel, animal care staff, and researchers to ensure proper work procedures and safety protocols are in place and followed to maintain a safe and productive work environment.
- Ms. Dee Zimmerman taught an eight-hour class on “BSL-3 Operations and Management.” The course covered the most important aspects of a BSL-3 facility from two points of view: management of the facility and daily operations. She covered the unique management aspects of BSL-3 operations, such as hiring and training of lab workers, maintenance support, occupational health concerns, waste management, maintenance and monitoring of the physical facility, and emergency management plans. The course covered operations issues, including the selection and use of Personal Protective Equipment, waste handling, facility cleaning, equipment maintenance procedures. It also covered the development of manuals, SOPs, and training.
- Dr. Anne-Sophie Brocard co-taught an eight-hour class on “Advanced Risk Assessment.” Through a case study approach, attendees learned how to follow a research project as it evolves over time from basic to multifaceted in vitro and in vivo scenarios based on actual research protocol submissions. The course covered risk assessments that build upon each other from the discovery of a novel virus to determining the efficacy of experimental vaccines in humans. Dr. Brocard covered risk assessments and risk mitigation strategies.

- Mr. Miguel Grimaldo taught an advanced eight-hour class on “Advanced BSL-3 Facility Operations.” This course focused on detailed aspects of biocontainment operations of BSL-3, ABSL-3 and enhanced BSL-3 laboratories. It covered risk assessments for biocontainment equipment, facility operations and maintenance SOPs, as well as training requirements for maintenance personnel. The course covered the facility verification process in detail, including recommended test methodologies, solid and liquid waste decontamination equipment and procedures, ventilation control methodologies and equipment configurations, documentation and recordkeeping.

Mr. Miguel Grimaldo's class on Advanced BSL-3 Facility Operations was well attended at the 2013 ABSA Annual Conference in Kansas City.



Sokoine University of Agriculture (SUA), Tanzania. NBTC trainer Dr. Anne-Sophie Brocard has continued her involvement with the One Health Summer School at Sokoine University of Agriculture in Morogoro, Tanzania. This program is part of the Southern African Centre for Infectious Disease Surveillance. Over the last 12 months, the NBTC has provided training and education to 24 individuals and has developed and presented material on biosafety and biosecurity as part of a master's degree program for students studying molecular biology. In addition, a training agreement was signed between UTMB and SUA to provide lab safety training to all SUA laboratorians. Dr. Brocard has remained involved in the curriculum development process and will travel to Tanzania in August 2014 to teach coursework for the program focused on biosafety. The enormous concern over infectious diseases in Africa underscores the importance of this program, which is being designed to train a new generation of African researchers to address the heavy burden and threat of emerging infectious diseases in Africa. The aim is to help generate discoveries that can potentially be translated into diagnostics or control methods to improve human and animal health.



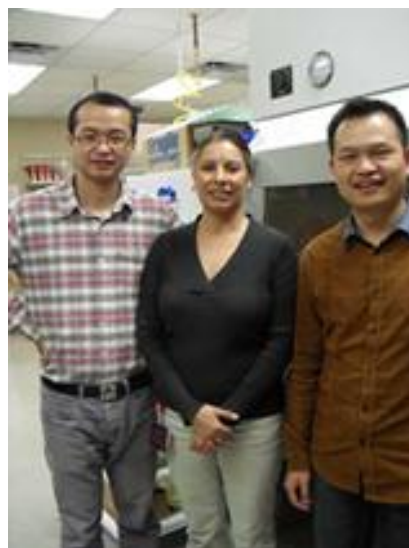
ABOVE: Tanzania Training -- Dr. Gerald Misinzo, Senior Lecturer, SUA, and Principal Investigator, Global Emerging Infections Surveillance (GEIS); Professor Mark Rweyemamu BVSc, PhD, FRCVS, Executive Director of the Southern African Centre for Infectious Diseases and Surveillance (SACIDS), SUA; Dr. Brocard; Professor Meck Mattee of Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania; and Dr. Christopher Kasanga, Virologist, SACIDS, SUA. Pictured bottom right: Martha Betson, an instructor at Sokoine from the Royal Veterinary College of London and Dr. Brocard.

Institute of Medical Biology in Kunming, China. Dr. Longding Liu, a scientist, and Qing Dai, an engineer (pictured below, right), traveled to the GNL to participate in an intensive two-week NBTC biocontainment engineering fellowship. They worked alongside GNL biocontainment engineer Miguel Grimaldo to review comprehensive aspects of facility operation and management in preparation for the opening of a new biocontainment laboratory under construction at their Institute in Kunming. The training program was customized to the needs of the two individuals and included:

- Laboratory Facilities and Primary Containment Requirements
- Primary Containment Equipment
- Filtration Systems
- Liquid and Solid Waste Decontamination
- Mechanical Systems - Ventilation and Controls
- Laboratory Facility Adjustment and Testing
- Decontamination Methodologies and Procedures
- BSL4 Specialized Equipment & Other Laboratory Equipment
- BSL4 Suits - Setup, Maintenance and Usage
- Annual Maintenance Shutdowns and Record Keeping
- Special Topics on Biocontainment Operation



The collaboration with the Institute of Medical Biology continued later in the year when Dr. Jiandong Shi and Dr. Lei Guo participated in BSL-2 and BSL-3 training at the NBTC in Galveston with trainer Belinda Rivera. The training was provided in preparation for the opening of the new biocontainment laboratory being constructed in Kunming.



Dr. Jiandong Shi and Dr. Lei Guo with BSL-2 trainer Belinda Rivera in Galveston.

Global Outbreak Alert and Response Network. Representatives of the NBTC continue their involvement in this important international network. Dr. Thomas Ksiazek attended the GOARN Steering Committee meeting in Switzerland in December on behalf Dr. Jim LeDuc, and Dr. LeDuc participated in an emergency meeting of the Steering Committee held in early June, focused on the Ebola crisis in Western Africa and worldwide efforts to combat and contain it. As a follow-up to the meeting, Dr. Tom Ksiazek has agreed to lead a team of experts in support of the U.S. Centers for Disease Control and Prevention and will deploy to Sierra Leone for 30 days to provide his expertise in containment of the Ebola epidemic.

Federal University of Vicosa, Brazil. The NBTC has established a new collaboration with the Federal University of Vicosa (UFV) and the Center for Regional Technological Development of Vicosa (Center). Mr. Grimaldo was invited to provide a presentation on the "Requirements for successful construction and operation of BSL-3 and BSL-4 laboratories" at the workshop for Innovation and Technology in Biological Agents and Biosafety, March 27-28, 2014. UFV has been an active collaborator with UTMB in the area of rickettsial diseases research, and Center and UFV are planning a new technological center for Biological Agents and Biosafety at their new Technological Park located in Vicosa, Minas Gerais, and Brazil.



Tradeline, Inc. Scottsdale, Arizona, USA. In April 2014, Mr. Grimaldo was invited to speak at the 2014 International Conference on Biocontainment Facilities. The title of the presentation was "If I only knew then, what I know now: Operating Lessons Learned for Biocontainment facilities". Over 125 participants composed of Facility Directors, Engineers and Architects from Institutions in the United States and around the world participated on this year's conference. Mr. Grimaldo's presentation was voted as the top rated general session presentation.

Center for Technological Development in Health (CDTS) at Fiocruz, Brazil. Dr. Claudio Manuel Rodrigues spent a week in Galveston July 21st through July 25th attending the ABSL-2 training program. During his week he was provided with customized training based on an initial assessment of his knowledge and skills. He also participated in a module on Autoclave Operations and Cycle Validation. Upon completion of his training, he expressed plans to return to Brazil to develop training programs specific to what he had learned to share with his colleagues and the personnel involved in laboratory research at the CDTS.



Dr. Claudio Manuel Rodrigues (center) spent a week at the NBTC working with ABSL-2 trainers. He plans to take what he learned back to the CDTS in Brazil to share with other scientists and laboratory personnel. Shown with Dr. Rodrigues are Miguel Grimaldo and Dr. Jim LeDuc.

Aim 2. To provide the information and education necessary for a critical global discussion on the biosecurity, biosurety and related policy issues involved in the operation and maintenance of biocontainment facilities.

Background

Students, staff, and faculty, as well as those working in the biocontainment field here and abroad have an interest in understanding more about existing and developing policies in biosecurity, biosurety and other issues. The base of knowledge is still developing, providing an opportunity for education and discussion that helps build the foundation for the safe and secure operation and maintenance of biocontainment facilities. We continue to contribute to the growing foundation of knowledge on this topic through the execution of our “Topics in Biosecurity Symposia Series,” which features distinguished experts from government, academic, and corporate entities. We also continue to engage with national and international partners to share information, stimulate discussion, and develop solutions to emerging and shared concerns. Our participation in the ongoing efforts of the U.S. National Academy of Sciences, the World Health Organization and other organizations continue to focus on topics of international concern, including the creation and safe operation of biocontainment facilities in Europe, Central Asia, Asia, the Americas, Australia and in Africa. Our goal is to engage national and international leaders to develop and implement evidence-based policy discussions and eventual agreements that will enhance the security of biocontainment facilities around the world, including in areas where no biosecurity infrastructure currently exists. This is being accomplished by participation in national, regional and international meetings and conferences and ongoing outreach efforts. Numerous collaborative studies and investigations, personnel exchanges and fellowships, and educational programs are contributing to the advancement of this aim.

Progress

Topics in Biosecurity Symposia Series. Distinguished guest speakers continue to participate in the “Topics in Biosecurity Symposia Series” held at the Galveston National Laboratory. Seminars throughout the year were presented to several hundred participants. Guest speakers who traveled to Galveston to present topics of national and international interest included:

- **September 2013:** Tom Slezak, a bioinformatics expert with Lawrence Livermore National Laboratory. A trailblazer in the field, Tom pioneered the use of “bioinformatics” in DNA physical mapping. He and his pathogen bioinformatics team built the BASIS System to provide wide-area monitoring for bioterrorism and he was instrumental in the creation of the nation’s BioWatch System.
- **October 2013:** Dr. Roger Breeze, president of Centaur Science Group in Washington, DC and former director of the USDA Agricultural Research Service Plum Island Animal Disease Center. He currently advises the Defense Threat Reduction Agency (DTRA) within the U.S. Department of Defense on ways to reduce the biological weapons threat in the former Soviet Union. Dr. Breeze is also aligned with the Lawrence Livermore National Laboratory. In his seminar session he presented a compelling topical discussion on looking ahead in a world of biological threats.
- **November 2013:** Dr. Francisco Pinheiro, an expert on viral diseases with the Program of Communicable Diseases in the Division of Disease Prevention and Control at the Pan American Health Organization, presented “Reflections of a Brazilian Virologist on Arboviruses and Other Viruses in Latin America,” which included historical perspectives and insight into laboratory biosafety.



Dr. Pinheiro is pictured alongside students and faculty from Brazil who are in residence at UTMB, as well as the GNL’s Dr. Jim LeDuc.

- **May 2014:** Peter Jahrling, PhD, the Chief Scientist at the National Institutes of Health's NIAID Integrated Research Facility provided a seminar in May. He serves as chief of the Emerging Viral Pathogens Section at NIAID and spoke on "Perspectives on Building and Activating a Unique BSL-4 Laboratory."
- **June 2014:** Michael T. Osterholm PhD, MPH, director of the Center for Infectious Disease Research and Policy (CIDRAP), director of the NIH-supported Center of Excellence for Influenza Research and Surveillance within CIDRAP, professor in the Division of Environmental Health Sciences, School of Public Health, and an adjunct professor in the Medical School, University of Minnesota gave a lecture on the topic of "Emerging Infectious Diseases Worldwide."

Planning for the Fall 2014 seminars is underway, with confirmed speakers Dr. Kavita Berger, Associate Director of the Center for Science, Technology and Security Policy for the American Association for the Advancement of Science; Dr. Tara O'Toole, former Under Secretary for Science and Technology at the U.S. Department of Homeland Security; and Dr. Robert Miceli of the U.S. Department of Defense Intelligence Agency.

CDC External Laboratory Safety Group -Recent events at laboratories in the U.S. have underscored the need for the development and implementation of national policies on the vital topics of biosecurity, biosurety and related policy issues that form the foundation for the safe and secure operation and maintenance of biocontainment facilities. Personnel from UTMB and the NBTC have been tapped to assist on several levels. Domenica (Dee) Zimmerman, Biosafety Officer, NBTC Instructor, and the Director of the Environmental Health and Biosafety Regulations and Requirements Core for UTMB has been appointed to serve on an external laboratory safety workgroup of the Advisory Committee to the Director of the CDC to assist in developing corrective actions for the CDC laboratories.

Aim 3. To develop and implement a dedicated program to facilitate the establishment, maintenance and administrative oversight of operations of biocontainment facilities.

Background

Biocontainment facilities are unique in their mechanical, security and safety infrastructures, and there are very few educational programs available that prepare professionals for their operational requirements. Today, with more international laboratories being constructed, the Galveston National Laboratory has taken on the role of sharing expertise on the unique engineering, maintenance and administrative challenges of running a safe biocontainment operation. The goal: to help ensure that all labs that deal with infectious pathogens operate safely. While every facility is unique in the research being conducted and the pathogens being handled, there are general principles that must be followed. As a national resource with a large variety of research projects underway, the GNL is in a unique position to share its expertise and lessons learned. Whether providing tours, one-on-one consultations, or formal training programs, the staff at the GNL is constantly sharing relevant, hands-on experience with the next generation of biocontainment industry leaders. An expanding list of the essential tools, skills and procedures critical to the safe and secure operations of a biocontainment laboratory are being compiled, documented, and shared to ensure that the best practices for fiscal stability, security, utility management, and equipment needs are available to biocontainment laboratories around the world.

Progress

NBTC Fellowship - Dr. Aysen Gargili. Program fellow Dr. Aysen Gargili completed a fellowship with the NBTC in the fall of 2013 and returned to her native Turkey. Since that time, she has continued her collaboration with the GNL and NBTC, with a project focused on Crimean-Congo hemorrhagic fever, which is fast-emerging in Turkey and Central Asia. She also has continued tick collection efforts as part of a CCHFV collaborative project with USAMRIID, and she has been planning design and construction for a new BSL-3 laboratory for Koc

University. She also participated in a Global Virus Network fellowship, where she visited Colorado State University, CDC and USDA National Wildlife Center in Fort Collins. At CSU she gave a talk about what she had learned about ticks and tick-borne diseases in her native Turkey, and at the CDC and NWRC, she met with the researchers and had the chance to observe their field study techniques and equipment. In addition, the knowledge she gained while at the University of Texas Medical Branch and Galveston National Laboratory was put to use training a group of 24 biocontainment laboratory workers in Turkey in January 2014. Dr. Gargili is a wonderful example of the success of the train-the-trainer strategy. Her efforts are ensuring well-trained personnel for the BSL-2 and BSL-3 laboratories in the Pendik Veterinary Control Institute, which is a national research laboratory under the Turkish Ministry of Food, Agriculture and Livestock. In summarizing her experience at the GNL, Dr. Gargili wrote:

“Overall, this fellowship provided me with an amazing opportunity to meet with an impressive array of researchers and begin laying the groundwork for collaborations in the near future. It was an invaluable chance to improve my understanding and current knowledge about the tick-borne studies that we’re planning as part of our work in Turkey and to exchange practices that I believe host institutions will find most useful.”



Photo of participants in a week long training course in biosafety and biosecurity organized by Dr Aysen Gargili (first row, center) for laboratory staff of the Pendik Veterinary Control Institute, a national research laboratory under the Turkish Ministry of Food, Agriculture and Livestock.

NBTC Fellowship – Dr. Han Xia. Dr. Xia came to Galveston from the Wuhan Institute of Virology in Wuhan, China. She is a graduate of the Chinese Academy of Sciences, where she received her doctorate degree in biochemistry and molecular biology. She arrived during the summer of 2013 to focus on research in the areas of viruses, diagnostic assay method of diseases, vaccine research, gene function, genomic and evolution analysis and epidemiology. Over the last several months Dr. Xia has completed theoretical BSL-3 training and laboratory training under Dr. Dennis Bente's mentorship. The U.S. Department of Justice cleared Dr. Xia for research work with select agents in late 2013, and in January 2014 she began her BSL-4 training, again working with Dr. Bente. She also participated in a BSL-4 facility training program alongside trainees from the Institute of Medical Biology in Kunming, China. From a research standpoint, Dr. Xia has made tremendous progress on her Crimean-Congo hemorrhagic fever project – in collaboration with U.S. Centers for Disease Control and Prevention (CDC) – in which parts of the genome are being cloned. She is also being trained by UTMB's Dr. Naomi Forrester to set up a next-generation sequencing pipeline for Crimean-Congo hemorrhagic fever virus. As reported last quarter, Dr. Xia continues to make excellent progress in developing her scientific projects. She has constructed the CCHFV (Crimean-Congo hemorrhagic fever virus) M segment with Nanoluciferase marker based on a rescue system developed by scientists at CDC and shared with UTMB. Working with Dr. Bente in the BSL-4 laboratory, studies are underway on the viral replication and pathogenicity in vitro and in vivo of this labeled recombinant virus. Dr. Xia's research is leading to important new knowledge at the molecular level regarding CCHFV transmission between ticks and vertebrate hosts. Through her fellowship, Dr. Xia is not only receiving ongoing training in high level biocontainment laboratories, but she is learning about the oversight and administrative responsibilities of operations while also conducting important research.

Amerikan Hastanesi (American Hospital) in Istanbul, Turkey. In May 2014, Mr. Grimaldo provided a week long training on BSL-3 Biocontainment Operations to Esra Kora (Project Manager), Muhammet Ali Süngü (Mechanical Engineer), and Birkan Kankatan (Arquitect). The American Hospital is in the process of completing the construction of a new BSL-3 Laboratory.

Representatives of the Amerikan Hastanesi in Istanbul learned essential components of BSL-3 operations while at the NBTC.



International Veterinary Biosafety Workgroup in Pirbright, England. In June, Mr. Grimaldo participated in and presented at the 16th Workshop of the International Veterinary Biosafety Workgroup in Pirbright, England. Mr. Grimaldo did a presentation on "Primary Containment Challenges for Medium Size Animals in ABSL-4 Facilities". The meetings were held at the Pirbright Institute. The International Veterinary Biosafety Workgroup is made up of high and maximum containment facility safety officers and biocontainment engineers with the purpose of cross-training and the exchange of experiences in the operation of these types of laboratories. Mr. Grimaldo has been a member of this working group since 1998; he has served as secretary of the group in the past and serves currently as the America's representative.

Latin American Laboratories, Mexico. In June 2014, Mr. Grimaldo provided a week-long training on BSL-3 Biocontainment Operations to a Latin-American group of scientists, engineers and biosafety officers. Jairo Betancourt from University of Miami, Cesar Esquivel from Universidad de Monterrey - UDEM, Mexico, and from Universidad Autonoma de Nuevo Leon - UANL, Mexico, Lenin Espinosa, Beatriz Lopez, Cristina Padilla, Lydia Rivera and Jose Vasquez.



Trainees from University of Miami, Universidad de Monterrey - UDEM, Mexico, and Universidad Autonoma de Nuevo Leon - UANL, Mexico trained at the NBTC in June 2014.

Center for Technological Development in Health (CDTS) at Fiocruz, Brazil. The goal of the CDTS is to fuse individual research projects with industrial production partners and to play a prominent role in Brazil's developing science, technology, and public health policies. As part of a developing partnership between UTMB/NBTC and the CDTS, senior engineer Marcos Denicio Da Silva De Souza traveled from Brazil to Galveston in July to work with Miguel Grimaldo and his team at the GNL. Mr. De Souza spent a week learning about facility design, specialized equipment, maintenance schedules, administrative record-keeping and other operational procedures. He planned to return to Brazil to share what he learned with other engineers and personnel, as well as with other laboratories and scientific organizations.



Marcos Denicio Da Silva De Souza (center) spent a week training with Miguel Grimaldo (left) and his staff on facility design, maintenance, and operations issues specific to biocontainment laboratories. His customized training was recognized with a certificate presented by Dr. James LeDuc (right) and will be utilized in his position with the Center for Technological Development in Health in Brazil.

Sinclair Knight Merz (SKM)/Jacobs Engineering, Melbourne VIC, Australia. Research facility design professionals Colin Sakinofsky and Jim Hargreaves visited the facilities of the Galveston National Laboratory in July to learn about specialized engineering concerns for air quality and safety from GNL engineers and facility operation experts. A customized training session was provided to assist them with design issues for laboratories being constructed in Australia.

Aim 4. To develop and implement training opportunities that focus on the safe and secure operations of novel laboratory instrumentation being introduced into the biocontainment laboratory environment.

Background

The rate of change in laboratory instrumentation and adaptation of novel technologies to the laboratory setting is progressing rapidly. Routine laboratory procedures are becoming more and more automated, saving technicians and investigators time and effort. Technologies that once were so costly as to limit their use to only a few facilities are now affordable for many laboratories. For example, the sequencing of a pathogen or host that once required months or even years of specialized investigation and costly outsourcing, now can be provided in a matter of hours through the use of automated, high throughput instruments never before available to the research community.

As these modern advances make their way into biocontainment laboratories where highly dangerous pathogens are studied, it is not always clear what safety concerns might exist. For instance, many automated pieces of equipment such as flow cytometry include procedures that could generate an infectious aerosol during wash steps or other routine operations. This could place laboratory workers at risk of accidental infection if appropriate precautions are not utilized. Decontamination of such instrumentation for service and maintenance is another major challenge. In addition, modern imaging equipment is now finding greater application within the research community. Both in vivo and in vitro imaging techniques and equipment are becoming available for use within the biocontainment laboratory environment for use in pathogenesis studies involving live animals or cell cultures infected with especially dangerous agents. Further, it is now possible to grow relatively large volumes of pathogens using modern bioreactor technology. The development of safe operating procedures, guidelines for product processing, and training on the safe use of each piece of equipment necessary for the production, processing and storage of the resultant product is required. There is an urgent need to develop well-validated procedures to safely and securely conduct these important studies while ensuring the safety of investigators and the surrounding environment.

Progress

Under this aim, personnel have been focused specifically on testing and documenting the use of instruments involved in the BSL-2 laboratories, while also examining their use within the BSL-3 and BSL-4 laboratories. In particular, standard operating procedures for use of instruments with processes that might generate infectious aerosols when live pathogens are investigated and decontamination procedures have been studied and documented. As with all procedures at the Galveston National Laboratory, a focus of this effort is on the development of specialized safety interventions to be used to protect workers at all levels of biocontainment.

Assay Development. Over the last several months, the assay development services division (ADSD) has continued to provide training, optimization and validation of much needed assays at lower containment for export to the BSL-3 and BSL-4 facilities. Such training includes basic methodologies as well as service and maintenance of the equipment that often is designed to be partially or completely automated. The ADSD has also developed and validated methods to eliminate infectivity while preserving the quality and quantity of nucleic acids. Such disinfecting methods have been exported to both BSL-3 and BSL-4 level containment through staff training and collaboration, ultimately providing safe egress of samples to the ADSD laboratory where automated and well-controlled processing can take place. A goal has been to reduce the amount of high maintenance equipment in the higher level containment laboratories. Downstream applications of the processed material include deep sequencing of disinfected pathogen genomes, transcriptional profiling of both the pathogen and the host species and basic proteomic evaluations.

Training has been completed for 4 research staff, 3 medical fellows, 2 PhD students, and several post-doctoral fellows involved in collaborative projects that can be or have been exported to higher containment. Additional training is underway. We have evaluated the integrity and sequence composition of nucleic acid stocks of several BSL-4 viral pathogens, training lab members in the process.

Specific instrumentation includes the Pyromark 96ID (Qiagen) and Ion Torrent PGM platforms (from Life Technologies). The ADSD group has also assisted and trained personnel from several laboratories on PCR-based array technologies utilizing the Tecan EVO liquid handling system to create pre-plated qPCR and qRT-PCR arrays for pathogens and underserved small animal host species (e.g. guinea pig). They also have developed methods to evaluate human microbiomes in clinical samples. These materials are created at low containment and can then be transferred to higher containment, reducing time and labor in the higher containment lab. This work has included training of researchers on the method and providing raw materials for completing work at distant sites, while testing both shipping and storage methods.

The ADSD, in collaboration with the division of clinical cytopathology, has developed tools to analyze nucleic acids from archived human tissue in the form of fine needle aspirates, paraffin embedded tissues and other biopsy materials. These nucleic acids can be interrogated for the presence of specific pathogens and host responses to these infections in material that is at least 10 years old and has been sub-optimally stored. For these assays we have been able to detect specific host polymorphisms that may contribute to susceptibility or inability to clear infections. Importantly, this may contribute to increased transmission during epidemic events. These same materials can also be subjected to sequencing to establish haplo-groupings for the human host from which the material was collected. Work with specialized instrumentation for purposes of developing standard operating procedures and improving safety conditions continues.

Real Time Plethysmography. New instrumentation and software that accurately measures actual inhaled volumes in non-human primates is being tested and will be implemented in the aerosol biology labs at the GNL. The system, called “real time plethysmography,” has shown promising results for measuring lung capacity during studies conducted with the assistance of the manufacturer. The GNL’s aerosol biology lab personnel are currently writing new standard operating procedures for using the system in animal studies, and software implementation should be completed during the next quarter.

Select Agent Inventory Management. A new automated system for managing select agent inventories is being piloted within the laboratories at the GNL. Training for those in the pilot program will be underway during the next quarter. More information on this technology will be provided in future reports.

Aim 5. To develop and implement policies, procedures and training programs for the safe and secure conduct of preclinical studies to be undertaken within biocontainment at biosafety laboratory levels 2, 3 and 4 (BSL2, 3, 4) in compliance with the U.S. Food and Drug Administration(FDA) Good Laboratory Practice (GLP) regulations (21 CFR Part 58).

Background

There is a growing requirement for the development of diagnostic tests, drugs and vaccines for use in the recognition, treatment and prevention of biological terrorism threats and emerging infectious disease agents. Bioterrorism threats are among the most dangerous infectious pathogens known to humankind, and their safe and secure handling must be done within the confines of specially constructed biocontainment laboratories. The level of biocontainment needed is specific to each particular pathogen and is layered from the lowest level, BSL-2, to “high containment” found in BSL-3 facilities, to “maximum containment” found only in BSL-4 laboratories.

In order to be formally approved for use in humans, products developed for potential application in humans must be evaluated for safety and efficacy during preclinical studies using laboratory animals under safe conditions of biocontainment prior to undergoing clinical safety and efficacy testing in human clinical trials. In addition, in certain cases where efficacy testing in humans is logistically or ethically impractical, products may be approved under the FDA’s “Animal Rule” which allows for efficacy to be demonstrated in appropriate animal models. Preclinical safety and animal rule efficacy studies must be conducted by appropriately trained personnel under standardized conditions using well defined procedures and validated equipment as described in 21 CFR Part 58, commonly referred to as Good Laboratory Practices. Each of these studies is likely to encompass activities across multiple levels of in vitro and animal biocontainment and, to date; few organizations have undertaken carefully regulated studies on these highest threat pathogens. Processes and procedures needed for formal GLP studies in biocontainment have generally not been created or have not been tested in actual working biocontainment facilities.

Progress

Representatives of the GNL and NBTC were integrally involved in 2014 FDA-sponsored “Achieving Data Quality and Integrity in Maximum Containment Laboratories” course, which was held at the Natcher Conference Center on the campus of the National Institutes of Health from April 28 – May 2, 2014. Personnel from the GNL, UTMB’s Institutional Office of Regulated Nonclinical Studies (ORNcS) and the NBTC served as faculty for the course. Trainees also had the chance to visit the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) and the National Institutes of Health Integrated Research Facility (IRF). Continuing Education Units (CEUs) were awarded to attendees who completed the four and one-half day course, which covered topics such as:

- Regulatory Mechanisms for Development and Approval of Medical Countermeasures
- Communications with the FDA
- The Animal Rule
- Data Quality and Integrity
- Case studies and Practical Experiences in a BSL-4 Lab

The ORNcS and GNL leadership have continued to develop a Study Director-centric model for the conduct and oversight of regulated studies that occur as precursor studies to fully compliant GLP studies. Advancement of medical countermeasure products requires carefully planned and administered studies under a quality system based on the principles of the FDA GLP regulations. Additional information on progress toward these goals will be provided in future reports.

Key Research Accomplishments

Significant progress has been made in addressing each of the Aims identified for study. The level of international engagement with laboratory scientists, engineers, biosafety officers, and growing organizations around the world has continued to expand. The demand for and acceptance of the training we are offering continues to grow. The trainers involved in these efforts have been warmly received by colleagues from around the world who have appreciated and embraced the training provided in both laboratory procedures and biocontainment building maintenance and operations. The opportunity to expand training and influence the safe and secure operations of biocontainment laboratories around the world is virtually unlimited. We are confidently providing a critically important link in the continued safe and secure operations of biocontainment laboratories and continue to be at the forefront of developing and sharing best practices.

Reportable Outcomes

Important partnerships and exchanges have been established both with international biosafety associations and with the individual leadership of international biocontainment laboratories. Key individuals from respected organizations around the world have benefited from extensive training on site at UTMB or at their home facility. These are significant steps towards helping to ensure safety and security at facilities where important research on infectious diseases and dangerous pathogens is being conducted. We are helping to develop highly trained and educated leaders in the field of biocontainment. This will provide the foundation for the continued dissemination of best practices to a much wider international audience.

Conclusions

Providing one-on-one training to international biocontainment professionals is a key to ensuring national security. The leadership and expertise that is being provided through training and the sharing of standards not only provides goodwill but helps to ensure that our counterparts throughout the world are able to move forward with scientific pursuits in a safe and secure manner. The collaborations that are being forged are building a foundation for long-term cooperation, as well as an international culture of trust and transparency that directly enhances global security.